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Neuromodulation in neurogenic pain and headache

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Neuromodulation in neurogenic pain and headache

Topic editors

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Editorial: Neuromodulation in neurogenic pain and headache

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Editorial on the Research Topic
Neuromodulation in neurogenic pain and headache

This section of Frontiers in Neurology provides a dynamic platform where neurologists, pain specialists, anesthesiologists, and neurosurgeons converge to explore innovative strategies for managing neurogenic pain and headaches. The collaborative nature of this forum fosters interdisciplinary insights, ultimately aimed at optimizing patient care.

Migraine, following tension-type headache—which has the highest prevalence at ~26%—is a significantly disabling neurological disorder, affecting nearly 14% of the population. Notably, its incidence is more than three times higher in women than in men. One particularly impactful study in this section suggests that delaying the onset of sexual activity in adolescents may serve as a protective factor against migraine. The authors found a robust causal association between age at first sexual intercourse (AFS) and migraine prevalence. This groundbreaking research highlights the importance of social and behavioral factors in the pathogenesis of migraine. Neuroendocrine, cytokine, and autonomic mechanisms are proposed as plausible mediators of this link, underscoring the biopsychosocial complexity of this relation (Zhu et al.).

Functional neuroimaging studies further deepen our understanding. One notable cohort study revealed altered brain connectivity in patients with migraine with aura. Specifically, these individuals exhibited reduced functional connectivity between the default mode network and the subgenual anterior cingulate cortex, along with increased activity in the supracallosal anterior cingulate gyrus, compared to healthy controls. These findings suggest also disrupted emotional and visual network integration in patients with migraine with aura (Cheng et al.).

Another intriguing investigation focused on breast cancer patients experiencing chronic neuropathic pain and comorbid depression. Resting-state functional MRI revealed significant changes in brain connectivity, linking affective and sensory processing pathways—reflecting the interplay between chronic pain and mood disorders (Liu R. et al.).

Recent advances in molecular research have led to promising therapeutic avenues, particularly the use of monoclonal antibodies targeting key inflammatory pathways. The trigemino-vascular origin of migraine is increasingly associated with genetic predispositions, including elevated levels of NLRP3 and MMP9 inflammasome components in these patients. These biomarkers present a compelling rationale for immunomodulatory therapies aimed at reducing neuroinflammation (Rushendran et al.).

Clinical case reports continue to offer valuable insights. An exceptional case of nummular headache—a localized, coin-shaped scalp pain syndrome—was successfully managed using botulinum toxin therapy, complemented by a ketogenic diet. This dual-modality approach illustrates the potential of integrating pharmacological and dietary interventions (Tereshko et al.).

In contrast, a case series exploring cranial electrical stimulation (CES) combined with transcutaneous electrical nerve stimulation (TENS) for burning mouth syndrome did not yield significant clinical benefits. Despite the use of advanced neuromodulation techniques, results were comparable to placebo, emphasizing the need for more refined therapeutic strategies. The study also underscored the importance of comprehensive outcome assessments, employing tools such as the Pittsburgh Sleep Quality Index (PSQI), Oral Health Impact Profile (OHIP-14), and multiple psychiatric scales (PHQ-D, HAMD, HAMA, HADS) to capture the full spectrum of patient experience. The team from Rostock exemplified rigorous clinical trial design aimed at minimizing placebo effects in neuromodulation research (Palmer et al.).

The integration of vagus nerve stimulation (VNS), a neuromodulation technique, into clinical practice for the management of neurological and psychiatric disorders—particularly chronic pain represents a promising development. A well-defined protocol for a systematic review and meta-analysis assessing the efficacy and acceptability of VNS in fibromyalgia has been presented and is both timely and compelling (Cai et al.).

Cervicogenic headache (CH), which affects up to 20% of patients with chronic headaches, continues to receive growing attention due to its impact on daily functioning. As literature on CH expands, further research is essential to elucidate pathophysiological mechanisms and refine treatment protocols (Xu et al.).

A Chinese research group proposed an innovative treatment for CH involving fluoroscopically guided meridian sinew Tuina injections targeting the occipital nerves. Their randomized controlled trial (RCT) protocol represents an excellent example of integrating traditional Chinese medicine with available imaging techniques (Huang et al.).

The burden of neuropathic pain accompanied by depression presents a significant clinical challenge. A prospective 3-month study evaluated the efficacy of vortioxetine, a multimodal serotonergic antidepressant, in patients with painful polyneuropathy due to entrapment or metabolic disturbances. Results indicated both analgesic and antidepressant benefits, with minimal adverse effects. The drug's potential to enhance neuroplasticity adds a promising dimension to its therapeutic profile (Eliaçık and Erdogan Kaya).

Management of acute herpetic neuralgia and postherpetic neuralgia remains a critical concern for neurologists and pain specialists. Conservative approaches using lidocaine patches, pregabalin, and gabapentin are first-line treatments. However, pulsed radiofrequency thermocoagulation of thoracic dorsal root ganglia represents a minimally invasive alternative aimed at modulating central sensitization with satisfactory effects (Wang et al.).

For patients with refractory trigeminal neuralgia and atypical facial pain unresponsive to pharmacotherapy, deep brain stimulation (DBS) has emerged as a viable solution. Targeting the periventricular and periaqueductal gray regions of the thalamus, DBS achieves nearly 50% pain reduction at 1-year follow-up by modulating ascending nociceptive pathways (Mandat et al.).

In terminal patients with pancreatic cancer experiencing mixed nociceptive and neurogenic pain, CT-guided chemical neurolysis of the celiac plexus has shown to reduce opioid consumption and improve quality of life, albeit without affecting survival. This technique should be incorporated as a core element of comprehensive palliative care strategies (Lu et al.).

Finally, non-pharmacological interventions remain essential in chronic pain management. Exercise has been extensively documented to promote neuroplasticity, enhance circulation, improve muscle function, and reduce inflammation. A meta-analysis by a Chinese group demonstrated that physical activity significantly raises both thermal and mechanical pain thresholds, supporting its inclusion as a standard component in neuropathic pain rehabilitation protocols (Liu S. et al.).

In conclusion, this section highlights the multifaceted nature of neurogenic pain and headache disorders. The diversity of contributions- ranging from molecular research and neuroimaging to case reports and clinical trials—demonstrates the field's rapid evolution. This collaborative platform highlights evidence-based, multidisciplinary strategies for pain management, with a specific emphasis on the advancing field of neuromodulation.

Author contributions

PS: Writing – original draft, Conceptualization.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Deficits in ascending pain modulation pathways in breast cancer survivors with chronic neuropathic pain: A resting-state fMRI study

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Purpose: Breast cancer (BC) is the highest frequent malignancy in women globally. Approximately 25–60% of BC patients with chronic neuropathic pain (CNP) result from advances in treating BC. Since the CNP mechanism is unclear, the various treatment methods for CNP are limited. We aimed to explore the brain alternations in BC patients with CNP and the relationship between depression and CNP utilizing resting-state functional magnetic resonance imaging (rs-fMRI).

Methods: To collect the data, the female BC survivors with CNP ($n = 20$) and healthy controls ($n = 20$) underwent rs-fMRI. We calculated and compared the functional connectivity (FC) between the two groups using the thalamus and periaqueductal gray (PAG) as seed regions.

Results: Patients with BC showed increased depression and FC between the thalamus and primary somatosensory cortices (SI). Moreover, the Hospital Anxiety and Depression Scale-Depression (HADS-D) and pain duration were linked positively to the strength of FC from the thalamus to the SI. Furthermore, the thalamus-SI FC mediated the impact of pain duration on HADS-D.

Conclusion: In BC patients with CNP, the ascending pain regulation mechanism is impaired and strongly associated with chronic pain and accompanying depression. This research increased our knowledge of the pathophysiology of CNP in patients with BC, which will aid in determining the optimal therapeutic strategy for those patients.

KEYWORDS

breast cancer, functional MRI, chronic neuropathic pain (CNP), depression, functional connectivity (FC)

Introduction

Breast cancer (BC) is the highest prevalent malignancy affecting women globally (1). With increased treatment efficacy (surgery, radiotherapy, hormonal treatment, chemotherapy, or combined treatment), this disease has more survivors than ever (2). However, many survivors suffer from chronic pain, including chronic neuropathic

pain (CNP), with approximately 25–60% of women with CNP after receiving BC medication (3). CNP is a collection of distinct chronic pain manifestations induced by harm or disorder of the somatic sensory system, such as post-surgical nerve and tissue damage and inflammation exceeding 3 months. It is a syndrome caused by nerve dysfunction due to extensive nerve fiber injury (4, 5). Symptoms include all kinds of debilitating pain, including burning, shooting, and stabbing, which usually lasts indefinitely (4, 6). Accordingly, the mechanism of the CNP is still unclear, and the symptoms are more resistant than other types of pain to available treatments (7). Therefore, patients frequently experience complications for the remainder of their lives. Depression, observed in 18–54.4% of patients with BC, is among the highest prominent psychological conditions (8–11). Depression seriously affects mental health, work, and life (12). Meaningfully, depression is related to elevated deaths in patients with BC (13). Depression is the primary factor affecting the functional status of patients with BC (14). A good correlation exists between pain and depression in patients with BC (15, 16). Although this is a common phenomenon, its brain mechanism remains unclear.

Functional MRI (fMRI) is a commonly recognized method to examine brain function, especially in pain research. CNP involves morphological changes and functional adaptations of brain processing (17, 18). Damage to the ascending and descending pain regulation mechanisms may account for the aberrant sensory manifestations of people with chronic pain (19). The thalamus can transmit nociceptive signals to the somatosensory cortices (SI) through the spinothalamic projection, which is crucial in the ascending pain pathway (20). The descending pain regulation mechanisms are significantly involved in pain perception. These pathways project to neurons in the dorsal horn of the spinal cord to control the ascending information of pain, and the higher cortex dominates the periaqueductal gray (PAG), which is the main control center in the descending pain regulation pathway (21). Li et al. (22) discovered aberrant functional connectivity (FC) patterns across ascending and descending pain mechanisms in individuals with post-herpetic neuralgia, where the thalamus and PAG were utilized as seeds. In numerous chronic pain cases, abnormal FC of the pain regulation system has been reported, such as migraines (23), low back pain (24), painful diabetic neuropathy (25), chronic neuropathic pain (17), trigeminal neuralgia (26), sciatica (27), and neuropathic pain (28). Nevertheless, it is unclear how the ascending and descending pain regulation systems lead to CNP in patients with BC. Moreover, the connection between chronic pain and depression in patients with BC remains unexplored.

Herein, we utilized fMRI to evaluate neural changes in ascending and descending pain mechanisms in BC patients with CNP and to assess the link between CNP and depression in depth. We speculated that the FC between the thalamus, PAG, and other brain areas in BC patients with CNP was disrupted and that a defective FC may be associated with pain features and depression. If the hypotheses are confirmed, our study will enhance the understanding of the CNP in BC, which will greatly benefit the development of new treatments for BC.

Methods

Subjects

Our research complied with the recommendations of the Declaration of Helsinki, and the Local Ethical Institutional Review Board accepted the procedures. Before each procedure, all subjects signed informed consent. This research involved 20 right-handed patients with BC (20 women: mean age 52.25I ± 6.55 years) and 20 ideally suited healthy right-handed controls (20 women: mean age 49.95 ± 6.06 years).

The inclusion criteria included (1) patients with BC survived 1-year or more post-therapy and experienced CNP for at minimum 3 months, (2) 18 years of age or older, and (3) a pain rating equal to or exceeding 3 out of 10. Exclusion criteria included (1) cognitive decline; (2) brain metastases; (3) past psychiatric disorders; (4) receiving central pain treatment throughout 1 month; (5) concurrent illnesses, like severe infection or systemic illness (rheumatologic, cardiac, respiratory, gastrointestinal, neurological, and endocrine); (6) past events of neural disorders or dementia, psychiatric illnesses, or failure to accomplish the test methods and MRI scans; and (7) an unwillingness to participate in the study.

Demographic and clinical features

At admission, demographics (marital status and education) and clinical data (cancer stage, surgeries and therapies administered, and antidepressant and/or pain killers use) were acquired through self-reports and electronic health records.

Pain

Peripheral painkillers were stopped 1 week before the fMRI scan, and no painkillers were given during the scanning to ensure the accuracy of the data. We recorded the duration of CNP for each patient as pain duration. The CNP of patients with BC was evaluated using the visual analog scale (VAS) score (0–10 cm, with greater scores showing increased pain). Subjects indicated their current and historical pain levels by pointing to a spot on the line between the two faces. One experienced pain specialist measured the VAS (past) and VAS (during scanning) of patients to evaluate the pain intensity.

Depression

The hospital anxiety and depression scale (HADS) is a 14-item self-reported survey with anxiety and depression subscale scores (29). HADS performs well in evaluating anxiety disorders and depression symptoms in patients with BC (29–32). We assessed the incidence and degree of depressive manifestations using the hospital anxiety and depression scale-depression (HADS-D). Each HADS-D item varies from 0 (no symptoms) to 3 (severe symptoms), while depression total scores are calculated as aggregates varying from 0 to 21. The reference range is 0–7, 8–10 indicates the status, and 11 or more indicates depression. The HADS-D has demonstrated reliability and validity for depression in different demographics, including patients with BC. The measure requires around 3 min to complete. We measure all subjects using HADS-D.

Statistical analysis

Using two-sample *t*-tests, age and educational years variations between patients with BC and healthy controls were determined. A Chi-square test was utilized to examine gender disparity between the two groups.

fMRI data acquisition and preprocessing

A Philips Ingenia 3T MR scanner (RoyalPhilips, Amsterdam, the Netherlands) was employed to obtain 3T fMRI results. Subjects were asked to maintain their heads steady throughout scanning, and a sponge pad was utilized to limit unconscious head motion. Also, subjects were instructed to stay awake and close their eyes, and refrain from engaging in specific or intense thinking.

BOLD signals were acquired utilizing a gradient-echo-planar imaging sequence (EPI) with the next metrics: TR (repetition time) = 2,000 ms, TE (echo time) = 30 ms, flip angle = 90°, slices = 36, slice thickness = 4 mm, slice spacing = 4 mm, matrix = 128 × 128, volumes = 200, volume interval = 2 s, and voxel size = 2 × 2 × 2 mm^3. Concurrently, high-resolution T1-weighted structural photos were acquired using a 3-dimensional magnetization prepared rapid acquisition gradient echo sequence (MPRAGE) with the next scanner metrics: TR = 7.44 ms, TE = 3.46 ms, flip angle = 8°, sagittal slices = 301, slice thickness = 1.2 mm, slice spacing = 0.6 mm, image matrix = 240 × 240, volume = 1, and voxel size = 1 × 1 × 1 mm^3.

A brief description of preprocessing pipeline was as follows: (1) the initial 10 volumes of each functional scan matching every subject acclimation to the scanning setting and magnetization stabilization were neglected; (2) movement adjustment was conducted to lessen the impacts of head movement; and (3) functional photos were co-registered to structural photos and spatially normalized to the Montreal Neurological Institute template. Each voxel was resampled to 3 × 3 × 3 mm^3; (4) the liner-drift, Friston-24 criteria, the white matter signal, and the CSF signal were retrieved as covariates and regressed to lessen non-neural signals; (5) a scrubbing action was also conducted for high motion time points; and (6) eventually, a band pass filter (0.01–0.08 Hz) was used to eliminate high-frequency noise influences and smoothed with an 8 mm full-width-half-maximum isotropic Gaussian kernel. Therefore, the collected finding was analyzed deeper.

Considering that the thalamus and PAG are important nodes in the ascending and descending pain mechanisms, they were selected as the starting points for the FC analysis of resting-state fMRI (rs-fMRI) data. To ensure homogeneity among all participants following standard fMRI analysis pipelines, the thalamus seed was derived from the Harvard Oxford subcortical structural atlas (90% threshold), a population-based probability atlas in MNI-152 standard space (33). The PAG seed was determined using the Duvernoy atlas of the Human Brainstem and Cerebellum in MNI-152 standard space (34). Resting-state seed-based FC analysis was conducted utilizing the toolbox Data Processing Assistant for rs-fMRI (DPARSF; http://www.restfmri.net/forum/DPARSF) pipeline.

The mean time series of the thalamus and PAG were extracted, and voxel-wise FC was calculated between the thalamus and the remaining voxels within the brain. The same method was used to calculate the FC of PAG. The differences in the seed-based FC in patients with BC and HC were assessed using a general linear model within the gray matter masks. The grouping information was set as contrast while age, gender, and educational years were set as covariables to regress their linear effect on FC. $p \leq 0.001$ was corrected for multiple comparisons using familywise error correction at the cluster level, matching to an adjusted $p \leq 0.05$, using statistical parametric mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm). Subsequently, the mean value within the resultant cluster was extracted and linked to the clinical indicators in patients with BC.

Mediation analysis

A bootstrapped mediation analysis was employed to evaluate the mediatory link among pain duration, HADS-D, and seed-based FC. Using 2000 bootstrap samples and the PROCESS macro (http://processmacro.org, vs. 2.16.3) in statistical product service solutions (SPSS; IBM, vs. 23.0), 95% confidence intervals (CI) for model parameters were determined. The objective of the mediation analysis was to examine if a significant variation existed between the total effect (path c) and the direct effect (path c') that the mediator (M) accounts for. Two models were evaluated using the thalamus-SI FC as the mediator: (1) pain duration to be the independent variable and HADS-D

TABLE 1 Demographic and clinical data of breast cancer (BC) patients and healthy controls (HC) (mean ± SD).

	BC patients	Healthy controls	*T*	*p*
Female	20	20	-	>0.05
Age (year)	52.25 ± 6.55	49.95 ± 6.06	1.153	0.256
Education (year)	11.10 ± 2.79	11.80 ± 3.47	0.703	0.487
Pain duration (month)	5.05 ± 0.95			
VAS (past)	5.65 ± 1.66			
VAS (scanning)	5.15 ± 1.63			
HADS-D	7.40 ± 3.35	0.75 ± 1.52	8.1	<0.001

VAS, Visual Analog Scale; HADS-D, Hospital Anxiety and Depression Scale-Depression.

ratings to be the dependent variable and (2) HADS-D ratings to be the independent variable and pain duration to be the dependent variable. A mediation was considered significant when bootstrapped upper as well as lower 95% CIs showed a number except zero.

Validation analysis

To examine the consistency of the present findings. We also regressed the global signal in our current data and performed FC, correlation, and mediation analyses identical to our previous analyses.

Results

Demographics, pain, and depression features

Table 1 summarizes sex, age, years of education, pain duration (month), pain intensity [VAS (past) VAS (during scanning)], and depression (HADS-D) in patients with BC and HC (Figure 1A). Sex ($p > 0.05$), age ($t = 1.153$, $p = 0.256$), and educational years ($t = 0.703$, $p = 0.487$) demonstrated a non-significant variation between the two groups. Therefore, the quantified depression condition using HADS-D scales showed significant elevation in the BC group contrasted with the healthy group ($T = 8.1$, $p < 0.001$; Figure 1B). Eight (40% of the total) patients with BC had a HADS-D score ≥ 8.

Associations between pain characters and HADS-D

For patients with BC, Pearson correlation analysis demonstrated that pain duration and VAS (past) scores were positively linked to HADS-D scores (pain duration vs. HADS-D: $r = 0.53$, $p = 0.01$; VAS (past) vs. HADS-D: $r = 0.49$, $p = 0.02$; Figure 2). Furthermore, VAS (past) was positively related to VAS (scanning) ($r = 0.60$, $p = 0.005$; Figure 2).

Seed-based FC

Patients with BC displayed significantly stronger FC with the primary SI and inferior parietal lobule (IPL) than healthy controls when the thalamus was set as the seed $p \leq 0.001$ (familywise error correction, corrected $p \leq 0.05$ at cluster level; Table 2, Figure 3). FC between the thalamus and cerebellum of patients with BC was weaker than that of healthy controls $p \leq 0.001$ (familywise error correction, corrected $p \leq 0.05$ at cluster level; Table 2, Figure 3). Importantly, HADS-D scales and pain duration were positively correlated with the FC between the thalamus and SI (HADS-D vs. FC: $r = 0.71$, $p < 0.001$; pain duration vs. FC: $r = 0.58$, $p = 0.007$; Figure 4). We identified a non-significant association between thalamus-SI FC and HADS-D in healthy controls. Using PAG as the seed region showed a non-significant variation in FC between the two groups.

Mediation analysis

The thalamus-SI FC mediated the pain duration effect on HADS-D (direct effect = 0.36; indirect effect = 1.56, $p < 0.05$; 95% CI: [1.23, 2.12], Figure 5, left panel). In contrast, the impact of HADS-D on pain duration showed no mediation role by the thalamus-SI FC (direct effect = 0.26; indirect effect = 0.22; 95% CI: [−0.27, 1.12], Figure 5, right panel).

Validation analysis

Our results from validation analyses were consistent with our previous results above. Contrasted to the control group, the BC group exhibited raised FC between the thalamus as well as SI, correlating with the HADS-D score and pain duration. The thalamus-SI FC mediated the impact of pain

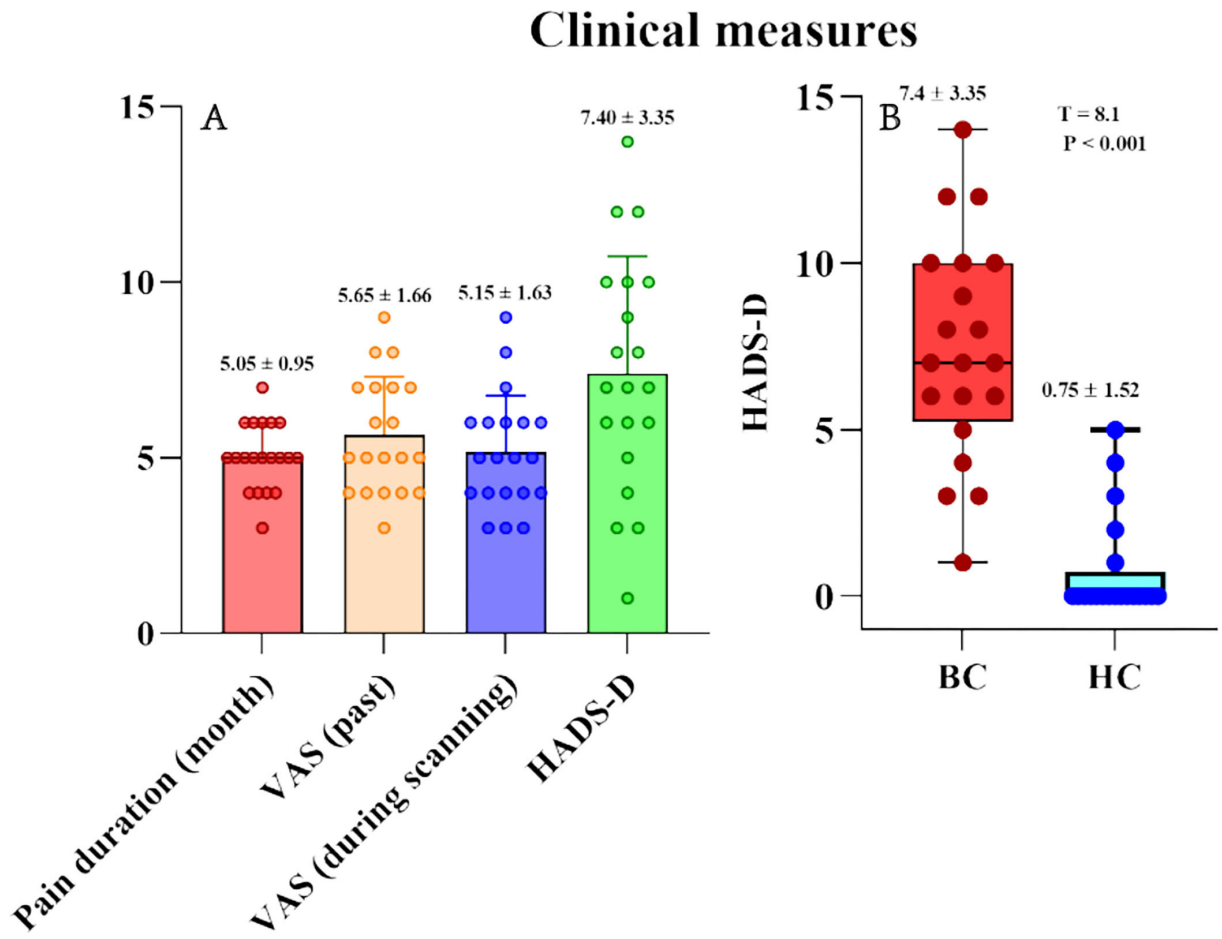

FIGURE 1
Pain characteristics (VAS and pain duration) and psychological variables (HADS-D) of BC patients and healthy controls. **(A)** Pain characteristics (VAS and pain duration) and HADS-D in BC patients. **(B)** HADS-D were significantly larger in BC patients than that in healthy controls. HADS-D, Hospital Anxiety and Depression Scale-Depression.

duration on depression. The above results are presented in the Supplementary material.

Discussion

Herein, we acquired three primary findings: (1) 40% of patients with BC with CNP had depression, and the HADS-D score was significantly linked to pain duration and VAS (past). (2) Contrasted to the control group, the BC with CNP group exhibited higher FC between the thalamus as well as SI, correlating with the HADS-D score and pain duration. (3) The thalamus-SI FC mediated the impact of pain duration on depression.

Breast cancer is the highest frequent malignancy in women globally and accounts for 25% of female cancer cases (35). CNP and depression are the most common comorbidities in patients with BC, significantly reducing their quality of life and ability to return to society (7). Herein, the incidence of depression in patients with BC was 40%, similar to the reported incidence by previous studies. We also found that depression (HADS-D) was positively correlated with pain duration and VAS (past), consistent with previous studies (15, 16). However, previous studies focused only on this phenomenon and unillustrated their internal connection. Furthermore, we investigated the association between depression and pain in BC patients with CNP through brain function mechanisms.

The neuroimaging study of chronic pain has always focused on the study of pain modulation effects, including pain-associated brain areas and their pain regulation (36, 37). Since the thalamus and PAG serve as the main nodes of the ascending and descending pain regulation pathways, we performed FC analysis using them as seeds. The primary outcome of the fMRI analysis is that the FC between the thalamus and SI and IPL were significantly increased contrasted to the control group. The FC with cerebellum was significantly decreased. The thalamus

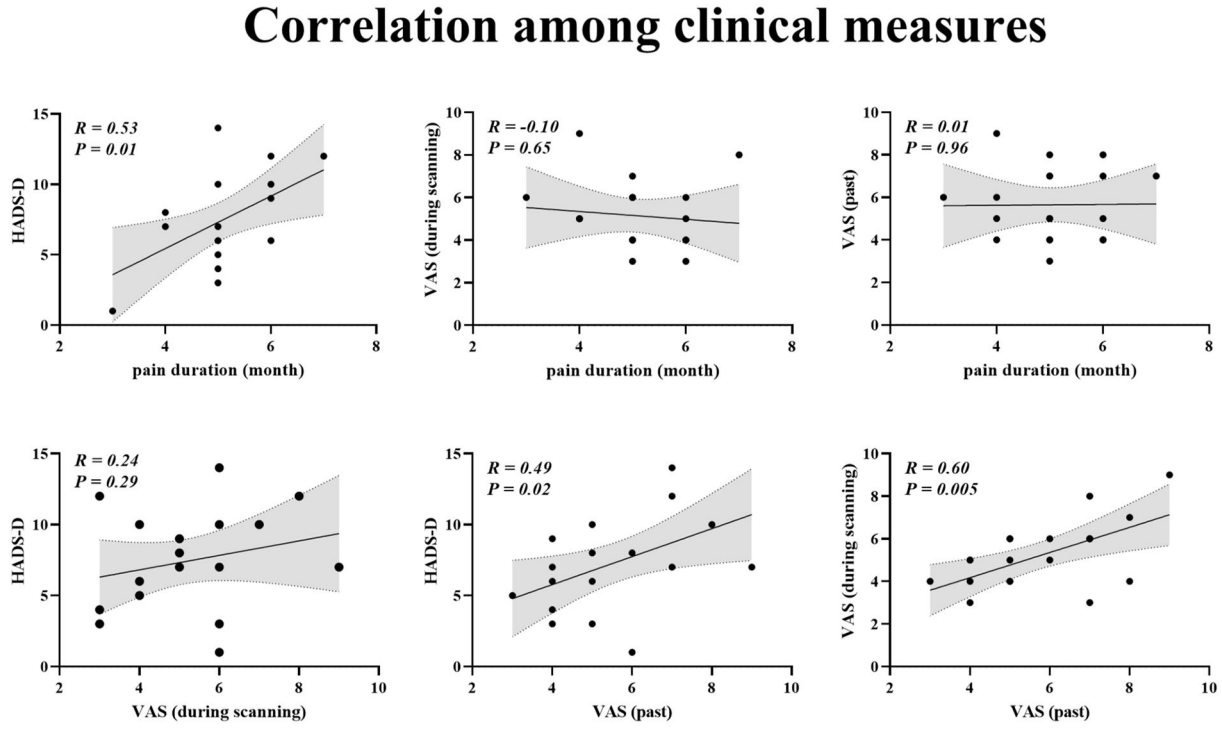

FIGURE 2
Correlation among clinical measures.

TABLE 2 Clusters that exhibited significant seed-based (thalamus) resting-state functional connectivity differences between BC patients and healthy controls.

Area	Side	Peak MNI coordinates (x, y, z)			Cluster size	*T*-value
IPL	L	−50	−40	44	30	4.88
SI	R	33	−27	65	46	4.56
Cerebellum	R	−17	−84	−33	63	−5.03

BC, breast cancer; IPL, inferior parietal lobule; SI, postcentral gyrus.

is the key node of the ascending pain regulation mechanism, transmitting the afferent nociceptive signal from the peripheral receptor to the pain-associated brain region (38). The thalamus plays a crucial role in initiating and maintaining neuropathic pain, like trigeminal neuralgia (39) and chronic back pain (19), and disruption of the thalamocortical network may act as a potential neurobiological indicator of chronic pain (40–43).

Herein, the raised FC of thalamus-SI showed probable function impairments in the ascending pain regulation mechanism in CNP-affected patients with BC. The overloaded input of spontaneous pain in the thalamocortical network might strengthen the association between the thalamus and SI (44), representing that patients with BC were in chronic pain. Moreover, IPL, as a critical component of the default mode network (DMN), is implicated in the brain modification of chronic pain, such as chronic jaw pain (45), chronic musculoskeletal pain (46), and low-back-related leg pain (47). We found that the FC of IPL and the thalamus in the BC group was elevated compared to the control group, suggesting that the sensory monitoring activity can be affected in BC patients with CNP (48, 49).

As the main node in descending pain regulation, PAG is involved in many chronic pain disorders (50–53). Unfortunately, our study undetected changes in the FC of PAG with other brain regions compared with healthy control; the insufficient sample size may be the cause.

We further found that HADS-D and pain duration positively linked to FC between the thalamus and SI through linear regression analysis. This indicated that the malfunction of ascending pain regulation system was strongly linked to CNP and depression. We agreed with prior studies that the thalamus increased resting-state FC with the SI when the

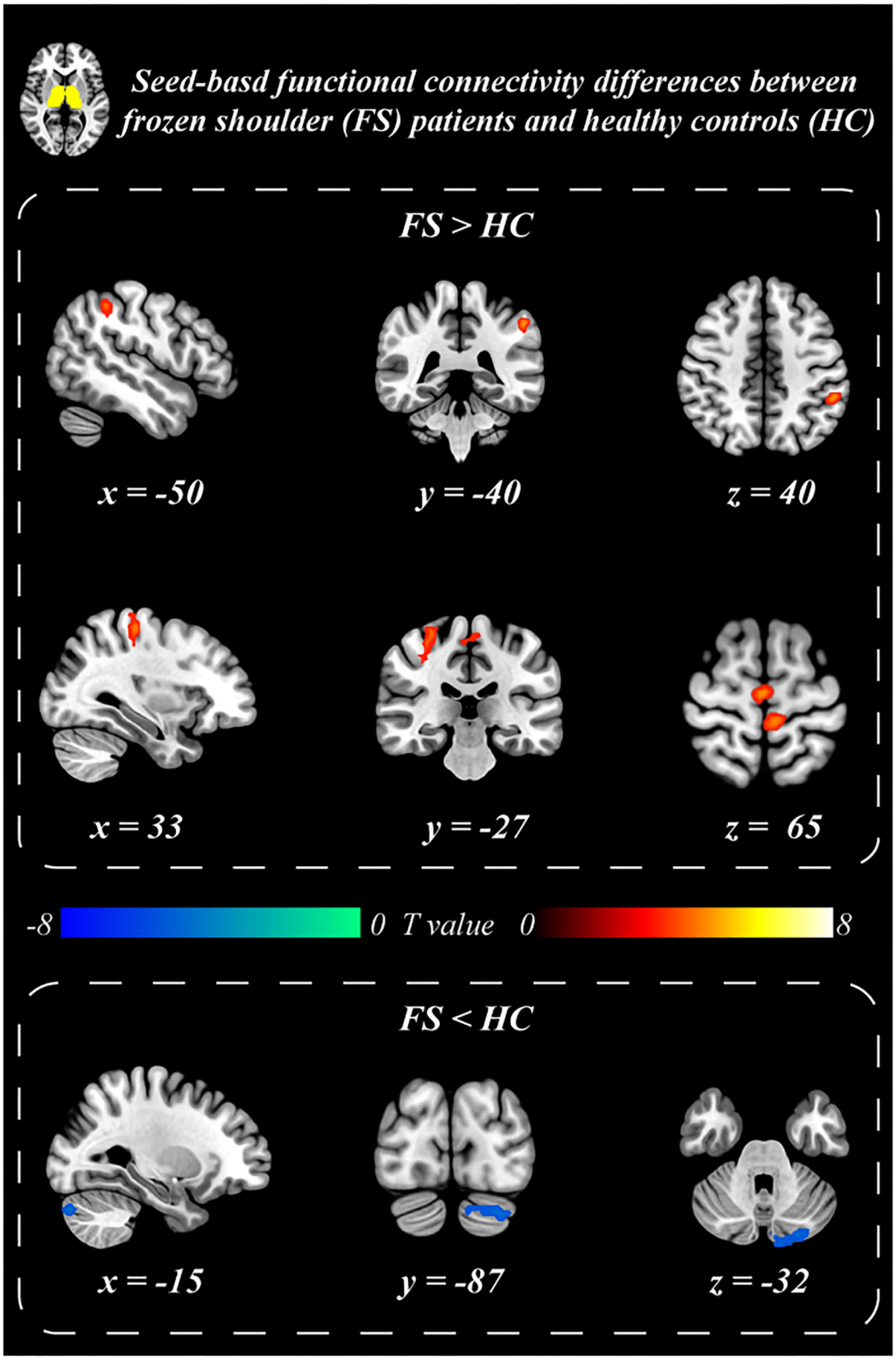

FIGURE 3
Seed-based functional connectivity differences between BC patients and healthy controls. Thalamus exhibited stronger resting-state functional connectivity with postcentral gyrus (SI) and inferior parietal lobule (IPL), and weaker functional connectivity with the Cerebellum in BC patients than that in the healthy controls.

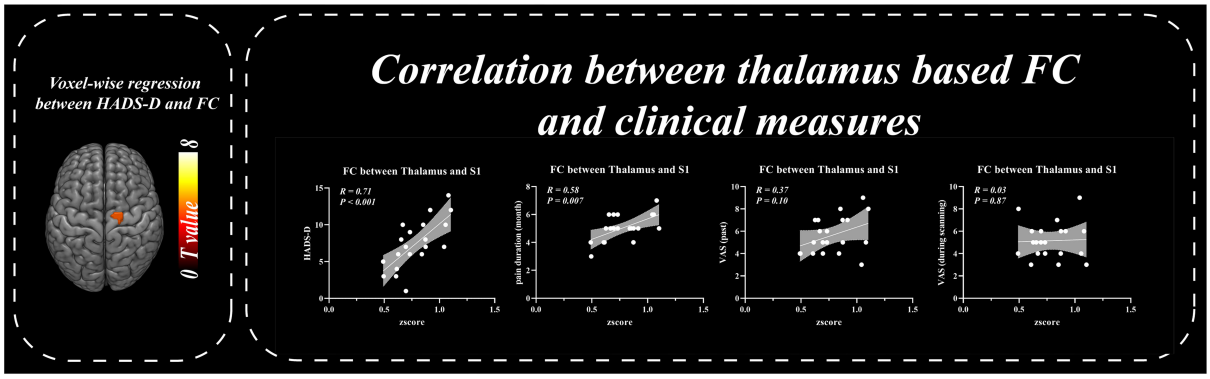

FIGURE 4
Correlation between thalamus based functional connectivity and clinical measures. Resting-state functional connectivity between thalamus and SI was positively correlated with HADS-D and pain duration in BC patients.

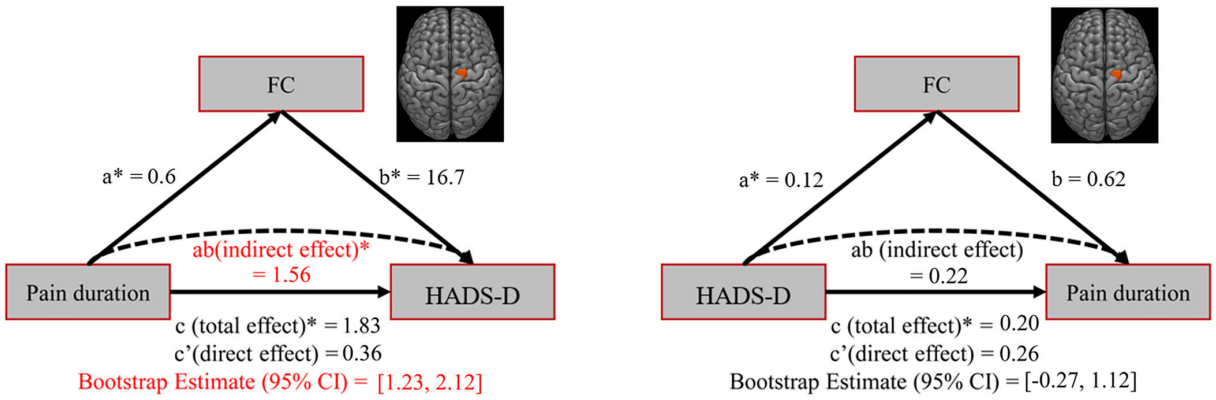

FIGURE 5
Mediation analysis. **(Left)** The effect of pain duration on HADS-D was mediated by the Thalamus-SI functional connectivity. Path c is the total effect of pain duration on HADS-D; path c' is the direct effect of pain duration on HADS-D after controlling for the Thalamus-SI functional connectivity; the product of a and b (ab) is the indirect effect of pain duration through the Thalamus-SI functional connectivity on HADS-D. **(Right)** The effect of HADS-D on pain duration was not mediated by the Thalamus-SI functional connectivity. Path c is the total effect of HADS-D on pain duration; path c' is the direct effect of HADS-D on pain duration after controlling for the Thalamus-SI functional connectivity; the product of a and b (ab) is the indirect effect of HADS-D through the Thalamus-SI functional connectivity on pain duration. HADS-D, Hospital Anxiety and Depression Scale-Depression. *, $p < 0.05$.

intensity and duration of pain increased (22). To explore the relationship among the factors, we performed a mediation analysis of pain duration, HADS-D, and thalamic-SI FC. Moreover, mediation analyses demonstrated that the thalamus-SI FC mediated the impact of pain duration on HADS-D. In contrast, the thalamus-SI FC unmediated the impact of HADS-D on pain duration. A reciprocal correlation existed between pain and depression in patients with chronic pain (32). Chronic pain in patients with BC is a good predictor of depression (54). However, they unexplained the exact mechanism of this phenomenon. Our study explained this phenomenon in terms of brain neural mechanisms, deepening the understanding of CNP and depression in patients with BC.

Accordingly, the present results demonstrated that patients with BC had impairment in ascending pain modulation pathways; pain duration can cause depression through the thalamus-SI connection, which would suggest that even if the relationship between pain and depression is reciprocal, causative effects on one another could be achieved through different neural systems. Indeed, the detailed neural mechanisms responsible for the causative effects need further investigation.

Conclusion

The ascending pain regulation mechanisms exhibited deficits strongly linked to chronic pain and depression in

patients with BC. This research boosted our knowledge of the pathophysiology of CNP in BC, helping to determine the optimal therapy for the patients. The clinical treatment of early pain in patients with BC should be emphasized to prevent the development of CNP. If the patient has developed CNP, paying attention to the depression and dealing with it in time while treating the pain is necessary.

Limitations and implications

This study has some drawbacks. First, our investigation of the acute association between clinical symptoms and subcortical/cortical dysfunctions was hampered by the limited sample size of individuals with various disease severity and duration. Second, the thalamus has heterogeneous subregions, limiting the illustration of other detailed mechanisms. Third, this study is a complete analysis of the FC method in rs-fMRI, excluding other indicators (amplitude of low-frequency fluctuation and regional homogeneity); we will do further research. Accordingly, we unselected the fMRI data of BC patients with CNP after medication and unexplored the functional differences of the brain after medication. In the future, we will use fs-fMRI to observe brain function changes after medication. Finally, we unexplored peripheral nerve conduction, which may require further clarification using fMRI of the spinal cord.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Affiliated Hospital of North China University of Science and Technology. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.959122/full#supplementary-material

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Global trends in research on cervicogenic headache: a bibliometric analysis

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Background: There has been a marked increase in cervicogenic headaches in recent years, significantly affecting sufferers' daily lives and work. While several treatments exist for this type of headache, their long-term effects could be improved, and additional data from large clinical samples are needed. This study aims to systematically examine the current state of research in cervicogenic headaches through a bibliometric analysis, identify areas of current interest, and provide insight into potential future research directions.

Methods: This article examines research trends in the field of cervicogenic headache through a bibliometric analysis of scholarly articles in the field of cervicogenic headache over the past four decades. The bibliometric analysis method employed included searching the Web of Science database using topics related to cervicogenic headaches. Inclusion criteria were limited to articles and review papers on cervicogenic headaches published between 1982 and 2022. The retrieved dataset was then analyzed using R software and VOSviewer to identify the major research areas, countries and institutions, the most influential authors, journals and keywords, co-citations in the literature, and co-authorship networks.

Results: This study analyzed 866 articles published between 1982 and 2022, involving 2,688 authors and generating 1,499 unique author keywords. Neuroscience and neurology were the primary focus, with participation from 47 countries, primarily led by the United States, which has the most published articles (n=207), connections (n=29), and citations (n=5,238). In the cervicogenic headache study, which involved 602 institutions, the University of Queensland received the most significant number of citations (n=876), and Cephalalgia was the journal with the most published articles and received the most local citations (n=82) and highest growth (n=36). Two hundred sixty-nine journals have published articles on cervicogenic headaches. Among researchers studying cervicogenic headache, Sjaastad O had the most published articles (n=51) and citations (n=22). The most commonly occurring keyword was "cervicogenic headache." Except for the fourth most impactful paper, as determined by the Local Citation Score, which analyzed clinical treatments, all the top documents emphasized investigating the diagnostic mechanisms of cervicogenic headache. The most commonly occurring keyword was "cervicogenic headache."

Conclusion: This study used bibliometric analysis to provide a comprehensive overview of the current research on cervicogenic headaches. The findings highlight several areas of research interest, including the need for further investigation into the diagnosis and treatment of cervicogenic headaches, the impact of lifestyle factors on cervicogenic headaches, and the development of new interventions to improve patient outcomes. By identifying these gaps in the

literature, this study provides a foundation for guiding future research to improve the diagnosis and treatment of cervicogenic headaches.

KEYWORDS

cervicogenic headache, bibliometrix, visualization, network analysis, research frontiers, Web of Science

1. Introduction

Cervicogenic Headache (CEH) is a headache caused by neck or paravertebral soft tissue lesions (1). This headache can be episodic or chronic, characterized by recurrent, one-sided headaches with accompanying neck pain and stiffness (1–3). This headache is thought to account for 15% to 20% of all headaches (4). Studies have shown that CEH is prevalent among individuals over 50 with headaches, with estimates ranging from 0.4% to 42% (5). Lifestyle changes have influenced the incidence of CEH in recent years. Prolonged sitting in a poor posture can increase the risk of CEH (6, 7), because prolonged sitting can cause muscular imbalances, joint stiffness, and trigger points, leading to increased tension and pain in the neck muscles (6, 8). Repetitive neck movements, such as those performed during manual labor or computer work, have been associated with an increased risk of CEH (9, 10) because they can cause strain on the neck muscles and joints, leading to increased tension and pain. CEH can significantly impact the daily life and work of sufferers, leading to decreased productivity and quality of life. While various treatments are available for CEH, their efficacy is limited, and the long-term clinical effectiveness and availability of extensive sample data require improvement (11).

"Bibliometrics," as first introduced by Pritchard (12), constitutes a formidable technique for analyzing the advancement of scientific research. It enables quantifying information extracted from online science citation databases on a particular topic, including the distribution of authors, publications, and research institutions within the field. Furthermore, bibliometrics can identify important literature in a research area, providing relevant keywords, information about institutions, connections to countries, and a visual representation of the distribution of the literature in the form of a knowledge map. This information can identify current and future trends in research topics and guide future research directions (13). For example, a study by Zhao et al. (14) used bibliometric analysis to identify the most influential articles and authors in migraine research. Similarly, a study by Downes et al. (15) used bibliometric analysis to examine the trends and therapeutic applications of vagal nerve stimulation research. These studies demonstrate the value of bibliometric analysis in understanding the structure and evolution of headache research and inform the design of future studies and interventions, ultimately benefiting patients. As such, we utilize bibliometric analysis to identify the most influential authors, publications, articles, countries, and institutions in headaches, examine current and future research trends of CEH, and provide insights into potential directions for future research.

2. Methods

2.1. Literature retrieval strategy

Studies have shown that the Web of Science (WOS) database is the most suitable bibliometric analysis database (16). This paper aims to explore the literature on CEH using bibliometric analysis. We used the WOS Core Collection All database to retrieve 1,031 documents (Query date is 1 January 2023) related to CEH using the search formula TS = ("Cervicogenic headache*" OR "Cervical headache*"). We exported all records as "Plain text files" with "Full Records and Cited References." The purpose of this search is to provide valuable insights into the structure and evolution of the field of CEH research, including identifying key authors, institutions, and research trends.

2.2. Bibliometric analysis

In their publication, Aria and Cuccurullo et al. (17) detailed a bibliometric analysis utilizing a five-step methodology: study design, data collection, analysis, visualization, and interpretation (18–20). Figure 1 illustrates a schematic representation of this approach. The study design phase involved selecting the topic of CEH and using the WOS Core Collection All database as the data source. We conducted the literature search during the data collection phase. To maintain the validity of the research and ensure reliable scientific communication (20), we use document-type filters on WOS and only include articles and review papers. We imported all the records using Biblioshiny Web, then converted them to Bibliometrix Rdata and Excel for further analysis. We created a matrix of all the papers using R 4.2.2 and used different data analysis and visualization tools. Specifically, we used the following tools:

1. biblioshiny: we used the biblioshiny package to open Biblioshiny Web, clean, preprocess the data, and generate descriptive statistics.
2. tidyverse (ggplot2): we used tidyverse, belong the ggplot2 package, to create high-quality graphics and visualizations.
3. VOSviewer 1.6.18: we used VOSviewer to generate concept maps, co-citation networks, and alternative graphs for further analysis.

Bradford's law is a bibliometric principle that explains how scientific literature is distributed across various publications in a given field. It states that a small group of highly productive publications, known as 'core' publications, publish most articles in that field. The remaining articles are published in a larger number of less productive

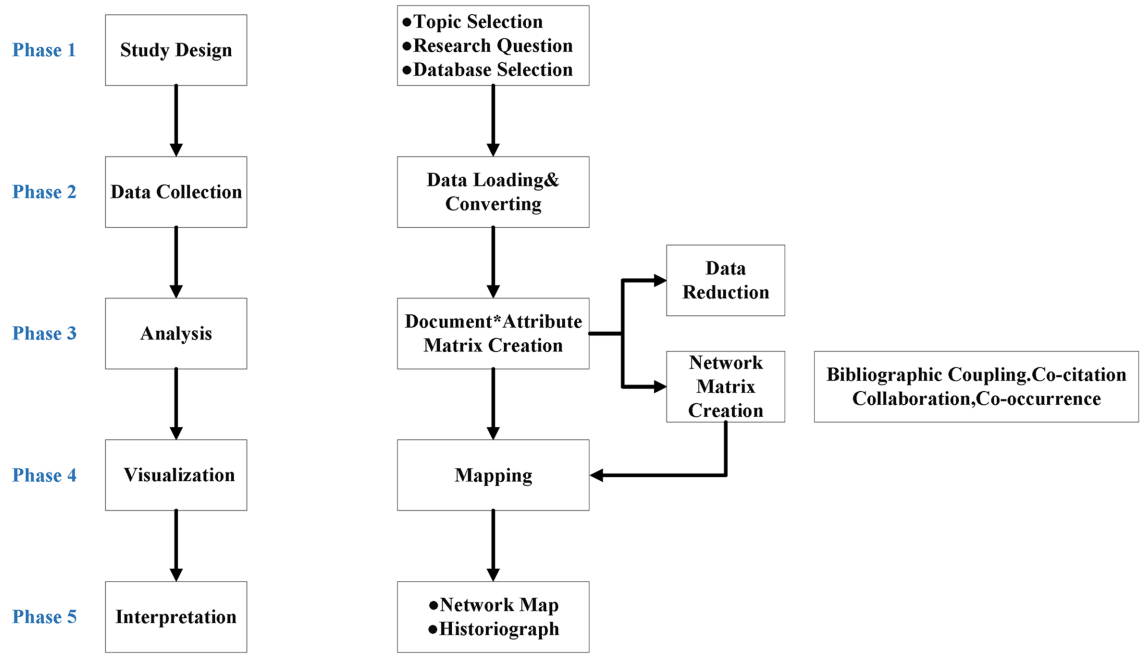

FIGURE 1
Schematic depicting bibliometric analysis methodologies.

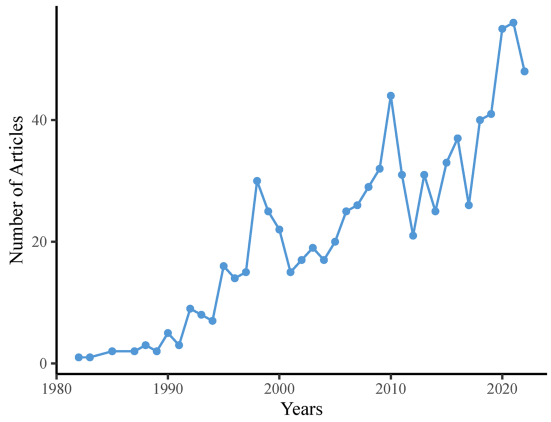

FIGURE 2
Scientific production of CEH-related literature between 1982 and 2022.

publications, called 'dispersed' publications. This principle is based on the observation that the number of articles published in a given publication is inversely proportional to its rank when publications are ranked by decreasing productivity (21). Bradford's law was then employed to examine the distribution of journals and pinpoint influential sources. The data analysis and visualization results, including insights obtained from Bradford's law, will be discussed in the latter half of the paper.

The authors conducted this bibliometric study alone. We searched the WOS database using specific search terms to identify the relevant articles and limited our results to articles published between 1982 and 2022. We then extracted the necessary data, such as author affiliations, publication year, and citation counts, and conducted a detailed analysis of the results.

3. Results and discussion

The preliminary findings of the bibliometric analysis present a comprehensive overview of the statistics in the field, and we ended up including only 866 papers published between 1982 and 2022. Subsequently, we analyze the aspects such as authors, journals, themes, keywords, and countries represented in the relevant literature to delve further into the research.

3.1. Descriptive bibliometric analysis

During the study period, Figure 2 depicts the overall scientific findings. The year 1982 marked the debut of CEH research with the publication of "The True Cervical Headache" (22) in the WOS database, with only a single paper that year. CEH-related paper publication increased after 1982, with some interruptions in 1984 and 1986. The trend fluctuated over the four decades from 1982 to 2022. However, CEH-related studies increased significantly after 2017 and reached 56 in 2021. Table 1 summarizes the key statistics of the 866 CEH-related articles published in the WOS Core Collection All database between 1982 and 2022. Over 40 years, the average number of CEH research papers published annually is 22, with average of 24.58citations each paper. These studies involved 2,688 authors, including 68 single-author documents. Additionally, the CEH research papers generated 1,499 author keywords.

TABLE 1 Primary statistics of CEH-related literature derived from bibliometric analysis.

Main information	Description	Value
Documents	Total number of documents	866
Sources	The frequency distribution of sources as journals, books, etc.	269
Timespan	Years of publication	1982–2022
References	Total number of references	18,019
Author's keywords (DE)	Total number of author's keywords	1,499
Keywords plus (ID)	Total number of phrases that frequently appear in the title of an article's references	1,440
Authors	Total number of authors	2,688
Authors appearances	The authors' frequency distribution	3,776
Authors of single-authored documents	The number of single authors per articles	68
Authors per document	Average number of authors in each document	0.322
Co-Authors per documents	Average number of co-authors in each document	4.36
Average citations per documents	Average number of citations in each document	24.58

3.2. Research areas

According to Clarivate Analytics (23), the WOS research areas were used to categorize research papers. Each paper in the WOS database can be allocated to at least one research area. The research shows that the coverage of CEH research fields has expanded from a single field in 1982 to 24 fields in 2021. These were the top 10 most productive research areas in CEH (Figure 3A): Neuroscience and Neurology, Rehabilitation, Orthopedics, General and Internal Medicine, Anesthesiology, Sport Sciences, Surgery, Integrative and Complementary Medicine, Health Care Sciences and Services, and Psychiatry. They made up 87.46% of the total CEH-related publications. Figure 3B provides a visual representation of how the focus areas of CEH research have changed over the years. Between 1982 and 2022, the leading research area was Neuroscience and Neurology, reaching its peak in terms of publication numbers in 2010.

3.3. Research countries and institutions

The findings demonstrate that 47 countries currently invest in CEH research. The United States of America (United States; $n = 207$), Norway ($n = 71$), Australia ($n = 70$), Germany ($n = 58$), and China ($n = 40$) are the top five nations regarding scientific output. After 2005, the number of publications from the United States experienced a steep and sustained increase and eventually came to dominate (Figure 4A). China's contribution to CEH scientific production demonstrates fluctuations between high and low levels, reaching a peak of 19.57 in 2019 (Figure 4B). In addition, to quantifying the production of scientific results, we can use country collaboration maps to gauge a country's research capacity. A global network of collaborations is represented by Figure 5 and reveals that the United States ($n = 29$) holds the most connections, followed by Germany ($n = 23$), Spain ($n = 22$), and the Netherlands ($n = 20$). Different countries exhibit fewer CEH research collaborations, with at most 20 connections.

After analyzing the data, we determined the overall paper count for each country. Additionally, we assessed each article's total number of citations and calculated the average number of citations to extract the top 10 countries (Figure 6). The United States was by far the most frequently cited country ($n = 5{,}238$), followed by Australia ($n = 4{,}195$), Norway ($n = 2{,}734$), Canada ($n = 1{,}630$), Germany ($n = 1{,}011$), the United Kingdom ($n = 727$), Spain ($n = 552$), Italy ($n = 513$), the Netherlands ($n = 447$), and Brazil ($n = 360$). Regarding average article citations, the top 10 countries demonstrate less variation. Australia holds the highest average citation count ($n = 59.93$), followed by Canada ($n = 47.94$), Norway ($n = 38.51$), the United Kingdom ($n = 36.35$), Brazil ($n = 25.71$), the United States ($n = 25.30$), the Netherlands ($n = 24.83$), Italy ($n = 19.00$), Germany ($n = 17.43$), and Spain ($n = 16.73$). These results highlight the dominance of the United States in CEH-related research.

A total of 602 institutions worldwide are involved in CEH research. Each institution's significance was measured based on the number of citations received for their published papers. The leading 10 institutions with the most citations for their papers were considered the most impactful. The study found that the influence of papers from different institutions varied significantly. The University of Queensland ($n = 876$) had the highest number of citations, followed by McMaster University ($n = 662$), NTNU ($n = 462$), Rey Juan Carlos University ($n = 292$), the University of Washington ($n = 280$), Newcastle Bone and Joint Institute ($n = 275$), the University of South Australia ($n = 264$), Neurology Institute ($n = 245$), Women's College Hospital ($n = 226$), Newcastle University ($n = 209$; Table 2). While Australia has a low number of publications, it has a significant quantity of citations, which significantly impacts CEH research.

3.4. Leading source journals

CEH-related studies have been reported in 269 journals. After analyzing the distribution of CEH research papers among the primary sources, we found that the top 5 journals published 219 papers. However, 172 journals published only one CEH paper, and 251 journals posted at most 10 articles. Figure 7 shows that the top 5 journals with the most published papers were Cephalalgia ($n = 82$), Headache ($n = 77$), Functional Neurology ($n = 30$), Journal of Manipulative and Physiological Therapeutics ($n = 29$), Manual

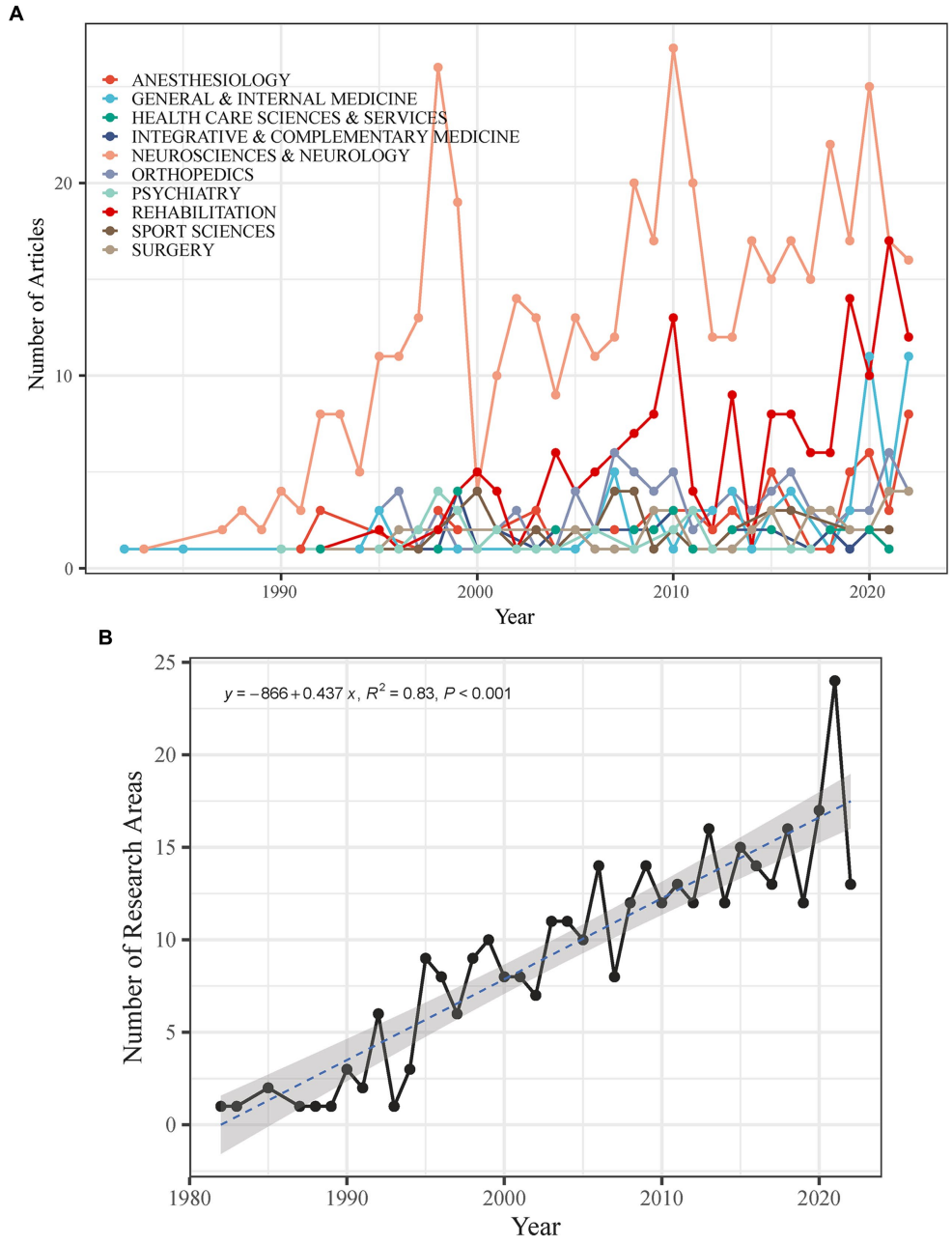

FIGURE 3
(A) Number of research areas in the CEH-related literature. **(B)** Temporal evolution of the top 10 most fecund research areas in the CEH-related literature.

Therapy ($n = 28$). Cephalalgia also had the highest growth in published papers and total local citations (Table 3). As determined by Bradford's law, the source journals for CEH research papers are scattered, and the top 10 journals are chosen based on the number of local citations. Journals marked with an asterisk are considered essential sources in the study of CEH based on Bradford's Law, including Cephalalgia, Headache, Spine, Journal of Manipulative and Physiological Therapeutics and Manual Therapy, Journal of Headache and Pain, Journal of Orthopaedic and Sports Physical Therapy, Functional Neurology. These journals have significantly influenced research in CEH.

3.5. Most influential authors

The H-index is a widely recognized metric for assessing the scientific impact of a researcher based on the number of citations received for their published papers (24). We calculated the H-index for all authors who had published papers on CEH research in our dataset of 866 papers, regardless of their position in the authorship list. We identified 10 authors with the highest H-index scores, including Sjaastad O. ($n = 22$), Jull G. ($n = 15$), Goldsmith C. H. ($n = 14$), Bovim G. ($n = 12$), Fernandez-De-Las-Penas C. ($n = 12$), Gross A. ($n = 12$), Bronfort G. ($n = 11$), Burnie S. J. ($n = 11$), Fredriksen T. A. ($n = 11$), and

Hall T. ($n = 11$; Table 4). Sjaastad O, the earlier recorded author in the WOS database for CEH research, was found to have the most significant number of published articles and citations. Three of the top 10 most influential researchers are from Norway, three are from Canada, and the rest are from United States, Australia, and Spain. In total, the study analyzed 866 papers, with 2,688 authors, with 68 authors having published single-authored literature. Co-authors per paper averaged 4.36, pointing to the tendency for CEH research to involve multi-author collaborations.

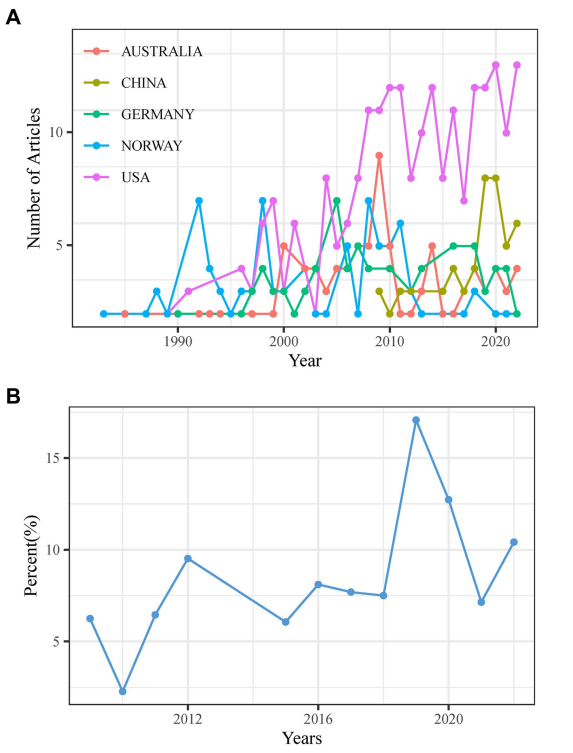

FIGURE 4
(A) Top 5 countries in annual scientific production. **(B)** Annual proportion of scientific production in China.

3.6. Most influential papers

We organized the most influential papers based on their Local Citation Score (LCS) and Global Citation Score (GCS), which are measures of the citation impact of a paper in a given field and across all fields, respectively (25). We used the LCS and GCS to determine the significance of each paper in the field of CEH. Papers with high LCS and low GCS scores were considered highly significant in CEH, while papers with high GCS and low LCS scores were considered highly significant across all fields (26, 27) (Tables 5, 6).

The first and second most influential papers in LCS (ranked 3 and 7 for GCS) were published by the author SJAASTAD O in 1998 and 1990, respectively. The latter paper develops the diagnostic criteria for CEH, and the former adds the signs and symptoms of neck involvement. This former paper also distinguishes the diagnosis of CEH from other headaches and clarifies the pain mechanism involved. The diagnostic criteria presented in this former paper are more comprehensive and offer a more robust understanding of the condition (28, 29). These two papers by SJAASTAD O have made a significant contribution to the field of CEH and continue to be highly cited and influential.

The article "'Cervicogenic' headache. An hypothesis" by SJAASTAD O has been identified as the third most influential paper in the literature on CEH by the LCS. Although not ranking in the GCS top 10, this paper is considered seminal. The study aimed to determine the specificity of CEH and propose partial diagnostic criteria for the condition. The author identified specific criteria for CEH through the diagnostic treatment of a cohort of headache patients. The results of this study have been valuable for subsequent research in the field (30). In a subsequent study, ranked fourth in the importance of the LCS (the number one GCS ranking), the author explored the effectiveness of manipulative and exercise therapy protocols applied alone or in combination for treating CEH. The results showed that both manipulative therapy and specific exercises significantly reduced the frequency and intensity of headaches, while neck pain and associated symptoms remained unchanged. Although the combined treatment was not significantly better than either treatment, 10% of patients achieved relief with the combined treatment. These findings support the use of a

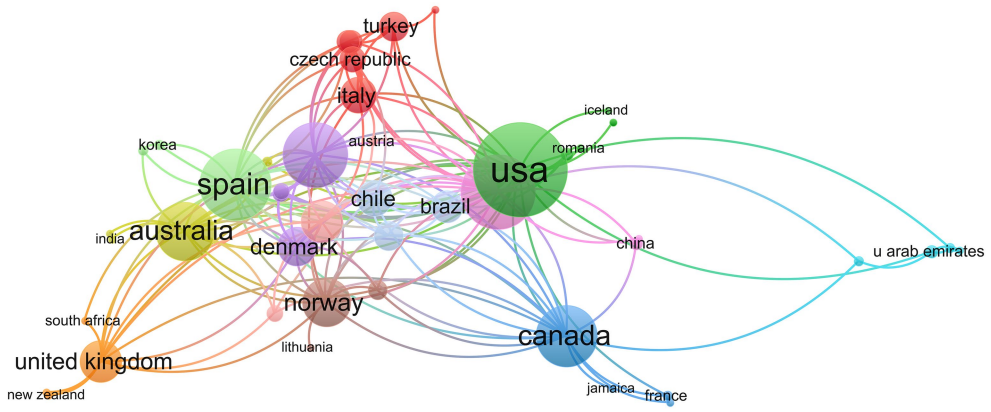

FIGURE 5
Map of inter-nation research collaboration.

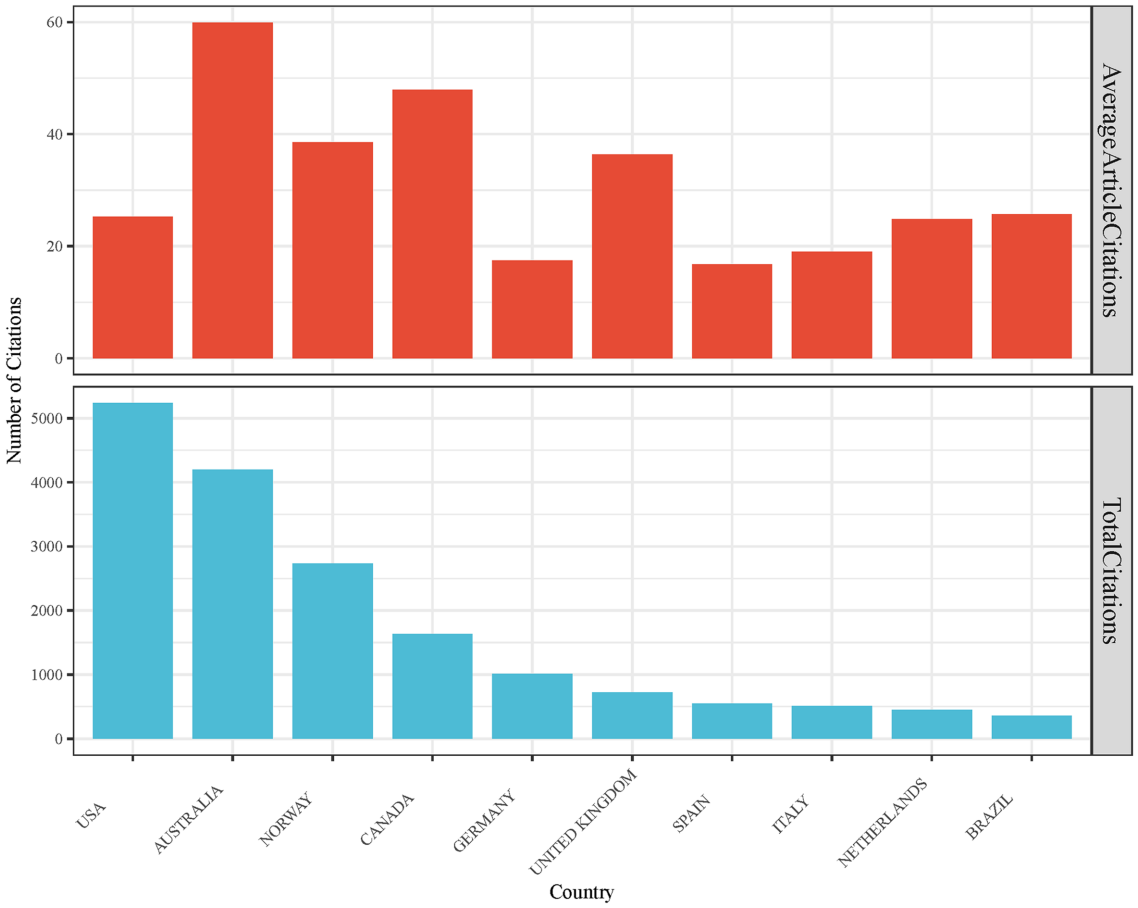

FIGURE 6
Total and average citations for the top 10 most frequently cited countries.

TABLE 2 Top 10 institutions based on total citations in CEH-related research.

Institution	Country	Total number of articles	Total number of citations
University Queensland	Australia	876	5
McMaster University	Canada	662	6
NTNU	Norway	462	6
University Rey Juan Carlos	Spain	292	8
University Washington	United States	280	2
Newcastle Bone and Joint Institute	Australia	275	2
University of South Australia	Australia	264	1
Neurol Institution	United Kingdom	245	1
Women's College Hospital	Canada	226	2
University Newcastle	Australia	209	4

NTNU, Norwegian University of Science and Technology.

combination of manipulative therapy and exercise as a potential treatment option for CEH (31).

The fifth-ranked article in the LCS (GCS = 10) presents a comprehensive review of current knowledge and clinical evidence on CEH. The article examines the fundamental science behind CEH and addresses its recognition, diagnosis, and treatment. At the cervical trigeminal nerve center, a combination of neck and facial nerve signals causes pain in the cervical spine with CEH (32). The article provides evidence for the most effective treatments for CEH. Arthrofusion is the only effective treatment for pain arising from the lateral atlantoaxial joint. The only specific cure for pain from the C2-3 joint is a nerve-blocking procedure using radiofrequency energy (33). The review article provides an exhaustive analysis of current knowledge and clinical evidence about CEH, offering invaluable insights to

researchers, clinicians, and healthcare professionals in this domain. The LCS determined that the sixth most impactful study failed to make it to the top 10 list based on the GCS. This study investigated the underlying causes of upper cervical joint dysfunction and revealed that the C1/2 segment and the pectoralis minor muscle length were the primary contributors. Furthermore, compared to the control group, the study identified significant differences in upper cervical joint dysfunction between patients with CEH and those with migraines with Aura (34).

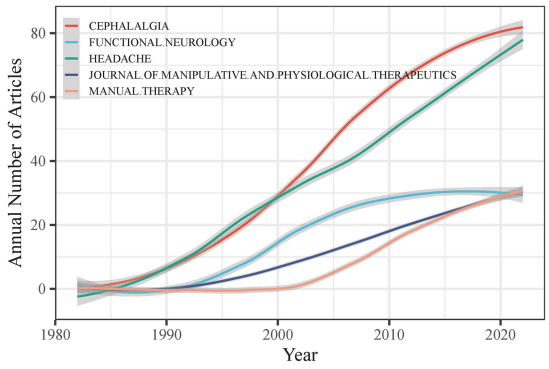

FIGURE 7
Temporal analysis of CEH-related study publication sources.

The papers ranked seventh and eighth by the LCS did not feature among the top 10 as determined by the GCS. A previous study investigated the response of patients diagnosed with CEH, migraine without aura, and tension headache to greater occipital nerve block (GON) and supra-orbital nerve block (SN). The results showed that pain reduction after occipital nerve block was more substantial in the CEH group compared to the other patient categories. The study also revealed that relief from forehead pain was mainly observed in CEH patients (35). Another paper investigated the characteristics of CEH in terms of prevalence and clinical indications in the general population. The study found that the prevalence of CEH was 4.1%, with no significant female predominance (F/M ratio of 0.71). The onset of pain in the neck/occipital region and its potential spread to the face were critical

TABLE 3 Ranking of the top 10 journals with the most local citations for CEH-related research.

Sources	Total number of local citations	Number of articles	IF	H index
Cephalalgia*	3,624	82	6.075	36
Headache*	2,883	77	5.311	34
Spine*	1,947	14	3.269	11
Pain	1,238	7	7.926	7
Journal of Manipulative and Physiological Therapeutics*	969	29	1.3	17
Manual Therapy*	833	28	2.622	22
Neurology	577	1	12.258	1
Journal of Headache and Pain*	574	14	8.588	12
Journal Of Orthopaedic and Sports Physical Therapy*	451	16	6.276	13
Functional Neurology*	409	30	0.51	12

X*, the core journal of CEH research as defined by Bradford Law; IF, impact factor in 2021.

TABLE 4 Top 10 most influential authors based on the H-index.

Author	H index	G index	Cited count	NP	PY_start	Country
Sjaastad O.	22	44	2,011	51	1983	Norway
Jull G.	15	23	1,800	23	1994	Australia
Goldsmith C.H.	14	16	1,181	16	2005	Canada
Bovim G.	12	12	776	12	1991	Norway
Fernandez-De-Las-Penas C.	12	18	432	18	2005	Spain
Gross A.	12	14	1,024	14	2005	Canada
Bronfort G.	11	11	1,118	11	2001	United States
Burnie S.J.	11	11	951	11	2009	Canada
Fredriksen T.A.	11	20	892	20	1987	Norway
Hall T.	11	17	646	17	2004	Australia

NP, number of scientific productions; PY_start, Year of first publication of articles.

TABLE 5 Top 10 papers with the highest local citation score.

Paper	DOI	Year	Local citation score	Global citation score
Sjaastad O, 1998, Headache	10.1046/j.1526-4610.1998.3806442.x	1998	240	308
Sjaastad O, 1990, Headache	10.1111/j.1526-4610.1990.hed3011725.x	1990	171	238
Sjaastad O, 1983, Cephalalgia	10.1046/j.1468-2982.1983.0304249.x	1983	142	189
Jull G, 2002, Spine	10.1097/00007632-200,209,010-00004	2002	124	447
Bogduk N, 2009, Lancet Neurol	10.1016/S1474-4422(09)70209-1	2009	117	188
Zito G, 2006, Manual Ther	10.1016/j.math.2005.04.007	2006	83	172
Bovim G, 1992, Pain	10.1016/0304-3.959(92)90007-X	1992	82	122
Sjaastad O, 2008, Acta Neurol Scand	10.1111/j.1600-0404.2007.00962.x	2008	78	95
Bovim G, 1992, Pain	10.1016/0304-3.959(92)90237-6	1992	77	99
Nilsson N, 1995, Spine	10.1097/00007632-199.509.000-00008	1995	73	96

DOI, Digital Object Identifier.

TABLE 6 Top 10 papers with the highest global citation score.

Paper	DOI	Year	Local citation score	Global citation score
Jull G, 2002, Spine	10.1097/00007632-200.209.010-00004	2002	124	447
Childs JD, 2008, J Orthop Sport Phys	10.2519/jospt.2008.0303	2008	12	398
Sjaastad O, 1998, Headache	10.1046/j.1526-4610.1998.3806442.x	1998	240	308
Watson DH, 1993, Cephalalgia	10.1046/j.1468-2982.1993.1304272.x	1993	60	264
Afridi SK, 2006, Pain	10.1016/j.pain.2006.01.016	2006	31	245
Jull GA, 2008, J Manip Physiol Ther	10.1016/j.jmpt.2008.08.003	2008	12	244
Sjaastad O, 1990, Headache	10.1111/j.1526-4610.1990.hed3011725.x	1990	171	238
Sterling M, 2003, Pain	10.1016/S0304-3959(02)00420-7	2003	7	236
Miller J, 2010, Manual Ther	10.1016/j.math.2010.02.007	2010	14	209
Jull G, 1999, Cephalalgia	10.1046/j.1468-2982.1999.1903179.x	1999	44	191

DOI, Digital Object Identifier.

features of CEH, with neck pain being a typical symptom of the condition (36).

The ninth most influential paper, as ranked by the LCS, was not in the top 10 according to the GCS ranking. The study investigated the potential susceptibility of small C2/C3 joints to neck trauma. The results showed that in instances where conventional GON blocks were ineffective in reducing pain, C2/C3 synovial joint injections and C3 nerve blocks could significantly alleviate pain and offer additional therapeutic options (37). According to the LCS, the tenth most highly ranked paper did not appear in the top 10 list based on the GCS. This study aimed to determine the prevalence of CEH in the general population and individuals with frequent headaches using a questionnaire-based approach. The findings suggest that CEH, similar to migraine, is a prevalent form of headache in the population (38).

The second most impactful article within the GCS is a clinical guideline that details a systematic overview of the classification, outcome metrics, and therapeutic interventions for musculoskeletal disorders affecting the neck (39). Despite not appearing in the top 10 list of the LCS, the paper holds considerable significance. The literature, which did not feature in the top 10 list of the LCS according to the fourth ranking of the GCS, reinforces the empirical observations made in patients diagnosed with CEH. Patients with this condition commonly display a prominent forward head position and a lack of strength and endurance in the upper cervical flexor muscles. These findings emphasize the importance of rehabilitation targeting endurance and head posture in the clinical management and prevention of CEH (40).

As ranked by the GCS, the fifth most influential paper did not make the LCS top 10 list. Its results suggest that the effects of GON injections on primary headache treatment are not immediate but occur through changes in pain processing pathways and brain plasticity. These findings are crucial for additional research into the different primary headaches (41). The LCS top 10 list did not include the sixth and the eighth most influential papers, as the GCS ranked. The former study confirmed the efficacy of utilizing craniocervical flexion maneuvers as a therapeutic intervention for individuals with neck pain disorders (42). At the same time, the latter investigation revealed the impact of TAMPA scores on functional alterations in the motor system following a neck injury (43).

The literature ranked ninth in the GCS is not included in the LCS's top 10 list. The paper, a thorough systematic review, examines the benefits of combining manual therapy with exercise for reducing symptoms of neck pain and whether problems in the neck's nerve accompany it. The review results demonstrate that manual therapy

and exercise provide a superior short-term reduction in pain compared to exercise alone. However, the review finds no significant disparities in the long-term results for patients with (sub) acute or chronic neck pain, with or without cervical radiculopathy (44). A study has revealed that individuals who present with neck headaches demonstrate significantly reduced performance in craniocervical flexion tests, specifically in the deep cervical flexor function. The researchers evaluated neck muscles and bones and discovered this finding. Moreover, the researchers discovered a significant association between the deep cervical flexors and the joints of the upper cervical spine. Notably, this finding ranked tenth in the GCS yet was not included in the top 10 list of the LCS (45).

Except for the fourth most impactful paper, as determined by the LCS, which analyzed clinical treatments, all the top documents emphasized the investigation of the diagnostic mechanisms of CEH. According to the GCS, a limited number of three out of the 10 most influential papers overlapped with those listed in the LCS, while the remaining studies centered on the examination of the neck musculoskeletal or comprehensive evaluations of treatments. In addition, research on pain disorders and patient experience is critical to understanding the mechanisms for diagnosing and treating CEH. For example, a study on neck pain by Falsiroli Maistrello et al. (46) highlighted the importance of considering the individual patient's neck pain experience. Another study by Rossettini et al. (47) emphasized assessing patient satisfaction with physical therapy procedures for musculoskeletal pain conditions.

In addition, there is a need for a comprehensive evaluation of treatment approaches to determine the most effective interventions for managing CEH. A recent study by Rondoni et al. (48) compared active neck range of motion (ACROM) measurements obtained using a technological device with those assessed using a low-cost device for patients with intra- and inter-assessor reliability and showed that there was no significant difference between the technical device and the low-cost device in terms of reliability. Another study by Viceconti et al. (49) investigated the relationship between pain and body perception in musculoskeletal and rheumatic disorders. The results of this study suggest that interventions targeting body perception may be beneficial in improving pain management and quality of life in patients with these diseases.

In conclusion, future research on CEH should focus on examining pain disorders, assessing patient experience, and making a comprehensive assessment of treatment to improve the management of this disease. By incorporating these factors into clinical practice, we can provide more effective treatment for patients with CEH.

3.7. Analysis of prominent research trends

This study comprehensively analyzed 866 CEH research papers published between 1982 and 2022. Our analysis revealed 1,499 author keywords. Figure 8 presents the author keywords trends over time, showing the publication year on the x-axis and the author keywords on the y-axis. To highlight the trend of research focus, we employed three quantiles (first, median, and third) of the year of publication corresponding to each keyword. The location of the green dot shows the first quantile, the red dot shows the third quantile, and the blue dot shows the median year of publication. The size of each dot indicates the number of papers corresponding to the keyword, with larger dots indicating a higher frequency of keyword occurrences. Two of the most regularly researched topics are "nerve" (50–52) and "neck" (53–55).

Additionally, "spine" (56–58) is another crucial research area that has received considerable attention in CEH research. The frequency of occurrence of keywords in CEH research is represented by blue dots in the center, with larger dots indicating a higher frequency. The top 10 keywords in the field of CEH research include "cervicogenic headache," "pain," "migraine," "tension-type headache," "prevalence," "cervical-spine," "neck pain," "reliability," "management," and "diagnosis." The most common keyword in CEH research was 'cervicogenic headache.' At the same time, 'pain' was also a significant area of study, consistent with previous research. "migraine" and "tension-type headache" are two well-researched headache disorders in the field of CEH and are closely related to its studies. Regarding research content, the keywords "cervical-spine" and "neck pain" are primarily used in orthopedic spinal operations (59) and studies investigating the prevalence of these conditions (60). Further significant research directions in the field of CEH include "prevalence," "reliability," "management," and "diagnosis."

Figure 8 illustrates a relationship between the position of red dots on the right-hand side and the magnitude of the blue dots. Additionally, the figure includes information on the release time of corresponding keywords in the CEH research field. According to the findings, the more recent the publication time, the larger the blue dot and the farther to the right the red dot. The trend reflects the research dynamics in CEH and underscores the significance of manual therapy and randomized clinical trials as critical topics. The recent hot topics in CEH research are "manual therapy" and "randomized clinical-trial." In clinical practice, manual therapy is widely used to alleviate musculoskeletal pain (61–63).

On the other hand, "randomized clinical-trial" are widely recognized for their superior reliability and rigor in the research process. However, the quality of reporting in randomized controlled trials (RCTs) remains suboptimal (64). In applying CEH clinical studies, "randomized clinical-trial" is mainly used in research investigating manual therapy (65–67).

The current study has uncovered trends in CEH research. The findings indicate a marked improvement in the quality of the diagnosis and treatment research of CEH and a growing diversity in research methodologies. Initially, CEH research focused primarily on "migraine" and "tension-type headache" studies. Subsequently, as the understanding of the research mechanism deepened and methodologies evolved, the sample size expanded. CEH is differentiated from other diseases, and diagnosis and treatment are becoming more accurate. The methodology of CEH research has also evolved. Initially, the research relied on questionnaire surveys and clinical case studies. With an increased prevalence of CEH, current research methods, such as RCTs and meta-analyses, have been incorporated.

3.8. Limitations

We conducted a comprehensive literature search of the WOS database, using topics relevant to our research questions. We limited our search to studies published in English from 1982 to 2022. Our search strategy may have introduced some bias because we included

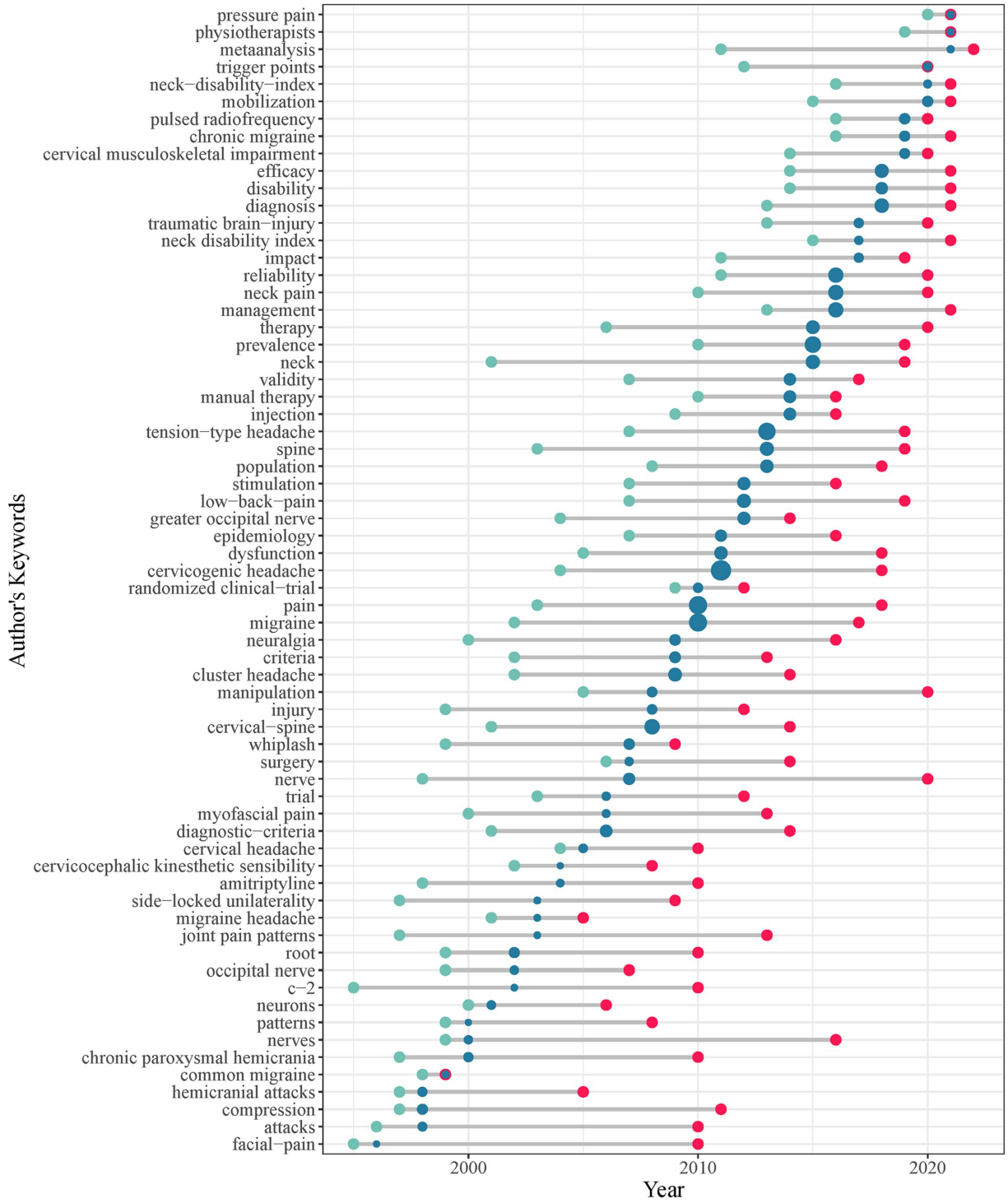

FIGURE 8
Temporal trends of the author's keywords.

only studies published in English and may have missed studies published in other languages. In addition, our search strategy only included WOS databases, which may have excluded studies published in other formats or databases. However, our search strategy was rigorous, and we selected the most appropriate databases for bibliometric studies to minimize bias. In addition, although studies were selected to minimize bias, the quality and risk of bias were not analyzed for the papers in section 3.6. This study covers a wide period to identify trends and changes in the field, but it also means that newer publications are more frequently cited than older ones. The authors are not well-represented in bibliometric studies. Nevertheless, the findings of this study provide valuable insights.

3.9. Critical points

In conducting bibliometric analyses, several critical points must be considered to ensure the study's accuracy. One of the crucial factors is the selection of appropriate keywords to use in the search query. Using good search terms may lead to excluding relevant studies, thus affecting the analysis results. It is also essential to select an appropriate time frame for the search, as this can influence the number and type of publications included in the analysis.

Another critical factor is the selection of appropriate databases to use in the search. While the use of multiple databases can increase the comprehensiveness of the search, it can also result in the inclusion of duplicate or irrelevant studies, which can affect the accuracy of the analysis. Additionally, the quality of the data sources used in the analysis can also impact its validity, making it essential to consider the reliability and validity of the data sources included.

In summary, by addressing these critical points, we can ensure that bibliometric studies provide a more accurate picture of research developments and trends in CEH.

4. Conclusion

The field of CEH has experienced a growth in publications in recent years. A bibliometric analysis was conducted to examine the developments and trends in CEH research from 1982 to 2022. The study found that the United States, Australia, Norway, Canada, and Germany contributed significantly to CEH research. The University of Queensland and McMaster University were identified as the primary research institutions. Sjaastad O., Myneni R. B., and Jull G. were the leading researchers in the field. The quality of research data sources has improved, and research methodologies have become more diverse. There has been a broadening of research areas, and the methodology of CEH research has evolved. Multidisciplinary integration is expected to be a significant trend in future research in CEH. Advanced data analysis methods and patient-friendly treatment experience will improve diagnoses and treatment accuracy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YX and YD: conceptualization and methodology. LW: data collection. YG and LJ: data curation. YX and YG: formal analysis. YD: funding acquisition and supervision. JY: software. ZY and YD: validation. YX: visualization and writing—original draft. YX, YG, LJ, LW, JY, ZY, and YD: writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Nummular headache: a case report of remission following ketogenic diet and botulinum toxin type A injections

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Nummular headache is an unusual facial pain disorder with no evidence-based therapy recommendations. The ketogenic diet is an alternative therapy that demonstrated to be effective in migraineurs, but it was never used in the setting of nummular headache. We describe a 58-years old female patient with nummular headache successfully treated with a 6-months ketogenic diet and botulinum toxin type A injections. Ketogenic diet could be an effective alternative/complementary therapy in nummular headache patients although more studies are needed to confirm our results.

KEYWORDS

nummular headache, ketogenic diet, botulinum toxin, pain, rare disorder

Introduction

Nummular headache is a rare primary headache, first described in 2002 (1), characterized by focal pain localized on the surface of the head in a small coin-shaped or elliptical area; this painful area has typically well-defined borders and no underlying lesions (2, 3). This disorder is mostly focal, and any region of the head could be affected although it's slightly more common in the *tuber parietale* of the parietal scalp and on the right side and tends to affect extra-trigeminal territories (4, 5). Multifocal, synchronous or asynchronous, painful areas have been described and, in some cases, the painful area extends across the midline (6). The pain, mild to moderate in intensity, is often described as stabbing or oppressive and, less commonly, throbbing, sharp, or even burning (7). Exacerbations can be triggered by mechanical stimulation or can be spontaneous (2). Patients often lament allodynia, paresthesia, and/or hypoesthesia restricted to the symptomatic area and autonomic signs are typically absent although trophic changes are described (1, 8). This disorder is more common in women, with spontaneous onset in the mid-forties (4). Most cases are chronic, and the pain could be persistent, intermittent, or fluctuating. Cases of spontaneous remission, or pseudo-remissions after treatment (when the pain is replaced by discomfort), are described in the literature (7). Since nummular headache is a rare disorder with only case series and no large studies in literature, there are no evidence-based recommendations regarding the therapy (9); moreover, the ketogenic diet was never used in this setting. Here we describe a case of nummular headache successfully treated consecutively with Ketogenic Diet and Botulinum Toxin type A injections.

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Case presentation

On January 2020, a 58-years old female patient came to our headache outpatient clinic complaining of moderate (mean NRS 6/10) persistent pain in the vertex and nearby right parietal scalp. The onset of the headache, which was spontaneous, was on the 12th of November 2019. The background pain was described as oppressive, with fixed and defined borders, ellipsoidal shape, and a 5–6 cm diameter. The patient denied nausea, vomiting, phonophobia, photophobia, or osmophobia. Physical activity did not influence the symptoms while stressful events worsened or exacerbated the pain; she reported daily exacerbations (NRS 9/10) with throbbing quality. This disturbance was partially responsive to paracetamol. She denied previous head trauma or infections. Her medical history comprehended asthma, hypothyroidism, arterial hypertension, and obesity; she had familiarity for migraine on her mother's side. She had also multiple allergies (acetylsalicylic acid, ibuprofen, mites, kiwi, strawberries, and aspartame). The neurological examination was unremarkable apart from allodynia in the site of the nummular headache. Head CT scan, brain MRI, and blood work-up were normal. Initially, she was diagnosed as New Daily Persistent Headache; the diagnosis was later changed to nummular headache based on the clinical features of her headache based on the ICHD-3 criteria (10). She started preventive therapy with amitriptyline 20 mg with no benefit. 3 months after the initial evaluation, she started venlafaxine 150 mg/day with slight benefit on intensity (NRS 9/10), but with no effect on the frequency of exacerbations of the headache or on the background pain, which remained persistent. Due to the efficacy of the dietary approach with the ketogenic diet on migraine (11), we decided to apply this dietary regimen to our case, although there are no cases in the literature that support its use on nummular headache. Since our patient had a BMI of 34.2, we opted for the Very-Low-Calorie Ketogenic Diet (VLCKD) that she started in November 2021 and concluded in May 2022. Her 730 Kcal diet consisted of a daily intake of 85 grams of proteins, 30 g of fats, and 30 g of carbohydrates. Her exacerbations and background pain improved both at 3-months and 6-months evaluations after diet's initiation (Table 1). Her BMI improved from 34.2 Kg/m^2 to 26.7 Kg/m^2 and her Fat Mass reduced from 34.8 Kg to 18.2 Kg. Ketonemia or urinary ketone levels were not monitored during the diet. The dietary intervention was well-tolerated by the patient, with no adverse effects.

In June 2022, the VLCKD was discontinued, as planned, and the patient started a normocaloric hypoglucidic diet (1,400 Kcal/day). Although no rebound weight gain was observed, the nummular headache gradually became more severe. In July 2022, we decided to treat the patient with BoNT/A (Botulinum Toxin type A) injections in the nummular headache location at a total dose of 50 U. In each treatment, a vial of BoNT/A was diluted with 1 ml of 0.9% sodium chloride (100 U/ml dilution). The treatment was performed with subcutaneous injections in the ellipsoidal-shaped area of pain, with 5 U per site and a total of 10 points (Figure 1). The injections were performed using a 30-gauge 0.3 mm × 8 mm needle. Treatment was performed three times with an interval time between one round and another of 3–4 months, since the duration of the effect was the same; the mean onset of the BoNT/A effect was 10 days after the injections. Her exacerbation pain was abolished, and background pain and allodynia gradually disappeared; the patient reported only slight discomfort located in the treated area. No adverse effects were reported. We evaluated the frequency and intensity of the exacerbations as well as the intensity of the background pain (Table 1).

TABLE 1 The trend in pain during the two treatments.

	Exacerbation pain NRS	Exacerbations frequency days/month	Background pain NRS
VLCKD therapy			
Baseline	9	31	6
3-month	2	6	2
6-month	4	2	2
BoNT/A therapy			
Baseline (July 2022)	7	4	5
1° BoNT/A session	0	0	2
2° BoNT/A session	0	0	2
3° BoNT/A session	0	0	0

Discussion

Nummular headache is a rare disorder, often underdiagnosed due to its rarity and the diversity of its clinical presentation. The incidence of this disorder is 6.4/100.000 per year (7) and the etiology is still unknown, but some authors suggest that it might be due to sensory dysfunction of a terminal branch of a pericranial nerve, configuring an unusual form of neuralgia; other authors hypothesize that nummular headache is a localized form of complex regional pain syndrome or epicrania. Other authors suggested a central mechanism because anesthetic nerve blockade was ineffective and the pain area could cross the midline (4). Young age, female sex, and early diagnosis are favorable predictors of response to therapy (9). Due to the rarity of this disorder, with only single case reports or limited case series, there are no evidence-based recommendations regarding the therapeutic approach. Nummular headache responds to NSAIDs and indomethacin (12) although some case series reported no clear improvement (13, 14). Gabapentin, pregabalin, carbamazepine, oxcarbazepine, topiramate, amitriptyline, metoprolol, valproate, lamotrigine, flunarizine were used as a preventive therapy with conflicting results (9, 12–14). In our patient, the nummular headache did not improve with amitriptyline while venlafaxine was slightly effective only on headache intensity, still not setting up a form of headache refractory to oral treatments given the failure of only two lines of therapy (15). Transcutaneous Electrical Nerve Stimulation (TENS), anti-CGRP monoclonal antibodies, and subcutaneous peripheral nerve field stimulation (3, 9, 12, 16–20) have also been used with some positive results. Lidocaine

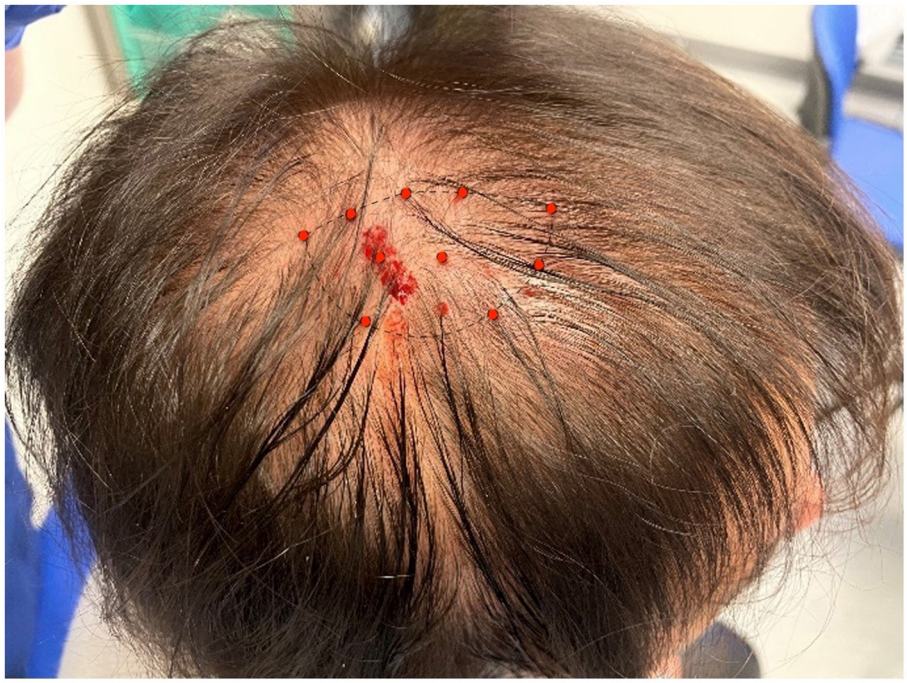

FIGURE 1
The location of the nummular headache of our patients. The borders are represented by the dashed line; the red dots indicate the sites of subcutaneous BoNT/A injections (5 U per site).

was reported to be ineffective (1, 13). Botulinum toxin type A has been used in this setting with encouraging, although partial, results: in 2008 Mathew et al. (21) described four patients with nummular headache treated with significant improvement with 25 U of BoNT/A in the affected area. Dusitanond et al. (22) treated 5 patients with a mean dose of 16 U reporting improvement in only three, while Ruscheweyh et al. (23) reported only one that responded to BoNT/A. However, the details were not reported in both studies. In 2018, Martins et al. reported 8 cases of nummular headache with excellent response while, in 2019, García-Azorín et al., treated 53 patients with BoNT/A in an open-label, non-randomized, prospective study and reported a significant reduction in both headache frequency and intensity. There are different approaches of botulinum toxin administration for nummular headache, those who prefer to inject the toxin in 4–6 sites, distributed in form of a cross (5, 24), and those who, as in our case adopt a circumferential approach, with injections sites around the perimeter of the painful area. The latter approach is aimed to targeting epicranial nerve endings (21), whose dysfunction is considered a possible pathogenic event, able to triggering nummular headache (23). Further studies should be conducted in order to test this hypothesis. In our case report, the patient was able to achieve remission with BoNT/A subcutaneous injections at a dose of 50 U, thus positively testing a higher dose than reported so far in the literature. Moreover, before BoNT/A injections, our patient underwent VLCKD treatment with significant improvement in nummular headache background pain, pain exacerbations and in frequency. KD is an effective therapeutic option in migraine (11) however, there are no studies regarding its effect on nummular headache. The analgesic mechanisms underlying the functioning of the ketogenic diet are not known at present, although it may be determined by its ability to reduce neuronal hyperexcitability, typical of both chronic pain and epilepsy, conditions in which such a diet is applied, acting through multiple mechanisms (25) with a probably key role related to the activation of adenosine receptors (26). Moreover, weight loss seems to be correlated with the reduction of migraine frequency and intensity (27). Due to its long-lasting effect (7 months) and the worsening of the condition after the scheduled interruption of KD, a placebo effect of the diet is unlikely, although impossible to rule out. We suppose that the improvement of nummular headache with VLCKD was due to its anti-inflammatory action and its ability to reduce neuronal hyperexcitability. Weight loss may have been also beneficial, but headache severity turned to increase with the end of VLCKD, although no rebound weight gain was observed.

Conclusion

There are no evidence-based data regarding the therapy for nummular headache. In our case report, KD therapy significantly improved background pain, exacerbation pain, and frequency. BoNT/A injections were able to achieve remission in our patient. If confirmed by further observations, KD could become a complementary approach and a possible alternative to the injections of onabotulinum toxin A, although the last one remains a more effective and long-term compatible option. In conclusion, the ketogenic diet could be part of the therapeutic armamentarium for patients with nummular headache, including pharmacological,

dietary, and topic therapies such as botulinum toxin, to be considered especially in drug-resistant forms.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

Writing—original draft preparation: YT and SD. Writing—review and editing: MV and GG. Supervision: CL, GM, and EB. All authors have read and agreed to the published version of the manuscript.

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Clinical implications

New therapeutic perspectives for the resolution of a disorder that, although rare, turns out to be particularly disabling.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Early versus delayed computed tomography-guided celiac plexus neurolysis for palliative pain management in patients with advanced pancreatic cancer: a retrospective cohort study

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Introduction: Abdominal and back pain is the most frequent symptom in patients with pancreatic cancer, with pain management being extremely challenging. This study aimed to evaluate pain control, opioid consumption, pain-interfered quality of life, and survival after early and delayed computed tomography (CT)-guided celiac plexus neurolysis (CPN).

Methods: A retrospective analysis of pancreatic cancer patients receiving CPN for pain ($n = 56$) between June 2018 and June 2021 was done. The patients were grouped as early group ($n = 22$) and delayed group ($n = 34$) on the basis of the presence of persistent refractory pain according to expert consensus on refractory cancer pain.

Results: Both groups were comparable in demographic characteristics and baseline pain conditions measured using the numeric rating scale (5.77 ± 1.23 vs. 6.27 ± 1.21; $p = 0.141$). The pain scores were significantly reduced in both groups; early CPN resulted in significantly lower scores from 3 to 5 months. The opioid consumption gradually decreased to a minimum at 2 weeks but increased at 1 month (35.56 ± 30.14 mg and 50.48 ± 47.90 mg, respectively); significantly larger consumption from 2 to 4 months was seen in the delayed group. The total pain interference was lower than baseline in all patients, with significant improvement after early CPN in sleep, appetite, enjoyment of life, and mood. The average survival time of the two groups was comparable.

Conclusion: Early application of CT-guided CPN for patients with advanced pancreatic cancer may help reduce pain exacerbation and opioids consumption, without influencing the survival.

KEYWORDS

celiac plexus, neurolysis, cancer pain, pain management, pancreatic cancer, palliative care

Introduction

Patients with pancreatic cancer frequently present with abdominal and back pain, with a reported incidence of 75% at the time of diagnosis and approximately 90% in patients with advanced staged cancer (1). Accordingly, optimal symptom control in the form of pain management is critical to improving the quality of life in these patients (2). Nevertheless, since the pain generation is due to multiple factors, such as perineural malignancy invasion, neurogenic inflammation, or ductal obstruction, pain control in patients with pancreatic cancer can be challenging (3, 4). Although the World Health Organization's (WHO) analgesic ladder provides effective pain alleviation in over 70% of patients with general cancer, there are certain limitations to this strategy in cases of advanced pancreatic cancer because of frequent pain exacerbations (5, 6). Consequently, interventional procedures are considered the fourth step in the WHO analgesic policy (7).

Celiac plexus neurolysis (CPN) is a well-established verified technique for relieving pain, reducing opioid consumption, and improving cancer symptom burden for patients with abdominal malignancy (8–10). Nevertheless, this procedure is usually undertaken as the last resort for the management of refractory pain, which can decrease its effectiveness due to the high rate of neural invasion in pancreatic cancer (11, 12). The existing literature suggests that the severity of pain correlates strongly with perineural invasion and an adverse tumor microenvironment, which are both associated with poor prognosis (13–15). The recently emerging concepts of cancer pain management offer more promising analgesic strategies, among which, the modified WHO analgesic ladder prescribes a two-way path for the treatment of cancer pain—to start high and move backward down (16). Some clinicians advocate the application of CPN as a first-line treatment option to achieve better pain control for pancreatic cancer in a palliative situation (6). This is supported by multiple pieces of research which indicate that early palliative care for patients with cancer pain can result in improved quality of life and emotional status (17–19).

Nevertheless, whether early CPN is more beneficial than a delayed procedure in patients with advanced pancreatic cancer remains unclear. Thus, we conducted this retrospective cohort study to evaluate pain control, opioid consumption, pain-related quality of life, and survival in patients with advanced pancreatic cancer undergoing early and delayed CPN.

Materials and methods

Study design

We conducted an observational retrospective cohort analysis of the medical records obtained from a single oncology specialized hospital of patients with advanced pancreatic cancer, who suffered from moderate to severe pain and underwent CPN at the pain management department, from June 2018 to June 2021. All patients signed an informed consent before receiving the interventional procedure. The data collection and publication protocols were regulated by the Institutional Review Board.

Pain specialists in our department are responsible for providing comprehensive pain assessment, analgesic, and interventional treatment, as well as health follow-ups for cancer patients. Accordingly, patients experiencing pancreatic cancer pain were initially evaluated for their pain and previous analgesic strategies and then assigned to receive CPN after adequate preoperative optimization. Using a percutaneous antecrural approach under computed tomography (CT) guidance, a total of 6 mL of iohexol (Omnipaque) and lidocaine compounds was injected bilaterally into the target antecrural space. After confirming the spread of the contrast and successful test block, 20 mL of 100% ethanol was injected. The patients were then admitted for 24 h observation; after discharge, they continued to receive analgesic modulation and follow-up in our outpatient clinic.

During the follow-up, the nurse specialist evaluated the following items at fixed time intervals (baseline, 1 day, 1 week, 2 weeks,1 month, 2 months, 3 months, 4 months, 5 months and 6 months after operation)—pain score using the numerical rating scale (NRS), frequency of breakthrough pain recorded when happening ≥3 times/day, analgesic consumption converted into morphine equivalent, and pain inferred quality of life measured by the brief pain inventory (BPI). The BPI is used to assess eight items of functioning interfered by pain: general activity, mood, walking ability, normal work, relationship with others, sleep, appetite, and enjoyment of life. Each item is rated from 0 (does not interfere) to 10 (complete interference). The pain scores and analgesics consumption were re-evaluated up to 6 months postoperatively, as the neurolytic effects reportedly remain stable for approximately 3–6 months (20, 21). However, we were not able to assess pain interference with BPI in most patients 4 months after the procedure because of rapid disease progression.

Participants and inclusion criteria

Data satisfying the following criteria was collected: (a) patients aged 18–80 years with advanced pancreatic cancer and received CPN at the pain management department; (b) having upper abdomen and/or middle back pain due to pancreatic cancer; (c) having NRS ≥4 points at baseline; (d) receiving analgesic medication and equivalent oral morphine ≥40 mg per day before procedure, and (e) having no invasion detected in the insertion path. Patients who were given further antitumor therapies or other interventions for pain control were excluded from the study.

Early and delayed intervention: definition

Patients were divided into the early CPN group—to receive the operation as soon as they fulfilled the criteria at the index visit, or the delayed group—those who underwent a wait-and-see analgesic titration and received CPN only when they developed persistent refractory pain or with intolerable adverse effects. This definition is based on the expert consensus from the Committee of Rehabilitation and Palliative Care of China, which identifies refractory cancer pain based on the following two criteria: (a) persistent pain score ≥4 and/or breakthrough pain ≥3 times/day and (b) unsatisfactory pain relief after at least 2 weeks of standardized medication and/or causes intolerable side effects (22).

Data collection and outcome measures

Demographic characteristics of all patients including age, gender, tumor classification, staging, course duration, comorbidities,

and history of antitumor treatment were extracted from the hospital's database. Data regarding pain score, adverse reactions, opioid consumption, and BPI pain inference were reviewed through previous follow-up records. Survival time data were obtained through the community health system before data analysis in December 2021.The sample size of the database study is primarily comprehensive, encompassing all the available data. However, a prior sample size calculation was conducted for scientific interpretation, focusing on the NRS scores at 3 months post-operation taking into account a potential dropout rate of 20%. This calculation aimed to provide 80% statistical power for detecting significant treatment differences, with a two-sided type 1 error set at 5% in a two-sample *t*-test. The outcome indicated the necessity of a sample size of 20 patients for each group.

As the primary parameter of interest, we performed a multidimensional assessment of the pain conditions, with respect to location, intensity, and breakthrough times. Subsequently, analgesic changes were analyzed with morphine equivalent conversion. To compare the overall pain interference between early and delayed CPN, a total BPI score (0–80 points) and that for the eight items individually were calculated.

Statistical analysis

We used SPSS version 26.0 (IBM Inc., Armonk, NY, United States) to perform all analyses. NRS, BPI scores, and opioid consumption were presented as means with standard deviation. A two-sample *t*-test was used to compare the mean differences between continuous variables in the case of normally distributed data; otherwise, the Mann–Whitney *U* test was used for analysis. Breakthrough pain, tumor classification, staging, and complications were presented as frequency and percentages (%), and chi-square (χ^2) or Wilcoxon rank-sum tests, as appropriate, were used for comparison between groups. Additionally, Kaplan–Meier survival curves were constructed for patient survival in months and compared using log-rank tests. A *p*-value of ≤ 0.05 was considered for statistical significance.

Results

Patient characteristics

A total of 63 patients with pancreatic cancer underwent CPN between June 2018 and June 2021 at our hospital. Of these, two patients were excluded since they were administered implantable drug delivery systems (IDDS) as a combined pain control solution. Three patients who received hepatic perfusion chemotherapy for metastases after CPN, and two who received iodine-125 seed implantation were also not included in the analysis. The final analysis included data for 56 patients (39 males and 17 females) (Figure 1). The majority of patients had cancer of the pancreatic body and tail ($n = 21$, 37.5%), followed by head adenocarcinoma ($n = 19$, 33.9%); 39 patients were at stage IV (69.6%), and 39 were in a malnutrition condition (69.6%). All patients had received multicourse oncology treatment before CPN. The time gaps between the first visit to receiving CPN were 3.45 (1.65) vs. 35.06 (9.98) days in the early and delayed group. Table 1 shows the basic clinical and demographic characteristics of the study population.

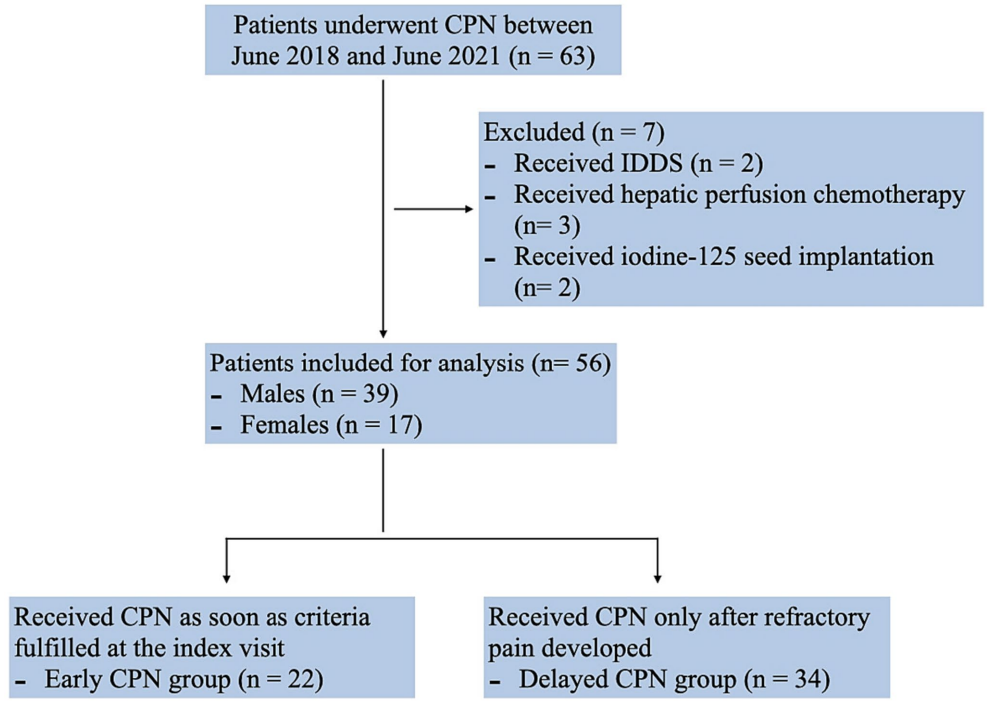

FIGURE 1
Flowchart of the subject selection.

Pain condition

Patients in both groups reported experiencing moderate to severe pain, with a baseline NRS of 5.77 ± 1.23 and 6.27 ± 1.21, respectively. A significant reduction in NRS scores was observed in both groups after the procedure; however, a trend for a rebound was detected from 1 to 6 months. Nonetheless, those receiving early CPN presented with a lower pain score than the delayed group, and a significant difference was observed from 3 to 5 months (Figure 2A). Additionally, changes in the breakthrough pain corresponded with the NRS, demonstrating a significant decrease after CPN. Although the frequency of breakthrough pain was higher in the delayed group, no between-group difference was observed (Figure 2B).

Analgesic consumption and adverse effects

The baseline equivalent oral morphine consumption was comparable in both groups, i.e., 78.89 ± 32.70 mg and 81.43 ± 48.09 mg, respectively. The analgesic consumption gradually reduced to a minimum at 2 weeks, followed by an increase in demand at 1 month (35.56 ± 30.14 and 50.48 ± 47.90 mg, respectively). Furthermore, patients in the delayed CPN group showed significantly greater opioid

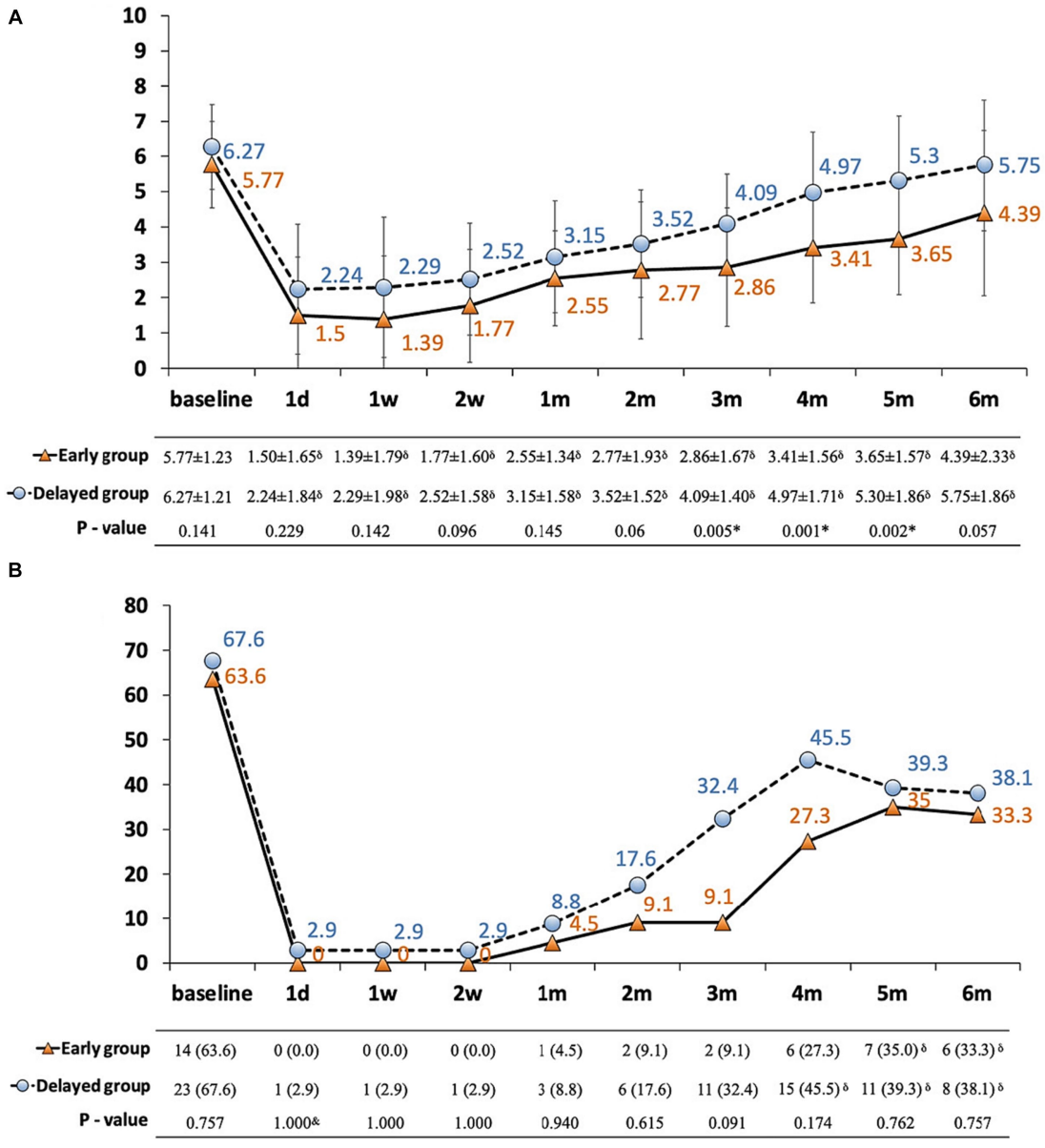

FIGURE 2
(A,B) Pain conditions in patients with pancreatic cancer between early and delayed CPN group. **(A)** NRS plotted against time; **(B)** incidence of breakthrough pain ≥3 times/day plotted against time. Solid line with orange triangles: early group; dashed line with blue dots: delayed group; thin bars represent standard error of the mean (SEM); *significance was detected between early and delayed group; $^{\delta}$significance was detected between follow-ups and baseline; NRS: numerical rating scale.

consumption from 2 to 4 months, and the increase in opioids started earlier compared with the early CPN group (Table 2). Both groups were statistically similar regarding CPN-related adverse reactions, the most frequent being dizziness ($n = 12$, 54.5% vs. $n = 15$, 44.1%), hypotension ($n = 7$, 31.8% vs. $n = 11$, 32.4%), and diarrhea ($n = 7$, 31.8% vs. $n = 10$, 29.4%) (Table 3). Additionally, one patient in the delayed group developed hematochezia on the second day after the operation, which was transient and resolved spontaneously after rehydration and fasting.

Pain-related quality of life and survival time

The interference of pain with daily activities and emotional status was evaluated using BPI. The posttreatment total interference was significantly lower than baseline in all patients, suggesting that the overall health status was improved after CPN. Patients in the early group reported significantly low interference from 1 to 4 months posttreatment (Figure 3). Specifically, mood-related interference in the early group was significantly lower than in the delayed group, mainly evident in the "enjoyment of life" and "mood" items (Figures 4A–C). Meanwhile, early CPN also led to better sleep and appetite improvement (Figures 4A–D). However, no significant differences were detected in the activity-related interference (the average scores of work and walking), except for general activity (Figures 4A–C). Figure 5 shows the survival rates for both groups calculated by Kaplan–Meier survival curves. The average survival time was 11.18 and 8.75 months in the early and delayed CPN groups, respectively. No significant between-group difference was found using the log-rank test ($\chi^2 = 2.501$, $p = 0.114$).

Discussion

The results of our study demonstrate that early CPN is beneficial in preventing pain progression and opioid consumption, besides improving the overall pain-interfered QoL. Pancreatic cancer is one of the most painful malignancies often associated with delayed diagnosis and the poorest prognosis rendering palliative pain management challenging for the patients (23). Chemical neurolysis is usually achieved by alcohol or phenol under imaging guidance, which can provide 3–6 months of pain relief for patients who have a limited life expectancy; moreover, substantial evidence suggests that, in contrast to general analgesia, CPN can provide even greater pain relief and result in reduced morphine consumption (21, 24, 25). However, many factors influence the effectiveness of pain relief from CPN, with retroperitoneal tumoral invasion being the most significant (26, 27). Therefore, patients delayed to CPN may experience relatively lower pain improvement. However, in most clinical cases, the patients with pancreatic cancer are under increasing opioids with unsatisfied pain relief. In this scenario, decisions between continued morphine titration or CPN have to be made. In our study we found that the time gap from the initial visit to the implementation of CPN could exceed 1 month between the two groups (3.45 days vs. 35.06 days), even though the diagnosis of refractory cancer pain could be made within 2 weeks. The parallel courses of opioid titration and disease progression may contribute to the delayed CNP decision. Recent studies support the application of a neurolytic procedure for pain control early after inadequate opioid therapy (28). Notably, a prospective study described using thoracoscopic splanchnicectomy as the first step of the analgesic ladder for pancreatic cancer pain and reported greater pain improvement, QoL, and longer survival time (12).

Although the pain scores were comparable between the two groups from 1 day to 2 months postoperatively, the early group was associated with significantly reduced NRS and the number of breakthrough pain from 3 to 5 months, suggesting a better prognosis with the early procedure. CPN aims to block nociceptive

TABLE 1 Basic conditions of the study population.

	Early group	Delayed group	*p*-value
	n = 22 (%)	*n* = 34 (%)	
Age (years)			
Mean (SD)	56.64 (13.70)	56.53 (9.91)	0.973
Gender			
Male	15 (68.2)	24 (70.6)	0.848
Female	7 (31.8)	10 (29.4)	
Pancreatic cancer location			
Head	8 (36.4)	11 (32.4)	0.605
Body/tail	8 (36.4)	13 (38.2)	
Whole pancreas	1 (4.5)	5 (14.7)	
Metastatic pancreatic cancer	5 (22.7)	5 (14.7)	
Time gap (days)			
Mean (SD)	3.45 (1.65)	35.06 (9.98)	<0.001[a]
Course duration (months)			
Mean (SD)	5.59 (4.16)	4.79 (4.28)	0.314
Cancer stages			
IIB	2 (9.1)	1 (2.9)	0.598
III	5 (22.7)	9 (26.5)	
IV	15 (68.2)	24 (70.6)	
Comorbidities			
Hypertension	5 (22.7)	8 (23.5)	0.933
Diabetes	3 (13.6)	5 (14.7)	
COPD	0 (0.0)	1 (2.9)	
Osteoporosis	0 (0.0)	1 (2.9)	
Liver dysfunction	4 (18.2)	6 (17.6)	
Renal dysfunction	0 (0.0)	1 (2.9)	
Malnutrition	15 (68.2)	24(70.6)	
Prior anti-tumor treatment			
Surgery	5 (22.7)	4 (11.8)	0.839
Radiotherapy	6 (27.3)	6 (17.6)	
Intraoperative radiotherapy	7 (31.8)	11 (32.4)	
Chemotherapy	12 (54.5)	11 (32.4)	
Other treatments	11 (50.0)	16 (47.1)	

[a]Significance was detected between early and delayed group.

transmission raised from the celiac plexus, which is located anterior to the abdominal aorta and the celiac trunk (29). Accordingly, an adequate spread of the neurolytic solution into the preaortic space is one of the key determinants of the successful block (30). Conversely, perineural invasion into the extra-pancreatic nerve plexus is the most common pathologic characteristic of pancreatic cancer (31, 32). Depending on these factors, an optimal time window should be considered when administering CPN for patients with pancreatic cancer.

We observed that both early and delayed groups demonstrated decreased opioids consumption compared with baseline levels. To avert any withdrawal symptoms, the analgesic use was not reduced abruptly after the operation, with the lowest opioids consumption achieved by 2–4 weeks. Subsequently, the ongoing adjustment of opioids was increased in both groups, but the delayed group required an earlier rise and higher requirement. This outcome was not unexpected and was consistent with the pain progression, as well as the analgesic strategy we applied, i.e., sufficient opioids were administrated as required. Since CPN is not an isolated form of palliative pain management but a part of the broader analgesic strategy, opioids remain the mainstay for cancer pain control (33). Nonetheless, several studies have demonstrated that successful and timely neurolysis reduces the need for opioid consumption until the end of life (34–36). Furthermore, recent data suggest that CPN administration via endoscopic ultrasound at the time of diagnosis may help avert the increased opioid consumption spiral (24); our results further corroborate these results.

TABLE 2 Changes in opioids consumption after CPN.

	Early group	Delayed group	*p*-value
	Mean ± SD	Mean ± SD	
Baseline	78.89 ± 32.70	81.43 ± 48.09	0.905
1 day	48.89 ± 38.18[b]	57.62 ± 46.57[b]	0.617
1 week	36.67 ± 29.90[b]	53.33 ± 46.94[b]	0.320
2 weeks	35.56 ± 30.91[b]	50.48 ± 47.90[b]	0.267
1 month	35.56 ± 30.14[b]	56.19 ± 58.78[b]	0.188
2 months	41.82 ± 34.73[b]	74.12 ± 50.52[b]	0.011[a]
3 months	47.27 ± 30.73[b]	77.65 ± 55.38[b]	0.035[a]
4 months	53.33 ± 30.68[b]	81.90 ± 55.82	0.045[a]
5 months	62.22 ± 35.57[b]	90.48 ± 58.61	0.160
6 months	66.67 ± 35.65	96.19 ± 59.62[b]	0.162

[a]Significance was detected between early and delayed group.
[b]Significance was detected between follow-ups and baseline.

TABLE 3 Comparison of CPN related adverse reactions.

	Early group	Delayed group	*p*-value
	n = 22 (%)	*n* = 34 (%)	
Hypotension	7 (31.8)	11 (32.4)	0.967
Diarrhea	7 (31.8)	10 (29.4)	0.848
Dizziness	12 (54.5)	15 (44.1)	0.446
Headache	0 (0.0)	1 (2.9)	1.000
Localized pain	3 (13.6)	5 (14.7)	1.000
Nausea	5 (22.7)	6 (17.6)	0.902
Vomiting	0 (0.0)	1 (2.9)	1.000
Hematochezia	0 (0.0)	1 (2.9)	1.000

No differences were noted between groups.

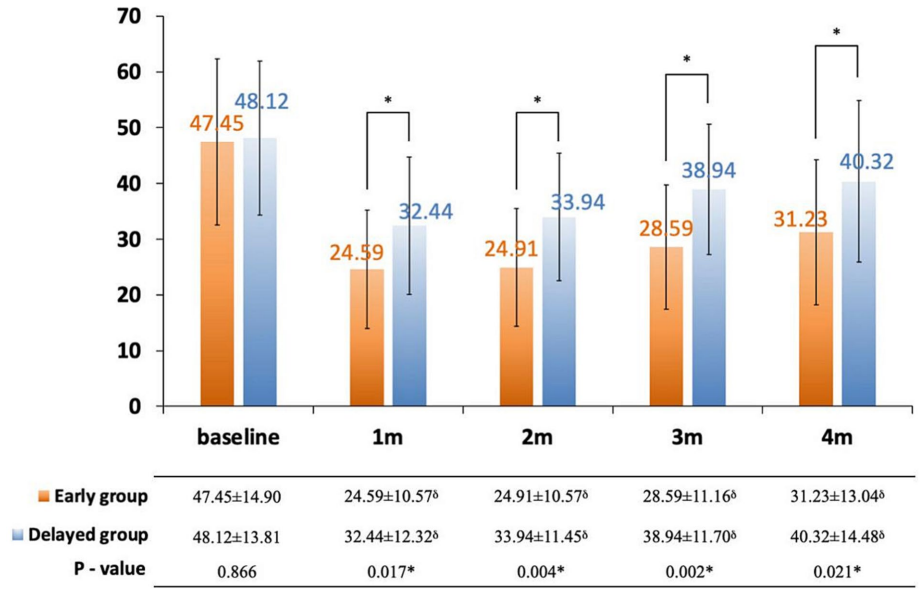

FIGURE 3
Change in total pain inference score between early and delayed group. Orange bars: early group; blue bars: delayed group; thin bars represent standard error of the mean (SEM); *significance was detected between early and delayed group; δsignificance was detected between follow-ups and baseline.

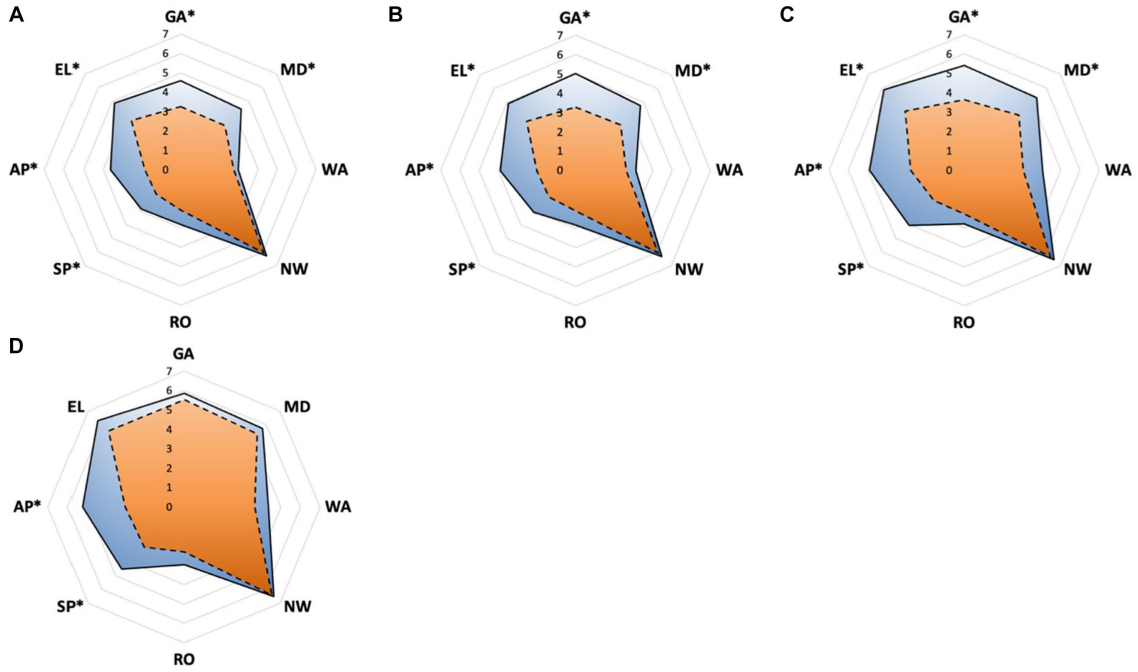

FIGURE 4
(A–D) Pain inference of eight sections measured by BPI between early and delayed group. **(A)** The domain scores at 1 month; **(B)** the domain scores at 2 months; **(C)** the domain scores at 3 months; **(D)** the domain scores at 4 months. Orange zone with dashed edge: early group; blue zone with solid edge: delayed group; GA, general activity; MD, mood; WA, walking ability; NW, normal work; RO, relationship with others; SP, sleep; AP, appetite; EL, enjoyment of life; *significance was detected between early and delayed group.

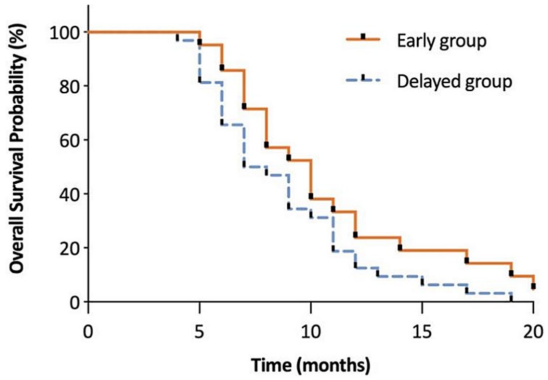

FIGURE 5
The evaluation of overall survival in months between early and delayed group. This figure shows the survival rates for both groups calculated by Kaplan–Meier survival curves. The average survival time was 11.18 and 8.75 months in the early and delayed CPN groups, respectively. No significant between-group difference was found using the log-rank test ($\chi^2 = 2.501$, $p = 0.114$).

Expectedly, the overall pain interference in QoL exhibited a greater improvement in patients who received early CPN, notably in terms of sleep, appetite, and mood-related interference items. However, early CPN did not produce a prominent improvement in work and walking. It is known that patients with advanced cancer experience improved mood and QoL, require less aggressive end-of-life care, and have longer survival by integrating early supportive care (19, 37, 38). Furthermore, neurolysis for patients with abdominal malignancy is reported to improve both the QoL and longevity, which can probably be attributed to a reduction in opioid-related side effects (39). However, contrary to the above findings, a retrospective case–control study suggested that patients who underwent celiac neurolysis had shorter survival compared with the controls who did not (40). We observed that the survival times in both groups were comparable. In particular, the initial CA19-9 levels, tumor stage, and treatment intensity are all prognostic factors that influence the survival time of patients with advanced pancreatic cancer (41, 42). A recent study identified pancreatectomy with chemotherapy as a favorable prognostic factor for metastatic pancreatic cancer and developed a nomogram to predict 6 months, 12 months, and 18 months overall survival probabilities, considering factors such as age, tumor size, marital status, gender, and tumor grade (43). However, it remains indeterminate whether CPN itself is an independent factor for survival.

There were certain limitations of this study. Since it was a retrospective study, our findings are based on limited data collected from baseline to 6 months from a single institution. Additionally, the BPI scores were only available for the first 4 months and patients in the delayed group had a poorer response to prior oncologic therapy and pain control, both of which may have affected the outcome. In terms of grouping, the definition of early and delayed intervention was based on whether CNP was performed from the first visit or after a wait-and-see policy after at least 2 weeks of analgesic titration. However, we believe that a refined grouping method or subgroup analysis which considering tumor staging or time from diagnosis may help determine the overall pain course, but was not available in our database.

Nevertheless, our study is the first to show the potential benefits of early application of CPN for pain control in patients with advanced pancreatic cancer, whom have experienced a poor response on moderate dose of opioids.

Conclusion

The results of this retrospective cohort study suggest that early application of CT-guided CPN for patients with advanced pancreatic cancer offers multiple potential advantages, including reduced exacerbation of pain, reduced opioids consumption, and improved pain-interfered QoL; nonetheless, it is not associated with improved survival. To investigate the optimal procedure timing in different subgroups, a further large-scale randomized-controlled trial is required.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Sichuan Cancer Hospital (Approval number: SCCHEC-02-2022-069). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

FL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. XW: Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – review & editing. JT: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – review & editing. XL: Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Periaqueductal/periventricular gray deep brain stimulation for the treatment of neuropathic facial pain

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Background: The Periaqueductal gray (PAG) and the periventricular gray (PVG) are the anatomical targets for deep brain stimulation (DBS) to treat severe, refractory neuropathic pain.

Methods: Seven (four female and three male) patients were qualified for PAG/PVG DBS because of neuropathic facial pain. Frame-based unilateral implantations of DBS were conducted according to indirect planning of the PAG/PVG, contralateral to reported pain (3389, Activa SC 37603, Medtronic). The efficacy of PAG/PVG DBS on pain was measured with Numeric Pain Rating Scale (NRS) and Neuropathic Pain Symptom Inventory (NPSI) before surgery and 3, 12, and 24 months after surgery.

Results: The mean age of the group at the implantation was 43.7 years (range: 28–62; SD: 12.13). The mean duration of pain varied from 2 to 12 years (mean: 7.3; SD: 4.11). Five patients suffered from left-sided facial pain and two suffered right-sided facial pain. The etiology of pain among four patients was connected to ischemic brain stroke and in one patient to cerebral hemorrhagic stroke. Patients did not suffer from any other chronic medical condition The beginnings of ailments among two patients were related to craniofacial injury. NRS decreased by 54% at the 3 months follow-up. The efficacy of the treatment measured with mean NRS decreased at one-year follow-up to 48% and to 45% at 24 months follow-up. The efficacy of the treatment measured with NPSI decreased from 0.27 to 0.17 at 2 years follow-up (mean reduction by 38%). The most significant improvement was recorded in the first section of NPSI (Q1: burning- reduced by 53%). The records of the last section (number five) of the NPSI (paresthesia/dysesthesia- Q11/Q12) have shown aggravation of those symptoms by 10% at the two-years follow-up. No surgery- or hardware-related complications were reported in the group. Transient adverse effects related to the stimulation were eliminated during the programming sessions.

Conclusion: PAG/PVG DBS is an effective and safe method of treatment of medically refractory neuropathic facial pain. The effectiveness of the treatment tends to decrease at 2 years follow-up. The clinical symptoms which tend to respond the best is burning pain. Symptoms like paresthesia and dysesthesia might increase after DBS treatment, even without active stimulation.

KEYWORDS

periaqueductal gray, periventricular gray, deep brain stimulation, neuropathic pain, face

Introduction

Chronic pain is a complex phenomenon described by Spinoza as a "localized form of sorrow." Neuropathic pain appears as a result of central, peripheral or autonomic nervous system damage. Neuropathic pain is undulating and persistent. Patients usually described neuropathic pain as a constant, burning sensation, but clinical phenotype might vary and various forms of attacks may additionally be present. Pain involves multiple neuronal circuits. The elementary understanding of neuropathic pain focuses on lateral pain pathways. The nociceptive stimuli are carried by A-delta and C fibers to the dorsal root ganglions, spinothalamic tracts and through the thalamus to the postcentral gyrus (1, 2). When the pain persists, an affective component of the neuropathic pain phenomenon becomes more significant. With the increased components of the affective and limbic systems, pain becomes less localized and discriminated (3). The limbic pathway projects to the thalamus, hippocampus, cingulate and nucleus accumbens. Involvement of affective and limbic pathways, with time impairs more significantly the quality of patients' life (4). Target treatments toward the limbic system from somatosensory pathways might result in significant improvement in neuropathic pain perception. In parallel to limbic, affective and somatosensory pathways, the cognitive functions construct the fourth pillar of neuropathic pain perception (2–4). Standard treatment is focused on pharmacotherapy (analgesic ladder) that includes antiepileptic and mood-enhancing medications. Psychological support is one of the key pillars of the treatment. Appropriate physiotherapy improves the results of the treatment. Surgical treatment might be considered if the effects of conservative treatment are unsatisfactory (5–7).

Deep brain stimulation (DBS) is a well-established method of neurosurgical treatment for movement disorders, especially: Parkinson's disease, essential tremor and dystonia (7, 8). Initial attempts to treat surgically movement disorders were undertaken in the first half of the twentieth century. Electric stimulation was used at that time, to test for side effects prior to execution of permanent thermal or chemical lesion of the basal ganglia or midbrain. The first applications of electrical stimulation to the brain prior to the thermal lesions in the treatment of pain were conducted as early as in the 1950s (5). In the 1980's with the introduction of modern DBS hardware and software with FDA approval, a renaissance of functional neurosurgery has begun. DBS has a better side-effect profile compared to ablative procedures (9–11). The stimulation parameters are adjustable and possible side effects are reversible. It is believed that functional neurosurgery is the fastest-growing supraspecialisation in neurosurgery today (8). It is estimated that almost two hundred thousand patients were implanted with DBS worldwide until 2022. The number of research papers linked to DBS surpassed 1,000 publications annually a decade ago. The possible applications for DBS, not only in neurological disorders are constantly expanding. DBS has been approved for pain, medically refractory epilepsy and psychosurgery. Through its reversible action, DBS has become an effective and invaluable preclinical and clinical research tool. With the application of DBS in laboratory models, neural networks are better understood today (10, 12, 13).

The periaqueductal gray (PAG) and the periventricular gray (PVG) were predominantly identified as the anatomical target for nociceptive pain, whereas the thalamus was aimed to treat neuropathic pain. The role of PAG/PVG in the pain regulation process can not be overrated. Ascending, nociceptive afferents run through PAG/PVG to the thalamus. In the other direction, reciprocal regulatory control of the PAG/PVG modulates the dorsal horns of the spinal cord activation following peripheral nociceptive stimuli. Stimulation of central gray matter of the tegmentum and midbrain (PAG/PVG) by inhibiting nociceptive responses and increasing endogenous opioid levels is believed to be effective for neurogenic pain. The effect of PAG/PVG DBS is pharmacologically reversible with the application of opioid antagonists (14–16). It is not clear if increased levels of endogenous opioids are related to direct or indirect stimulation of PAG/PVG (17–19). Mostly because of the size of PAG/PVG and the proximity of surrounding structures its sensing topography has not been described yet and requires further exploration. The role of PAG/PVG stimulation in the regulatory process of autonomic functions and mood alterations like fear have been described (17, 19).

There is a noticeable deficit of data about the mechanism of action of PAG/PVG DBS on neuropathic pain. The authors believe that the presented analysis will allow for a better understanding of the mechanism of action of PAG/PVG DBS on pain and will lead to further research. The objective of the study was to evaluate the effectiveness and safety of PAG/PVG DBS on neuropathic facial pain. The authors aimed to identify the most optimal clinical characteristics of pain for this invasive but reversible treatment.

Methods

Seven eligible patients were diagnosed with neuropathic facial pain according to the IASP Neuropathic Pain Special Interest Group (NeuPSIG) definition. Those patients were qualified by pain specialists, psychologists and neurosurgeons for PAG/PVG DBS. None of the patients had a history of psychiatric treatment. Patients underwent a standard battery of psychological tests performed for qualification for neuromodulation pain treatment. None of the patients suffered from major depression. Patients had psychological support before and after surgical treatment. All patients qualified for the surgery underwent typical conservative treatment including an analgesic ladder and adjuvant therapy that was ineffective (8, 12). No chronic comorbidities were reported. Consent forms were obtained from the patients before each interview. Ethics committee approval was not required as long as the patients underwent standard treatment and evaluation that included examining patients for co-morbidities, surgery and other non-invasive medical assessments. Demographic data were collected and analyzed: initials, age (date of birth), gender, disease duration and clinical status measured with the Numeric Pain Rating Scale (NRS) and the Neuropathic Pain Symptom Inventory (NPSI) of four male and three female patients (3, 6, 20). NPSI consists of 12 questions and five sub-scores (Q1- burning, Q2 + 3- pressing, Q5 + 6 paroxysmal pain, Q8 + 9 + 10- paroxysmal pain, Q11 + 12- paresthesia/dysesthesia). Additional questions: Q4 and Q7 represent overtime nuisance. The calculated total intensity pain score measured with NPSI consists of five sub-scores multiplied by two and divided by 100% (6, 20). The efficacy of PAG/PVG DBS on facial pain was measured with NRS and NPSI before surgery, 3, 12, and 24 months after surgery. Frame-based unilateral implantation of DBS was conducted according to indirect planning of the PAG/PVG contralateral to reported pain (Figure 1). The anatomical target of PAG/PVG DBS is parallel to the midbrain aqueduct. The stereotactic coordinates for PAG/PVG were: 2–3 mm lateral from the wall of the

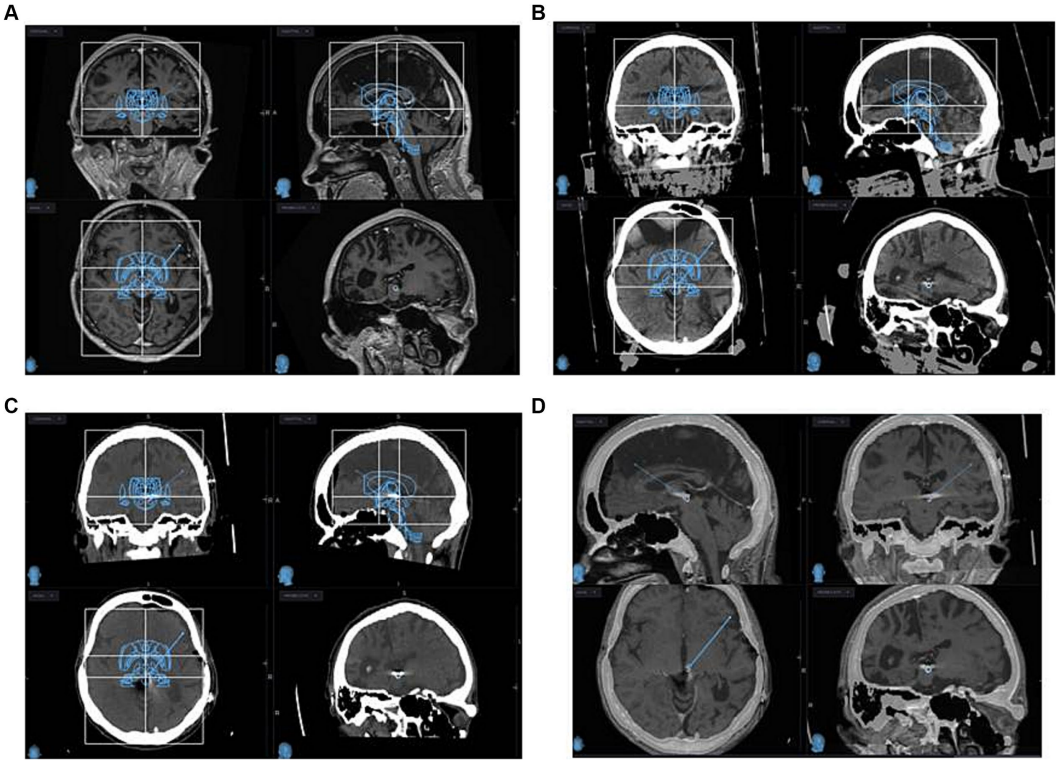


FIGURE 1
MRI **(A)** and CT with stereotactic frame **(B)** planning images of PAG/PVG DBS implantation are depicted. Post-implantation CT **(C)** and MRI **(D)** images are depicted. Infused Schaltenbrand Wahren atlas and Talairach grids are visualized for indirect identification of PAG-PVG **(A–C)** at coronal, sagittal, and axial projections.

third ventricle, 1–2 mm anterior to the posterior commissure at the level of the intercommiusural lane. The entry point was located one to three centimeters in front of the coronal suture and four to five centimeters lateral from the midline. The patients were sedated during the surgical procedure and no neurophysiological evaluations were conducted during surgery. All patients were implanted with 3,389 brain electrodes and Activa SC37603 internal pulse generator (Medtronic). On the day following implantation, a control brain CT was performed and the positions of the electrodes were confirmed with the presurgical planning (Figure 1). The stimulation was initialized on the day following implantation. The initial settings were: monopolar stimulation (case positive, contact 1 and 2 negative) with amplitude 1 V, frequency 50 Hz, and pulse width 60 µs. Depending on clinical response, the amplitude was gradually increased up to 5 V. The frequency and pulse width remained unchanged in the analyzed group. The main outcome measures were the NRS and NPSI scores. Possible adverse effects were recorded. The interviews for the pain evaluation and adverse effects were carried out at the outpatient clinic 3, 12, and 24 months after implantation. The statistical analysis was conducted with Statistica 8.0 PL and the graphs were prepared with MS Excel (Microsoft Corporation).

Results

Seven patients completed evaluation before the surgery and after PAG/PVG DBS implantation at the follow-up (3, 12, and 24 months following surgery). The mean age of the group at the implantation was 43.7 years (range: 28–62; SD: 12.13). The mean duration of pain varied from 2 to 12 years (mean: 7.3; SD 4.11). Five patients suffered from left-sided facial pain and two suffered right-sided facial pain. The etiology of pain among four patients was connected to brain ischemic stroke and one patient had a history of brain hemorrhagic stroke. The beginning of ailments among two patients was related to craniofacial injury. Two patients (#2, 3) in the group had a history of motor cortex stimulation that did not influence their pain score or quality of life. The systems were explanted 6 months and 10 months after implantation. Three patients (#1, 4, 7) underwent thalamic DBS without significant effect as well. Those systems were explanted 12, 16, and 21 months after surgery. One patient (#6) with a mixed character of pain (neuropathic facial pain and trigeminal neuralgia) had a history of microvascular decompression and radiofrequency lesions in the Gasserian ganglion that were ineffective. The mean NRS score before surgery was 8.7 (8–10; SD:0.78; Table 1). The mean NPSI score before surgery was 0.27 (0.22–0.4; SD: 0.096; Table 2). NRS decreased by 54% at 3 months follow-up. The efficacy of the treatment measured with NRS decreased at one-year follow-up to 48% and to 45% at 24 months follow-up (Table 1). The total pain intensity score measured with NPSI decreased from 52% before surgery through 38% after 3 months and 32% after 12 months to 34% at the two-years follow-up. The most significant improvement was recorded in the first section of NPSI (Q1: burning- reduced by 53%). The last section of the test (Q11 + 12: paresthesia/ dysesthesia) showed aggravation of the symptoms by 10% at the two-years follow-up (Figure 2).

Patients' age, sex, previous neuromodulation treatment, duration, etiology and laterality of pain were not prognostic variables for the efficacy of the treatment. Because of the small group of patients and additionally, because of its' inhomogeneity the results were not statistically significant. The best results were recorded among two patients: 28-year-old male (#2) with 3 years history of poststroke pain (NRS- 63% and NPSI- 43% improvement; Q1–71% improvement and unchanged score in Q2 + 3 subscale) and 36-year-old female (#4) with a 12 years history of posttraumatic pain (NRS- 66% and NPSI 45% improvement; Q1–75% improvement and 20% improvement in Q2 + 3 subscale). The worst results were recorded among two patients: 48-year-old female (#3) with a 12 years history of poststroke pain (NRS- 0% and NSPI- 13% improvement; Q1–25% improvement without change in Q2 + 3) and 48-years-old female (#7) with a 2 years history of posttraumatic pain (NRS- 33% and NPSI 45% improvement) (Tables 1, 3; Figure 2). The total intensity pain score in the whole group of patients decreased in the follow-up. The initial better response of the total intensity pain score recorded in 48-years-old woman (#3) with poststroke pain was reduced (Figure 3). PAG/PVG had a positive effect on overtime nuisance measured with NPSI (Q4 and Q7) (Figure 4). No surgery- or hardware-related complications were reported in the analyzed group. Transient adverse effects related to the stimulation including double vision, contralateral to the stimulation paresthesia and undefined by patients feeling of warmth or cold were eliminated during the same programming session by decreasing the amplitude of the stimulation or changing the polarity of the stimulation. Those adverse effects tend to fade away within seconds after reprogramming of the stimulation.

TABLE 1 Pain Numeric Rating Scale (NRS) score before surgery and 3, 12, and 24 months following surgery measured in the analyzed group of seven patients: (score and percentage of improvement are displayed) (3).

Subject	Before surgery	3 months		12 months		24 months	
	NRS score	NRS	%	NRS	%	NRS	
1	8	4	50%	4	50%	4	50%
2	8	3	63%	3	63%	3	63%
3	8	4	50%	6	25%	8	0%
4	9	4	50%	3	66%	3	66%
5	10	5	50%	5	50%	5	50%
6	8	4	50%	4	50%	4	50%
7	9	3	66%	6	33%	6	33%

Discussion

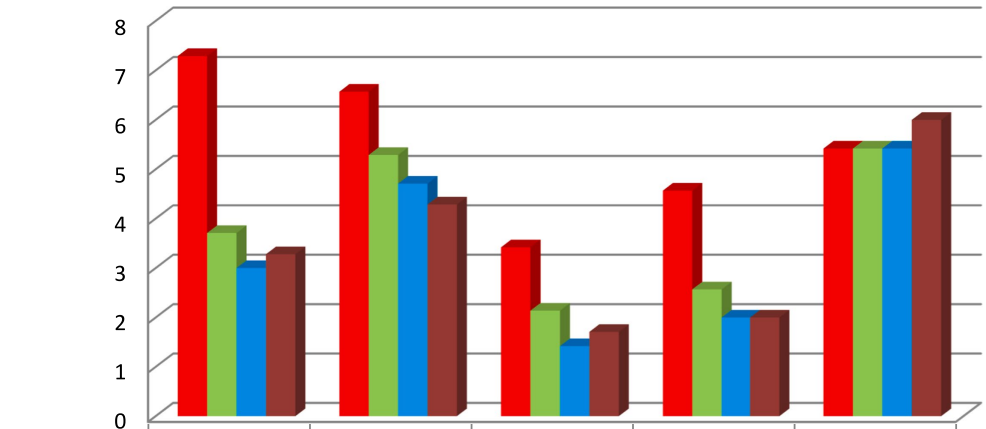
Various types of chronic pain affect 5–20% of the population. One of the main clinical targets of functional neurosurgery in parallel to movement disorders is chronic pain. The etiology of chronic pain qualified for DBS include: poststroke pain, cephalalgia, atypical facial pain, phantom limb pain, brachial plexus avulsion and spinal cord injury. In the presented group patients suffered from neuropathic facial pain whereas its etiology was: brain stroke, brain hemorrhage and craniofacial injury. There were no particular causes of neuropathic pain identified to respond the best to DBS (5, 17, 18). The same results were observed in the analyzed group, the cause of the neuropathic pain had no impact on the success of the treatment.

Potential mechanisms of DBS action include: inhibiting or excitation of neural activity and synaptic filtering. The complexity of the neuronal network affected by DBS adds new variables. The majority of theories analyzing the mechanism of DBS on pain are focused on the immediate (weeks) effects of the stimulation (5, 12). The leading theories indicate that electrical stimulation introduced by DBS restores neural network communication to a more physiological state (8, 10). Electric fields applied to axons surrounding the DBS electrode result in the opening and closing of voltage-gated sodium channels. The effect of DBS on action potentials and controlled release of neurotransmitters and the role of synaptic and neural plasticity at the long-term follow-up remain unclear (14–16, 21). Additionally, there is evidence of neurogenesis and synaptogenesis following DBS in animal models. In parallel to the effect of DBS on neurons, there has been shown also an effect on glial cells that alters the surrounding neurochemical environment and neurons (7, 8).

Three primary anatomical targets are identified for pain treatment with DBS: PAG/PVG, sensory thalamus (ventral posterior lateral or medial nuclei) and anterior cingulate cortex. The secondary targets for DBS include the posterior hypothalamus, centro-median-parafascicular complex, ventral and anterior limb of the internal capsule (8, 9, 17). As an alternative to DBS for: poststroke and posttraumatic pain, facial neuropathic pain,

TABLE 2 Neuropathic Pain Symptom Inventory (NPSI) subscales score measured before surgery in the analyzed group of seven patients: Subscales: Q1- burning (superficial); Q2- pressure and Q3 squeezing (deep); Q5- electric shocks and Q6- stabbing (paroxysmal); Q8- evoked by brushing, Q9- evoked by pressure and Q10- evoked by cold stimuli (evoked); Q11- pins and needles, and Q12 tingling (paresthesia/dysesthesia), Q4- spontaneous pain during the past 24 h, Q7- pain attack during the past 24 h (6, 20).

Subject	Q1	Q2 + 3	Q5 + 6	Q8 + 9 + 10	Q11 + 12	Q4	Q7
1	8	8	2	0	4	8	10
2	7	4	0	4	6	8	8
3	4	10	6	10	8	10	10
4	8	4	6	0	4	10	6
5	10	8	6	10	10	10	10
6	6	8	2	4	4	8	6
7	8	4	2	4	2	8	4



	Q1-	Q2+3	Q5+6	Q8+9+10	Q11+12
Before surgery	7.29	6.57	3.42	4.57	5.42
3 months	3.71	5.29	2.14	2.57	5.42
12 months	3	4.71	1.42	2	5.42
24 months	3.28	4.29	1.71	2	6

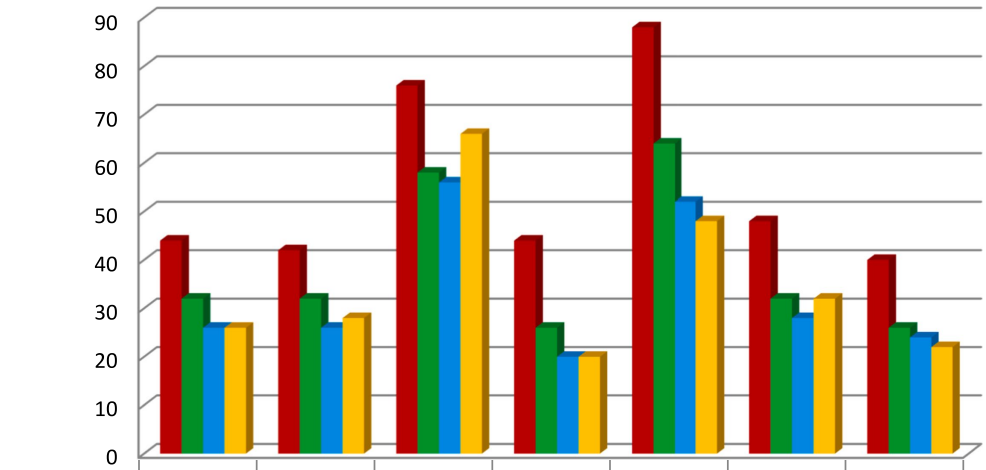
FIGURE 2
Mean variations of spontaneous pain measured with Neuropathic Pain Symptom Inventory (NPSI) subscales measured in the analyzed group of seven patients: Q1- burning (superficial); Q2- pressure and Q3 squeezing (deep); Q5- electric shocks and Q6- stabbing (paroxysmal); Q8- evoked by brushing, Q9- evoked by pressure and Q10- evoked by cold stimuli (evoked); Q11- pins and needles, and Q12 tingling (paresthesia/ dysesthesia) (6, 20).

TABLE 3 **Neuropathic Pain Symptom Inventory (NPSI) score (subscale 1–5) measured before surgery and 3, 12, and 24 months following surgery in the analyzed group of seven patients (score and percentage of improvement are displayed) (6, 20).**

Subject	Before surgery	3 months		12 months		24 months	
	NPSI	NPSI	%	NPSI	%	NPSI	%
1	0.22	0.16	27%	0.13	41%	0.13	41%
2	0.21	0.16	24%	0.13	38%	0.14	43%
3	0.38	0.29	24%	0.28	26%	0.33	13%
4	0.22	0.13	45%	0.1	54%	0.1	45%
5	0.44	0.32	27%	0.26	41%	0.24	45%
6	0.24	0.16	33%	0.14	42%	0.16	33%
7	0.2	0.13	35%	0.12	40%	0.11	45%

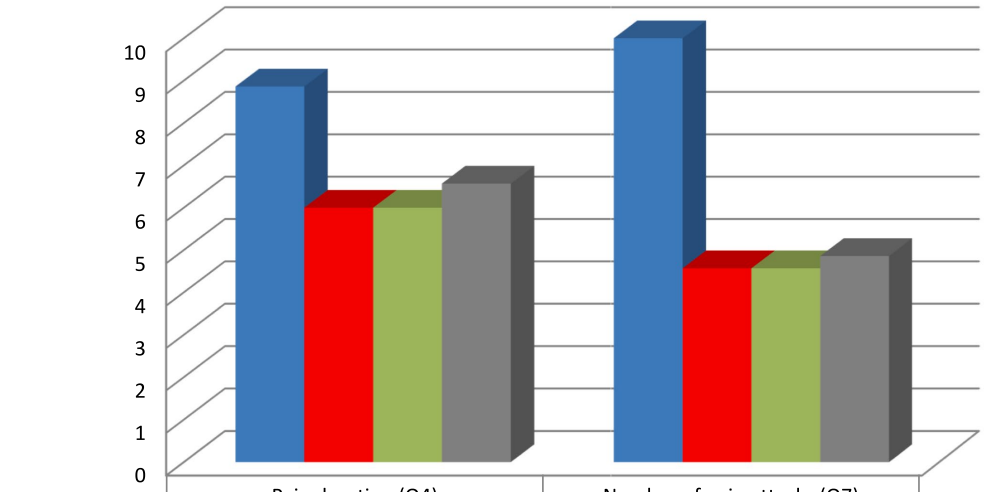
phantom limb pain, brachial plexus avulsion and complex regional pain syndrome is motor cortex stimulation (22, 23). Previously published data indicates that PAG/PVG DBS is particularly effective among patients with nociceptive pain whereas patients with neuropathic pain might benefit more from combined PAG/PVG and thalamic DBS. PAG is an area of gray matter located around the midbrain aqueduct. This structure ascends until reaches the third ventricle anteriorly and becomes PVG. PAG/PVG is involved in the coordination of behavioral and autonomic responses, especially pain. PAG/PVG integrates inputs from nociceptive and autonomic afferents, prefrontal cortex, amygdala, reticular formation and hypothalamus (1, 24). Recent studies demonstrated improvement following PAG/PVG DBS in autonomic functions, like cardiovascular (hyper and hypotension), lung function, bladder capacity and motor systems. In parallel PAG/PVG modulates nociceptive signaling to the brainstem and hypothalamus. It is believed that the effect of PAG/PVG DBS is intensified by engaging endogenous opioid-releasing neurons and by inhibiting or altering nociceptive stimulation (15, 22, 23). In the analyzed group the anatomical functions of the patients who underwent DBS implantation were not analyzed. In the analyzed group, all patients with neuropathic pain were qualified for PAG/PVG DBS. Two patients in the group had a prior history of motor cortex stimulation that did not influence their pain score. Three patients underwent thalamic DBS without significant effect as well. The mechanism of DBS on pain despite enormous progress is still not well understood (2, 16, 25).

The benchmark for good response and clinical usefulness for pain relief of neuromodulation is marked for 50% of pain reduction (3, 6, 20). The efficacy of PAG/PVG DBS for neuropathic pain related to stroke, trauma or amputation is estimated to be ~52% of good to excellent response (>50% improvement). It is estimated that 26% of patients will not benefit from the surgery or will respond poorly to the stimulation (<20% improvement). It has to be kept in mind that patients treated with PAG/PVG DBS are refractory to all other forms of treatment and even mild improvement can significantly improve



	1	2	3	4	5	6	7
Before	44	42	76	44	88	48	40
3 months	32	32	58	26	64	32	26
12 months	26	26	56	20	52	28	24
24 months	26	28	66	20	48	32	22

FIGURE 3
Total intensity pain score. Calculation based on a sum of Neuropathic Pain Symptom Inventory (NPSI) subscales measured in the analyzed group of seven patients: Q1- burning (superficial); Q2- pressure and Q3 squeezing (deep); Q5- electric shocks and Q6- stabbing (paroxysmal); Q8- evoked by brushing, Q9- evoked by pressure and Q10- evoked by cold stimuli (evoked); Q11- pins and needles, and Q12 tingling (paresthesia/dysesthesia) (6, 20).



	Pain duration (Q4)	Number of pain attacks (Q7)
Before surgery	8.86	10
3 months	6	4.57
12 months	6	4.57
24 months	6.57	4.86

FIGURE 4
Duration of pain and the number of pain attacks measured with NeuropathicPain Symptom Inventory (NPSI) in the analyzed group of seven patients: mean pain duration (Q4) and the number of pain attacks (Q7) (6, 20).

their quality of life (18, 26). The initial improvement measured with NRS following the stimulation in the analyzed group reached 50%. This beneficial effect decreased during 24 months of follow-up. Despite modification of the stimulation parameters and increased voltage of the stimulation, the beneficial effect of PAG/PVG decreased in the follow-up. Fading-away effect of the stimulation in the analyzed group is not clear. The affective and cognitive component of pain related to expectations following complex brain surgery, might play

an important role in this vanishing effect where the initial, beneficial effect was altered. The effect measured with total intensity pain score (NPSI) was not that significant. More accurate analysis showed NPSI subscales which tend to respond more, like burning (superficial) and subscales which do not respond to treatment, like pressing (deep). The patient has to be informed before qualification for the treatment that some symptoms might aggravate after surgery (paresthesia and dysesthesia) (8, 12).

The pathophysiology of neurogenic pain is intricate and includes alterations of multiple neural networks as stated above. Typically used DBS settings of stimulation frequency for PAG/PVG DBS are lower for pain than used for movement disorders. It is believed that lower frequencies (<50 Hz) cause analgesia and higher frequencies (>70 Hz) cause hyperalgesia. Typical settings of PAG/PVG DBS include low frequency (<50 Hz) with a wide spectrum of voltage 0.6–7 V and pulse width spectrum from 60 to 120 μs (19, 21). In the analyzed group, the initial settings were set for: monopolar stimulation (case positive, contact 1 and 2 negative) with amplitude 1 V, frequency 50 Hz, and pulse width 60 μs. At the follow-up visits, depending on clinical response the amplitude was gradually increased up to 5 V (14–16).

There are inherent surgical risks related to DBS. The mortality rate related to DBS is less than 0.4% (pulmonary embolism, myocardial infarction). Intracranial bleeding and intracerebral hemorrhage (1–2%) can cause the most serious complications. Thromboembolic complications, urinary infection and pneumonia are reported in less than 2% of patients. Typical adverse effects of the stimulation of PAG/PVG include: eye bobbing, eye deviation (spread to the superior colliculus and oculomotor nerve) and anxiety. Nausea and diaphoresis are the most common autonomic side effects observed especially with higher voltages. The positive effect of stimulation is frequently preceded by not precisely defined warmth/cold sensation or contralateral to the stimulation paresthesias. Possible adverse effects related to stimulation can be eliminated by changing the settings of the stimulation. Stimulation-related seizures are more frequently observed among patients with motor cortex stimulation (4, 22). Complications related to the implant are more frequent and include: lead migration and fracture (2–3%) and infection (3–8%) (5, 8, 26). At the 24-month follow-up in the analyzed group, no surgery- or implant-related complications were recorded. The majority of the patients reported warmth that appeared predominantly contralateral to the implanted PAG/PVG-mostly in the face, trunk or upper extremity. The feeling of warmth had a tendency to fade away within minutes after changing the settings of the stimulation. Observed eye deviation had a tendency to appear at higher voltages. Those were eliminated by the instant change of settings of the DBS. The mechanism of those adverse effects remains clear. The time frame of appearance and disappearance of those sensations related to the stimulation indicate that most probable mechanism is direct stimulation of surrounding PAG/PVG structures. The role of brain blood flow variations or alterations of endogenous opioid levels related to DBS is less probable. Less frequently patients complained of persistent paresthesia or dysesthesia after changing of the DBS settings. Increased by 10% subscore 5 of NPSI (paresthesia/ dysesthesia) at the 24-month follow-up might be identified as an adverse effect of PAG/PVG DBS even though the paresthesia did not vanish after changing of the DBS settings.

Conclusion

PAG/PVG DBS is an effective and safe method of treatment of medically refractory neuropathic facial pain. NRS is an easy-to-apply scale for pain evaluation. The effectiveness of the treatment tends to decrease at 2 years of follow-up. The application of NPSI helps to differentiate the type of pain that might respond the best to PAG/PVG DBS. The pain phenotypes which tend to respond the best to PAG/PVG are burning and superficial pain (subscore 1 of NPSI). PAG/PVG is least effective for subscore 2 of NPSI (pressing, deep pain). Symptoms like paresthesia and dysesthesia (question number 11 and 12- subscore 5) might increase after PAG/PVG DBS. Those aggravated symptoms tend to persist even when the stimulation is deactivated. Even though this composite effect of PAG/PVG on the complex phenotype of neuropathic facial pain resulted in poorer results measured with NPSI (compared to NRS), the authors believe that both scales should be applied to measure the efficacy of the treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the studies involving humans because the patients underwent typical neurosurgical treatment under standard regiment. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

VM prepared the manuscript and collected data. PZ, BK, KS, and HK conducted follow-up, collected data, and participated in surgery. KC analyzed data. TM performed surgery, conducted follow-up, and coordinated the creation of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Assessing the association between age at first sexual intercourse and migraine: a Mendelian randomization study

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Background and objectives: As indicated by observational and genetic variation studies, age at first sexual intercourse (AFS) may be associated with migraine attack, but there is a lack of evidence from real-world studies due to ethical concerns. Therefore, we conducted a Mendelian randomization study to determine the causal relationship between AFS and migraine.

Methods: We extracted instrumental variables from summary data of a genome-wide association study (GWAS) on AFS and migraine and then conducted two-sample Mendelian randomization analyses. GWAS data for AFS and migraine were obtained from 397,338 unrelated individuals (214,547 females and 182,791 males) and 306,314 individuals (18,477 patients and 287,837 control individuals), respectively.

Results: There was a causal relationship between AFS and risk for migraine (odds ratio (OR) = 0.73, 95% confidence interval (CI) [0.61 to 0.86]), both for migraine with aura (MWA; OR = 0.72, 95% CI [0.58 to 0.89]) and migraine without aura (MOA; OR = 0.66, 95% CI [0.51 to 0.86]). Stratified analyses provided suggestive evidence of the causal relationship between delayed AFS and a decreased risk of migraine for both males (OR = 0.71, 95% CI [0.59 to 0.84]) and females (OR = 0.73, 95% CI [0.61 to 0.89]). Reverse Mendelian randomization did not reveal any effect of migraine on AFS ($p > 0.05$). No pleiotropy was detected.

Discussion: A delayed AFS is a protective factor against migraine (for both MWA and MOA) in both males and females. This causal relationship indicates the presence of extracranial regulatory pathways of migraine.

KEYWORDS

migraine, Mendelian randomization, causal association, age at first sexual intercourse, GWAS

Introduction

Migraine is the second most disabling disease globally, and 45.1 million migraine sufferers are estimated to be limited by this disease in their daily lives (1). The pathogenesis of migraine is currently unclear, but increasing evidence suggests that sex hormones trigger episodes of migraine, especially in female patients (2).

Headache associated with sexual activity (HAWSA), which refers to an abrupt explosive headache during orgasm only or a worsening of headache intensity with increasing sexual excitement, occurs in approximately 1% of the population (3). The HAWSA was recognized as a high comorbidity of migraine (25%) (4). It has been discovered that there is a bilateral association between HSA and migraine (5). A genetic variation study revealed that the later the age at first sexual intercourse (AFS) was, the lower the risk of cardiovascular disease (6). In real-world studies, cardiovascular disease has been shown to be associated with migraine (7). Additionally, a genetic association of migraine with type 2 diabetes and blood lipids was also identified (8), and it was claimed that the risk of type 2 diabetes and elevated low-density lipoprotein increases with decreasing AFS (9).

We hypothesize that there is an undiscovered association between AFS and migraine, which is not widely known among the general public and needs explicit clarification. However, it is challenging to conduct a randomized controlled trial or a real-world observational study because it is morally and legally unacceptable to have underage individuals engage in sexual activities.

Mendelian randomization (MR) analysis uses instrumental variables (IVs), typically single nucleotide polymorphisms (SNPs), to explore causal effects between exposure and outcome. MR analysis can significantly reduce the impact of uncontrolled confounders in observational studies, making it suitable for use in situations where it is not feasible to implement randomized controlled trials. Based on the promising efficacy of MR for exploring causal relationships and the aforementioned reasons under comprehensive consideration, we aimed to explore the potential causal relationship between AFS and migraine by using MR analysis.

Methods

We followed the STROBE-MR Statement (10) in reporting the present study. Ethics approval and informed consent were not needed for this study, as the data used in this study were obtained from the original study, which was approved by their ethics committee (11).

Study design

Exposure was defined as AFS, and the outcome was defined as migraine. We planned to use SNPs strongly associated with exposure as IVs. Of note, IVs needed to meet the following criteria: (1) IVs were strongly associated with the exposure; (2) IVs were unrelated to any confounding factors to outcome; and (3) IVs affected the outcome only through the exposure pathway (10).

Data sources

We obtained genetic data from a genome-wide association study (GWAS) of 397,338 unrelated individuals in the GWAS Catalog.[1] Individuals under 12 years old were excluded. The methodological quality of the primary literature that provided the GWAS data (11) was assessed, and it was determined to be of high quality; the GWAS data were used by the authors of a previously published manuscript (6).

The migraine GWAS data were obtained from the ninth edition of the Finngen Biobank as of May 2023.[2] We selected the migraine cohort, which included all patients with migraine coded as G6-MIGRAINE. The diagnosis of migraine was made according to the International Classification of Diseases (ICD)-8, ICD-9, and ICD-10 codes. Stratification analysis was performed by extracting GWAS data for the migraine with aura (MWA) and migraine without aura (MOA) subgroups in the migraine cohort. The outcome data for the present MR analysis were GWAS data for MWA (7,917 cases and 287,837 controls) and MOA (6,730 cases and 287,837 controls). Table 1 shows the datasets that we included.

The present study is a *post hoc* analysis using secondary analyses of published data. As only summary statistics rather than individual-level data were obtained from the GWAS data, comprehensive statistical information regarding sample and genetic variant missingness was not possible.

In this study, exposures and outcomes were derived from two different large-scale GWAS databases, with a low probability of sample overlap. In addition, a study showed that single-sample MR study results with a large sample size ($n = 300{,}000$) were similar to those of double-sample studies, and the sample size we included met this criterion (12).

To ensure the possibility of a strong association between IVs and exposures, we excluded SNPs with a p-value $\geq 5 \times 10^{-8}$ related to AFS (13). We selected SNPs suitable for serving as IVs in the following steps: (1) we extracted SNPs strongly associated with exposure from GWAS by using the TwoSampleMR package (version 0.5.6) in R software (version 4.3); (2) to avoid the impact of linkage disequilibrium on the results, we set clump as $r^2 = 0.001$ and kb = 10,000; (3) we excluded palindromic sequences in SNPs; (4) SNPs that were strongly associated with exposure were matched with outcome GWAS; (5) to exclude the effect of confounding factors, we searched for SNPs that met the above criteria in PhenoScanner[3] and excluded SNPs that may be affected by confounding factors (MR hypothesis II) (14); and (6) we used the F-statistic to evaluate weak instrument variable effects.

The calculation formula was as follows: $F = \frac{\beta^2}{SE^2}$ (15) (β = effect size of exposure; SE = standard error of β). When the F-statistic was less than 10, we considered that there was a weak instrumental variable and that IV needed to be eliminated, or MR analysis was not

Abbreviations: AFS, Age at first sexual intercourse; AFSF, Age at first sexual intercourse of female; AFSM, Age at first sexual intercourse of male; BMI, Body mass index; CI, Confidence interval; CSD, Cortical spreading depression; GWAS, Genome-wide association studies; HAWSA, Headache associated with sexual activity; ICD, International Classification of Diseases; IVs, Instrumental variables; IVW, Inverse variance weighted; MOA, Migraine without aura; MR, Mendelian randomization; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; MWA, Migraine with aura; OR, Odds ratio; PACAP, Pituitary adenylate cyclase-activating polypeptide; SD, Standard deviation; SE, standard error; SNPs, Single nucleotide polymorphisms.

1 https://www.ebi.ac.uk/gwas/
2 https://r9.finngen.fi
3 http://www.phenoscanner.medschl.cam.ac.uk

TABLE 1 Characteristics of GWAS datasets.

Trait	Study	Data source	Sample size	Ancestry	Definition
Exposure					
AFS	Mills MC et al.	GWAS catalog	397,338 individuals	European	Not applicable
AFSM	Mills MC et al.	GWAS catalog	182,791 individuals	European	Not applicable
AFSF	Mills MC et al.	GWAS catalog	214,547 individuals	European	Not applicable
Outcome					
Migraine	FinnGen (Release 9)	FinnGen study	18,477 cases and 287,837 controls	European	ICD-8, ICD-9 and ICD-10
MWA	FinnGen (Release 9)	FinnGen study	7,917 cases and 287,837 controls	European	ICD-8, ICD-9 and ICD-10
MOA	FinnGen (Release 9)	FinnGen study	6,730 cases and 287,837 controls	European	ICD-8, ICD-9 and ICD-10

GWAS, genome-wide association study; AFS, age at first sexual intercourse; AFSM, age at first sexual intercourse of male; AFSF, age at first sexual intercourse of female; MWA, migraine with aura; MOA, migraine without aura; ICD, International Classification of Diseases.

recommended (16). We calculated the F-statistic for each IV and found no occurrence of $F<10$, with a minimum of 27.44 and a maximum of 171.49.

MR analysis

We used the Wald ratio method to obtain causal effect estimates of AFS on migraine risk. When a small number of SNPs were not detected in the outcome, these SNPs were excluded (15). We used three testing methods to conduct the present experiment. The random-effects Inverse-variance weighted (IVW) approach was considered the primary analysis method (17). We also used the weighted median and MR–Egger methods as supplementary analysis methods (18, 19).

We additionally conducted a robust analysis to avoid the influence of outliers (robust IVW and robust MR–Egger). The MR–Egger intercept test was used to assess and determine the existence of horizontal pleiotropy. The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) can sum each SNP's residuals to evaluate the magnitude of horizontal pleiotropy. After adjusting for horizontal pleiotropy, the IVW primary analysis method results were obtained. The overall horizontal pleiotropy of the IVs was evaluated by MR-PRESSO global assessment, while the abnormal SNPs that caused overall horizontal pleiotropy were considered by MR-PRESSO outlier assessment. In addition, the heterogeneity level was assessed by using Cochran's Q statistic. We also conducted a leave-one-out analysis by calculating the remaining SNP effect after excluding each SNP one by one. The leave-one-out method was used to evaluate whether significant SNPs affected our results when needed. A funnel plot was drawn to assess the existence of directional pleiotropy. The framework of the present research is displayed in Figure 1.

To ensure the reliability of the study results, we evaluated the influence of potential confounders. In the original study providing AFS GWAS data, researchers calculated the genetic association of AFS with six related categories containing 25 characteristics according to sex. Age at first menarche, age at menopause, age at starting oral contraceptives, teenage pregnancy, severe depression, weekly alcohol consumption, age at starting smoking, marijuana use, and body mass index (BMI) may serve as mediators of AFS contributing to migraine. However, the results of the overall genetic association revealed that AFS is genetically associated with age at smoking initiation and teenage pregnancy (11). In addition, we also searched for the genetic association of each IV and excluded IVs that were genetically associated with confounding factors. By excluding the abovementioned confounders, the reliability and stability of our present results were verified. PhenoScanner, a platform with comprehensive information on the association of genotype and phenotype (available at http://www.phenoscanner.medschl.cam.ac.uk), was used to query for traits related to the IVs ($P < 5\times10^{-8}$), and those IVs were subsequently excluded as potential pathways outside the AFS that may affect migraine. In previous MR studies, insulin-like growth factor 1 and diastolic blood pressure were found to be causally related to migraine, so we excluded SNPs associated with those traits (20, 21). Available studies have also shown that migraine is related to body fat percentage (22). Therefore, SNPs associated with those traits were also excluded. Finally, reverse MR was performed to evaluate whether migraine would affect AFS. Since migraine is a binary variable, in forward MR analysis, the results are presented in the form of odds ratios (ORs), which quantify the change in migraine risk with an additional increase in the standard deviation (SD) of the AFS. In reverse MR analysis, the results are presented as β values, which represent the number of SDs of AFS change caused by migraine.

Statistics

We calculated the power of the MR analysis using an online tool (23) (mRnd: Power calculations for Mendelian Randomization).[4] The basis of a type I error rate was set at 0.05. The proportion of variance explained by the SNPs for exposure was 5.8% (11). The detectable OR based on the GWAS of migraine with 80% power was less than 0.912 (or greater than 1.089) according to the calculation. The detectable ORs of MWA and MOA based on the GWAS were less than 0.869 (or greater than 1.132) and less than 0.857 (or greater than 1.143), respectively. All hypothesis testing was 2-sided. Given that stratified analysis was used, nine MR analyses were performed in this study. The nominal significance p-value was set to 0.05, and after Bonferroni correction, the p-value was adjusted to 0.05/9 (0.0056).

All the statistical analyses were performed using STATA 17.0 software (Stata Statistical Software: College Station, TX: Stata Corp LP) and R (version 4.3). MR analysis was conducted by the

4 cnsgenomics.com/

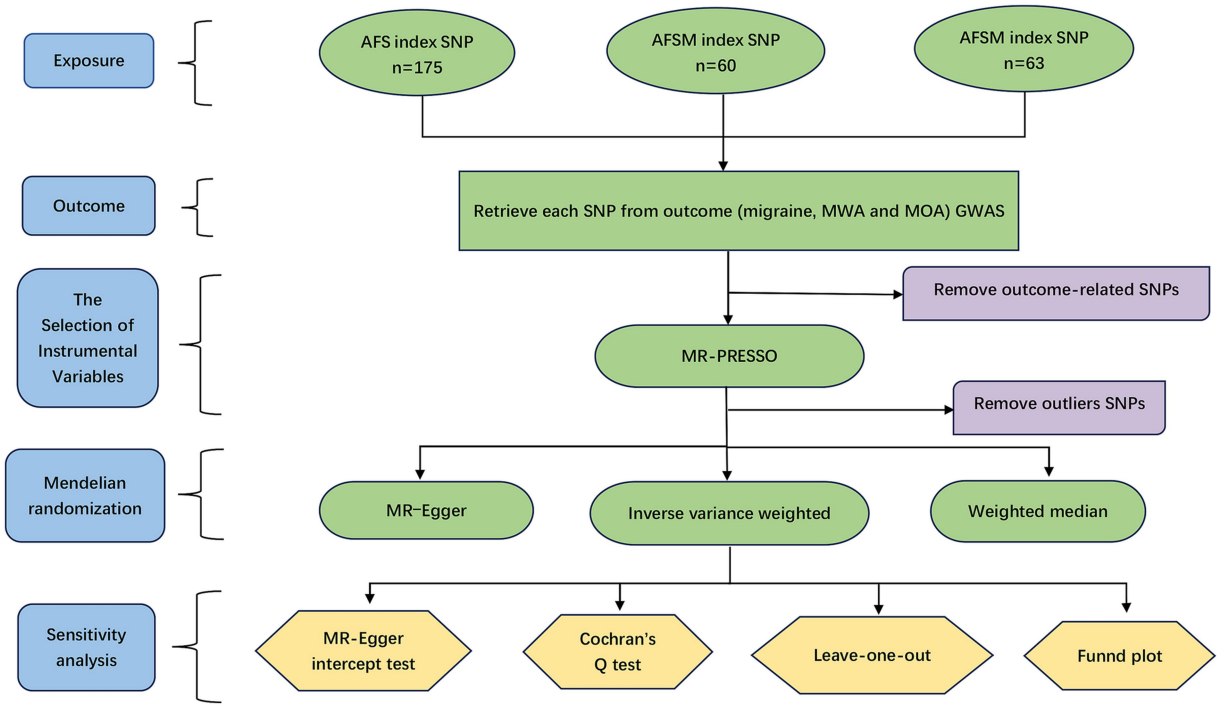

FIGURE 1
The research framework. AFS, age at first sexual intercourse; AFSM, age at first sexual intercourse of male; AFSF, age at first sexual intercourse of female; MWA, migraine with aura; MOA, migraine without aura; SNP, single nucleotide polymorphism.

TwoSampleMR (version 0.5.6), Mendelian Randomization (version 0.6.0) and MR-PRESSO (version 1.0) packages in R software. The execution date was May 2023.

Results

The migraine genetic data on a total of 397,338 unrelated European individuals (54% females and 46% males) from the GWAS Catalog and 306,314 individuals (including 6% patients and 94% control individuals) from the Finngen Biobank were ultimately included in the present study. Of the 16,516,521 SNPs, a total of 175 SNPs (including 32 proxy SNPs) were identified as strongly associated with AFS. The age at first sexual intercourse of males (AFSM) and females (AFSF) were included in 60 (including 11 proxy SNPs) and 63 (including 8 proxy SNPs) SNPs, respectively. These SNPs were not strongly associated with the outcomes ($p > 5 \times 10^{-8}$). The SNP information is displayed in Supplementary Tables 1–3.

Relationship between AFS and migraine

MR analysis showed that AFS had a significant causal relationship with migraine. The IVW method showed a significant result (OR = 0.73, 95% confidence interval [CI] [0.61 to 0.86], $p = 2.49 \times 10^{-4}$). Similar results were obtained using the weighted median method (OR = 0.76, 95% CI [0.61 to 0.95], $p = 1.33 \times 10^{-2}$). GWAS data with MWA and MOA outcomes were extracted from the Finngen Biobank for MR analysis. The results showed that AFS was significantly associated with both MWA (OR = 0.72, 95% CI [0.58 to 0.89], $p = 2.56 \times 10^{-3}$) and MOA (OR = 0.66, 95% CI [0.51 to 0.86], $p = 1.9 \times 10^{-3}$). The MR results are presented in Figure 2 and Supplementary Table 4.

Relationship between AFSM and migraine

The IVW results revealed a significant association between AFSM and migraine (OR = 0.71, 95% CI [0.59 to 0.84], $p = 1.22 \times 10^{-4}$). These positive results also appeared in the MR analysis for MWA (OR = 0.71, 95% CI [0.59 to 0.84], $p = 9.94 \times 10^{-4}$) and WOA (OR = 0.71, 95% CI [0.55 to 0.93], $p = 1.08 \times 10^{-2}$). The MR results are presented in Figure 2 and Supplementary Table 4.

Relationship between AFSF and migraine

Through MR analysis, we found a causal relationship between AFSF and migraine (the result of the IVW method showed OR = 0.73, 95% CI [0.61 to 0.89], $p = 1.69 \times 10^{-3}$). Stratified analysis determined that AFSF had a significant protective effect against both MWA (OR = 0.72, 95% CI [0.57 to 0.92], $p = 8.82 \times 10^{-3}$) and MOA (OR = 0.66, 95% CI [0.49 to 0.87], $p = 3.67 \times 10^{-3}$). The MR results are presented in Figure 2 and Supplementary Table 4.

For visualization of the results, we plotted scatter plots, which are displayed in Figure 3.

Sensitivity analysis

The MR–Egger method did not detect a significant association in any results of MR analysis. No horizontal pleiotropism was found in

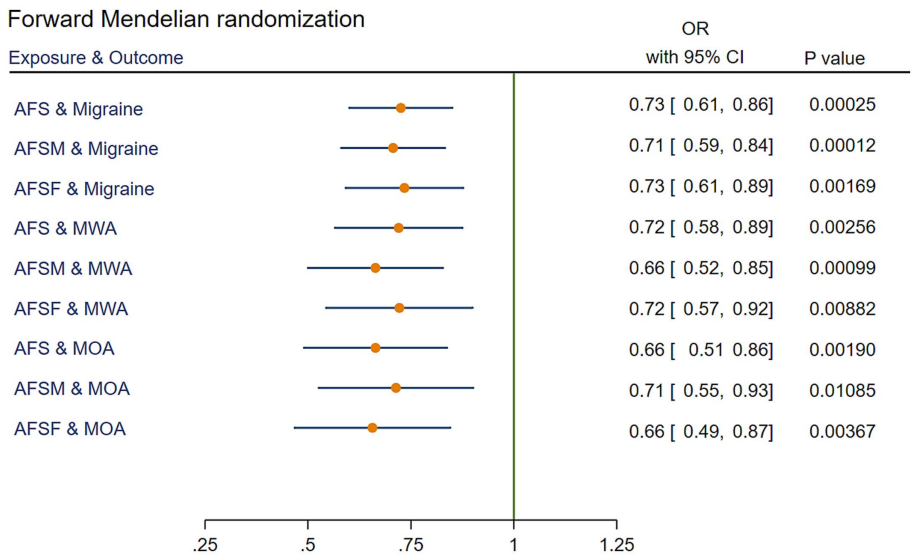

FIGURE 2
IVW results of forward Mendelian randomization. AFS, age at first sexual intercourse; AFSM, age at first sexual intercourse of male; AFSF, age at first sexual intercourse of female; MWA, migraine with aura; MOA, migraine without aura; MR, Mendelian randomization; IVW, Inverse variance weighted; OR, odds ratio; CI, confidence interval.

the MR–Egger regression ($P < 0.05$). Furthermore, the MR-PRESSO method did not identify any outlier SNPs. The results are presented in Supplementary Figure 1.

By using Cochran's Q statistic, we found heterogeneity in the results of AFS and migraine ($p = 4.02 \times 10–7$), AFSF and migraine ($p = 3.41 \times 10–2$), and AFS and MOA ($p = 2.16 \times 10–4$). There was no apparent heterogeneity in the other reported results ($p < 0.05$). The data are shown in Supplementary Figure 1.

The leave-one-out analysis did not reveal that any SNPs significantly impacted the results. The results of the leave-one-out analysis are shown in Supplementary Figure 2. No significant bias was found in the funnel plot, as shown in Supplementary Figure 3.

After excluding SNPs that may cause interference with confounding factors to migraine, the causal relationships in AFSM and MOA (OR = 0.83, 95% CI [0.60 to 1.14], $p = 2.43 \times 10^{-1}$) and AFSF and MWA (OR = 0.77, 95% CI [0.58 to 1.02], $p = 7.08 \times 10^{-2}$) were no longer statistically significant. The results are shown in Figure 4 and Supplementary Table 5.

Reverse MR analyses determined that migraine and the MOA had no significant impact on AFS, AFSF, or the AFSM (all $p > 0.05$). MWA had a nonsignificant effect on AFSF ($p > 0.05$). Due to the limitations of IVs, the impact of MWA on AFS and AFSF cannot be verified. The results are shown in Figure 5.

Discussion

To our knowledge, this is the first MR study to explore the causal relationship between AFS and migraine. Through two-sample Mendelian randomization analyses using data from large-scale GWAS databases, we determined that an earlier age at first sexual intercourse is related to susceptibility to migraine attack. To address clinical interest, we manually classified the exposures into AFS, AFSF, and AFSM. Correspondingly, the outcomes were classified into migraine, MWA, and MOA when performing pairwise MR analyses between each exposure and outcome. All the p values of the results were less than 0.05, except for two subgroups (AFSF and MOA and AFSM and MWA) whose p values did not meet the Bonferroni-corrected standard (adjusted $p < 0.0056$; see Supplementary Figure 4). Hence, the above results should be interpreted with caution, as the possibility of false-positive results produced by AFSF and MOA and AFSM and MWA might exist. As indicated by reverse MR analyses, migraine has no causal relationship with AFS. Then, the potential reciprocal effect between migraine and ASF could be excluded.

By excluding SNPs that are associated with other related factors of migraine, MR analyses on exposures and outcomes suggested that two results (AFSM and MOA and AFSF and MWA) were no longer statistically significant. After adjustment for age at menarche (a marker of puberty and estrogen changes), age of starting smoking, age of starting oral contraceptives, teenage pregnancy, and BMI in our analyses, the results of the mediation analyses still showed an association between AFS and migraine. This finding suggested that AFS is not merely an accompanying phenomenon influenced by factors such as puberty, hormonal changes, unhealthy behaviors (smoking, drinking), contraception, and pregnancy. In other words, the causal relationship between AFS and migraine is robust.

We determined that later AFS has a protective effect against migraine. This may be attributed to sexual intercourse leading to increased dopamine secretion in the hypothalamus, which increases the levels of cyclic adenosine monophosphate and protein kinase A (24, 25). Both are thought to be responsible for migraine attacks (26). Testosterone produced during sexual intercourse was found to increase the level of cyclic guanosine monophosphate, which is thought to be another contributor to MOA attacks (27, 28). Finding from an animal study has shown that mice experience a decrease in the trigeminal pain threshold and an increase in photosensitivity during the estrus phase, indicating that sexual activity may trigger migraine attacks as early as during the estrus phase (29). In addition,

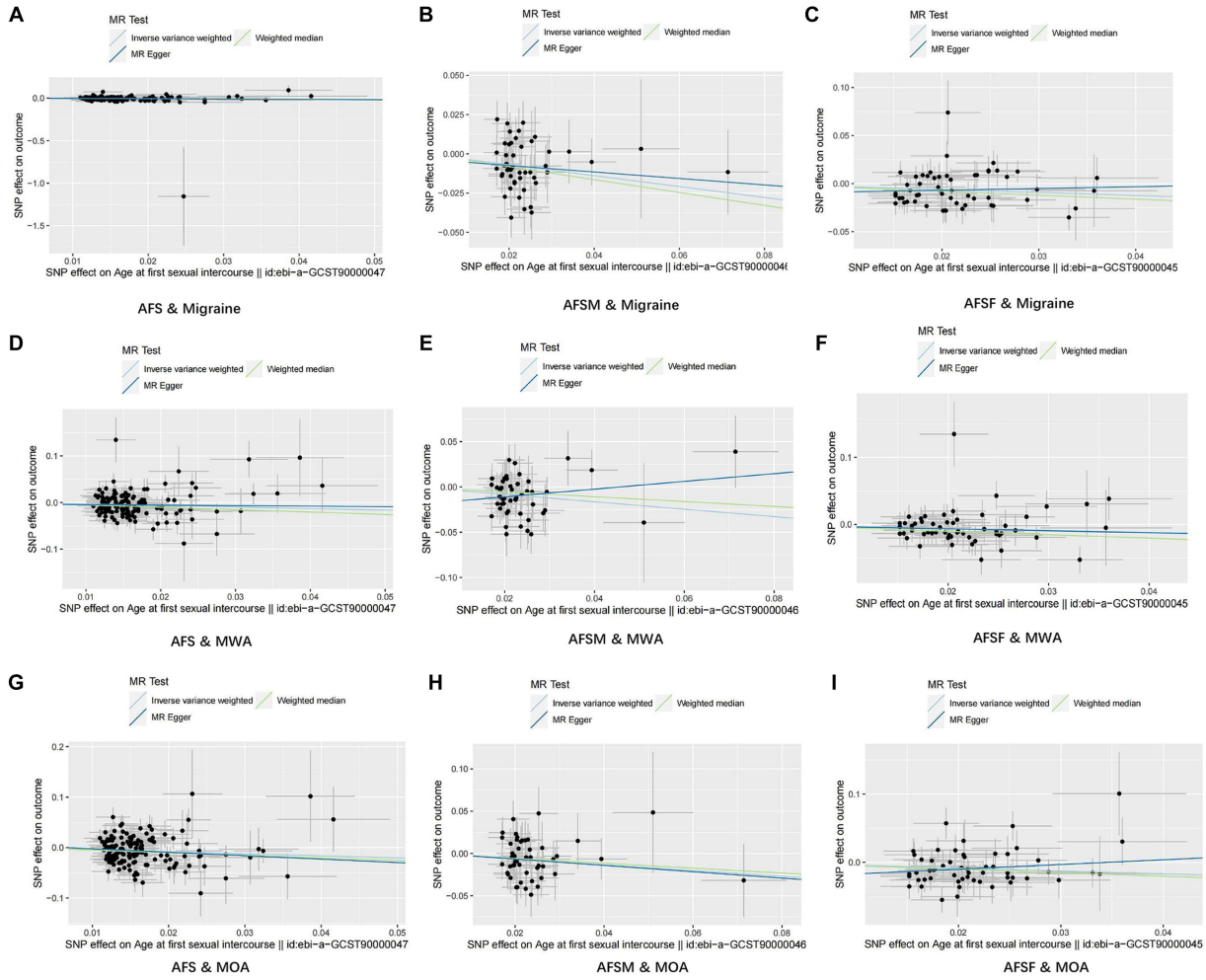

FIGURE 3
Results of scatter plots. **(A)** AFS & Migraine; **(B)** AFSM & Migraine; **(C)** AFSF & Migraine; **(D)** AFS & MWA; **(E)** AFSM & MWA; **(F)** AFSF & MWA; **(G)** AFS & MOA; **(H)** AFSM & MOA; **(I)** AFSF & MOA. AFS, age at first sexual intercourse; AFSM, age at first sexual intercourse of male; AFSF, age at first sexual intercourse of female; MWA, migraine with aura; MOA, migraine without aura.

penile-vaginal intercourse increases parasympathetic activity, which induces migraine by promoting the degranulation of mast cells (30, 31). Observational studies have shown a bilateral association between HAWSA and migraine (5). One study also reported patients who experienced migraine aura during sexual climax (32). All the above mentioned mechanisms theoretically supported the rationality of our present findings, and it is reasonable to believe that sexual activity has the potential to promote the occurrence of migraine.

In the stratification analysis, we found that a later AFS has a protective effect on MWA. Apart from the mechanism of migraine attack mentioned above, cortical spreading depression (CSD) inhibition is considered the main physiological mechanism of MWA, and susceptibility to CSD is modulated by hormones (ovarian and testicular) (33). Therefore, it is reasonable to infer that experiencing sexual activity at an early age involves migraine attack mechanisms, including migraine with aura. Delaying AFS is suggested for individuals with a high risk of migraine.

Another potential mechanism attributed to AFS and migraine may be related to the involvement of pituitary adenylate cyclase-activating polypeptide (PACAP), an essential target for migraine (34). In addition, PACAP is involved in the spermatogenesis process of mice (35), as well as in the production of steroids and the development of ovarian follicles (36). With premature sexual intercourse, the process of sperm production and the secretion of sex hormones are more frequently activated, hence promoting the increased synthesis of PACAP and thereby inducing migraine.

Our present finding on the causal relationship between AFS and migraine attacks could also be supported by real-world studies with respect to lifestyle changes. A cross-sectional study in Denmark revealed that AFS was associated with emergency contraceptive pill use (37). When hormonal contraceptive users are not taking hormonal contraceptives, migraine attacks worsen and last longer (38). Moreover, AFS will cause teenagers to bear more psychological pressure and feelings of vulnerability, which is considered a trigger factor for migraine (39, 40). Despite this indirect evidence, our present findings need future confirmation in a cohort study.

Sensitivity analysis was performed using conventional analysis methods and adjusted for the definition of association between exposure and SNPs. The MR-PRESSO method did not reveal evidence suggesting horizontal pleiotropy, indicating that the IVs did not affect migraine

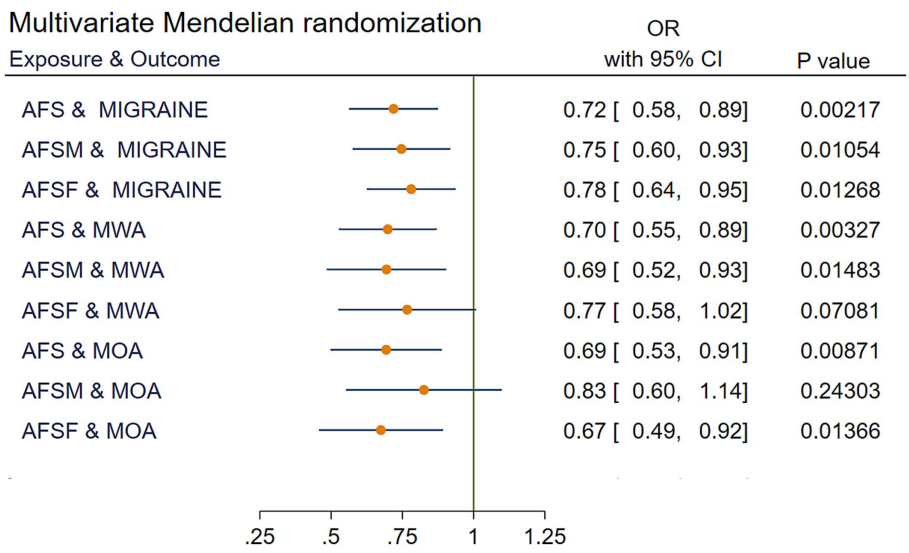

FIGURE 4
IVW results of multivariate Mendelian randomization. AFS, age at first sexual intercourse; AFSM, age at first sexual intercourse of male; AFSF, age at first sexual intercourse of female; MWA, migraine with aura; MOA, migraine without aura; MR, Mendelian randomization; IVW, Inverse variance weighted; OR, odds ratio; CI, confidence interval.

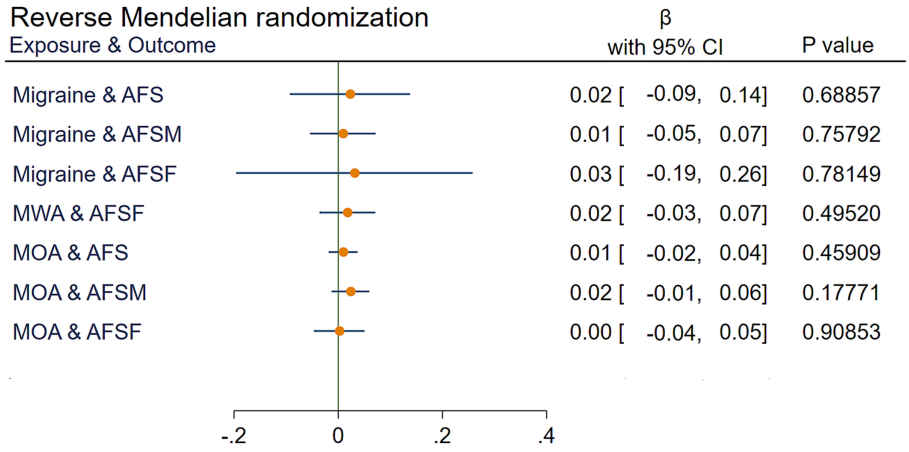

FIGURE 5
IVW results of reverse Mendelian randomization. AFS, age at first sexual intercourse; AFSM, age at first sexual intercourse of male; AFSF, age at first sexual intercourse of female; MWA, migraine with aura; MOA, migraine without aura; MR, Mendelian randomization; IVW, Inverse variance weighted; β, the estimated effect; CI, confidence interval.

through pathways other than AFS. When Cochran's *Q* test was used to explore heterogeneity across genetic variants in subgroups of AFS and migraine, AFSF and migraine, and AFS and MOA, we adopted a random-effects model to reduce the impact of heterogeneity on the results. By using leave-one-out analysis, we found that no single IV influenced the results, thus indicating the robustness of our results. Furthermore, there was an absence of directional pleiotropy, as exhibited in the funnel plot. Taken together, the sensitivity analyses verified that our present MR analysis results are reliable and stable.

Our research provides valuable recommendations for clinical work. First, AFS may participate in migraine attacks mediated through multiple pathways, including PACAP, dopamine and sex hormones. In addition, migraine sufferers, especially adolescents and those at high risk for migraine, are not encouraged to engage in sexual activity at an early age. Finally, well-designed cohort studies are encouraged in the future to explore the relationship between sexual activity and migraine. Taken together, these findings suggest that delaying the age at first sexual intercourse is recommended for adolescents. Patients with HAWSA might have a higher risk of migraine, but this topic needs further investigation in the future through prospective cohort studies.

There should be an awareness of the limitations of the present study. First, the GWAS data derived from European populations limit the generalization of our findings to people of other ethnic groups. Second, we were unable to assess the impact of unmeasured confounders on the results, which is encountered as a challenging issue in almost all MR analyses. Third, as information on the exact age

at first sexual intercourse was not available from GWAS data, we could not provide a particular recommendation on age at which sexual activity commenced. Finally, the diagnosis of migraine or MWA based on the ICD code is sometimes uncertain due to the retrospective design of the study, which may lead to overestimation of the disease. Notably, the FinnGen study identified disease traits with several healthcare registries (i.e., Drug Purchase and Drug Reimbursement and Digital and Population Data Services Agency, Digital and Population Data Services Agency, Statistics Finland; Register of Primary Health Care Visits, Care Register for Health Care; and Finnish Cancer Registry). Diagnosis of migraine may largely relay on physicians rather than according to the International Classification of Headache Disorders criteria by neurologists. All these may contribute to the higher proportion of MWA observed in the FinnGen study.

In conclusion, a causal relationship between genetically delayed age at first sexual intercourse and decreased risk of migraine is uncovered through our present MR analysis, which indicates the presence of extracranial regulatory pathways of migraine and needs further determination in future real-world investigations.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This study is a secondary analysis of centralized data from public databases, and the experiments providing this data have been approved by an ethical review and the participants' consent. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

GZ: Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft. MW: Data curation, Resources, Supervision, Validation, Writing – review & editing. YW: Supervision, Validation, Visualization, Writing – review & editing. FK: Conceptualization, Funding acquisition, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1347831/full#supplementary-material

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Efficacy of cranial electrotherapy stimulation in patients with burning mouth syndrome: a randomized, controlled, double-blind pilot study

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Background: The Burning mouth syndrome (BMS) is a chronic pain syndrome characterized by a burning sensation in the oral mucous membranes. The etiology and pathophysiology of BMS is largely unexplained. To date, there is no evidence-based treatment strategy for BMS. Cranial electrical stimulation (CES) represents a non-invasive treatment option with a low side effect profile that is approved for the treatment of pain, depression, anxiety disorder and insomnia. It has shown efficacy in studies for chronic pain such as fibromyalgia and neuropathic pain after spinal cord injury. This study aimed to investigate the therapeutic effectiveness of CES in combination with local transcutaneous electrical nerve stimulation (TENS) as an adjunct therapy in patients with BMS compared to sham stimulation.

Methods: This randomized, double-blind, sham-controlled pilot study enrolled 22 patients, aged 18 years and over, with the diagnosis of BMS meeting the ICHD-3 criteria from August 2020 to June 2021. The study duration was 4 weeks (28 days) per participant. After randomization, the active group participants ($n = 11$) received a 100 µA CES treatment for 60 min a day whereas the devices in the Sham group did not emit electricity. Simple linear regression was used to determine whether the interventions promoted significant differences in pain intensity.

Results: The linear regression showed that the period of stimulation significantly predicted decrease in the intensity of pain in the active group [$\beta = -0.036$; $t(26) = -7.219$; $p < 0.001$] as in the sham group [$\beta = -0.026$; $t(26) = -2.56$; $p < 0.017$]. With the applied cutoff of 30% pain reduction within the stimulation period, both the active and sham groups had 36% responders ($n = 4$) (Fisher's exact test, $p = 1.00$). In both groups (active stimulation and sham group), a significant decrease in the intensity of pain, somatic symptoms and an improvement in sleep quality over the study period was observed. Subjects reported no adverse events during the study.

Conclusion: Although CES is an easily applicable and safe therapeutic option for chronic facial pain, active stimulation was not superior to sham stimulation. Among other reasons, this could be due to the short double-blinded treatment period, duration of the daily stimulation session or the small sample size.

KEYWORDS

facial pain, headache, burning mouth syndrome (BMS), cranial electrotherapy stimulation (CES), transcutaneous electrical nerve stimulation (TENS), Glossodynia, chronic pain, neuropathic pain

Background

Burning mouth syndrome (BMS) is a poorly understood chronic pain disorder characterized by an intraoral burning sensation in the absence of any identifiable organic cause according to the International Headache Society classification (ICHD-3) (1).

The prevalence of BMS in the population ranges from 0.7 to 15%, depending on the diagnostic criteria used, with postmenopausal women being more frequently affected (2). The average age of BMS patients is 61 years. It is assumed that there is a male-to-female ratio of 1:5–1:7, and the prevalence seems to increase with advancing age in both genders (3, 4).

According to the current ICHD-3 classification the burning pain is felt superficially in the oral mucosa, recurring daily for more than 2 h per day over more than 3 months. In the physical examination, the oral mucosa has a normal appearance and clinical findings including sensory testing are normal (1).

The painful sensation predominantly affects the tongue (67.9%), with the anterior two-thirds of the tongue being most commonly affected. However, it may also extend to other regions of the oral mucosa, including the floor of the mouth and the lips (5). The pain experienced typically ranges from moderate to severe intensity, quantified within a range of 3.1–5.11 on the Numeric Rating Scale (NRS) (5). The most frequently described accompanying symptoms are a dry mouth (xerostomia), described in 46–70% of cases, followed by taste disturbances (5). Psychosocial and psychological comorbidities manifest in 85% of cases, with anxiety disorders and depression being particularly common (2). BMS Patients often report a bad sleeping quality (6). The consumption of foods with high acidity, spiciness, or temperature exacerbates the discomfort. Chewing gum and mouth rinses use to alleviate the pain (5).

The etiology and pathophysiology of BMS remains mostly unknown. Pathophysiological concepts include peripheral and central mechanisms. Neurophysiological concepts include damage to the chorda tympani, damage to the lingual nerve (a branch of the trigeminal nerve that supplies the oral mucosa), peripheral small-fiber polyneuropathy, altered cortical networks involving the "pain matrix" and descending inhibitory pathways as well as impaired dopaminergic inhibition (1, 6). A biopsy study by Lauria et al. on 12 BMS patients demonstrated a significant reduction in epithelial and subpapillary nerve fibers in the lingual mucosa, which strengthens the hypothesis of small-fiber polyneuropathy (7). There also appears to be a strong interaction with psychological factors, especially depression and anxiety disorders (8, 9).

On the other hand, "secondary" BMS is attributed to identifiable local or systemic factors. Local factors include odontogenic diseases, mechanical and chemical irritants, viral, bacterial, or fungal infections, as well as hypersensitivity reactions. Systemic factors may be induced by drugs, anemia, vitamin B12 or folic acid deficiency, Sjögren's syndrome, and diabetes mellitus (2). In this study, we adopted the ICHD-3 classification, in which BMS is diagnosed only after ruling out all potential local and systemic causes. BMS-like symptoms that can be attributed to the aforementioned factors should be labeled as symptomatic BMS and be treated with a targeted therapy for the causing factor (1).

A therapeutic strategy for BMS based on evidence from studies is missing. The treatment approaches can be differentiated into symptomatic and topical therapies. Topical treatments include capsaicin and benzodiazepines, systemic treatments pregabalin, gabapentin or tricyclic antidepressants like amitriptyline. Given the large psychiatric comorbidity, cognitive behavioral approaches complement pharmacologic treatments. Multimodal, multidisciplinary therapy with pharmaceutical and psychosocial approaches seems to be most effective. However, the evidence regarding the success of these treatment options is limited (2, 5). Cranial electrical stimulation (CES) is a non-invasive procedure involving transcutaneous application of pulsed, low amplitude (<1 mA) electrical voltage via electrodes to the earlobes. CES received FDA (Food and Drug Administration) approval in 1979 for the treatment of depression, anxiety disorder and insomnia (10). The exact mechanism of action of CES is unknown. Studies have shown that CES can affect the blood levels of various neurotransmitters, such as beta-endorphin or serotonin, and may act via the limbic system, the reticular ascending system (RAS) and the hypothalamus (11, 12). Changes in the EEG after CES use have been observed, including an increase in alpha and a decrease in beta and delta activity. These alterations indicate a possibly improved relaxation. CES also appears to influence the brain's default mode network (DMN) (13), which is significantly activated by serotonin and whose connectivity is altered in depression, sleep disorders, anxiety disorders and pain (13, 14). Many studies have investigated the benefits and effectiveness of CES. Also, in randomized, double-blind, controlled clinical trials, a positive effect for CES on pain was shown in patients with fibromyalgia (15) and in neuropathic pain after spinal cord injury (12). There is also supporting evidence for the amelioration of psychological comorbidities, which are highly

Abbreviations: BMS, Burning Mouth Syndrome; CES, Cranial electrotherapy stimulation; EQ-5D-3-L, European Quality of Life 5 Dimensions 3 Level Version; FDA, Food and Drug Administration; HADS, Hospital Anxiety and Depression Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; IASP, International Association for the Study of chronic Pain; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10 Version; ICHD-3, International Classification of Headache Disorders 3. Version; IHS, International Headache Society; NRS, Numeric Rating Scale; OHIP-G, Oral Health Impact Profile Germany; PDI, Pain Disability Index German Version; PHQ-D, Patient Health Questionnaire – German Version; PSQI, Pittsburgh Sleep Quality Index; SF-MPQ-D, Short Form McGill Pain Questionnaire German Version; TAS 26, Toronto Alexithymia Scale; TENS, Transcutaneous Electrical Nerve Stimulation.

prevalent among individuals with BMS, through CES. In a randomized, double-blind, controlled clinical trial, Barclay and Barclay showed significant improvement after CES in patients with anxiety disorder and comorbid depression (11).

In Transcutaneous electrical nerve stimulation (TENS) electrical currents are delivered to the skin through surface electrodes for pain relief.

The precise mechanism of TENS is not fully understood. Its analgesic effect is believed to be complex, involving peripheral, spinal, and supraspinal mechanisms. Animal studies demonstrated that the analgesic effect was partly mediated by peripheral mechanisms like a decreased peripheral response to serotonin and changes in antinociceptive α2A-adrenergic receptors (16). A spinal effect for electrical stimulation was initially demonstrated by Melzack and Wall's Gate Control Theory which suggests that afferent fibers can inhibit nociceptive activity in the dorsal horn of the spinal cord, resulting in reduced pain perception (17). Animal studies also indicate changes in neurotransmitter levels like GABA and Glycine associated with TENS (18, 19). Regarding central mechanisms, there is a suggestion that TENS stimulates descending inhibitory nerve pathways and increases the release of endorphins (20). Positive effects of TENS on pain have been demonstrated in patients with fibromyalgia (21) and neuropathic pain after spinal cord injury (22). Additionally, TENS has shown efficacy as a therapeutic option in trigeminal neuralgia, migraine, and cluster headache (23–27).

In this study we aimed to investigate the therapeutic effectiveness of CES in combination with local TENS as an adjunct therapy in patients with BMS compared to sham stimulation. We assessed the impact on pain intensity, sleep quality, and psychological comorbidities, such as somatic symptoms disorder, depression and anxiety disorders.

Methods

Participants

Subject recruitment was carried out at the University Medical Centre Rostock through the Department of Oral, Maxillofacial, and Facial Plastic Surgery and the Headache Centre North-East. Inclusion criteria included a physician-diagnosed BMS according to the ICHD-3 criteria of the IHS, a minimum age of 18, stable pain and antidepressant medication for at least 1 month (or the absence of such medication), and the commitment of subjects not to alter their medication during the study. Exclusion criteria included active implants (e.g., pacemakers, defibrillators), pregnancy or lactation, and limited contractual capacity.

Intervention

The study utilized "Alpha-Stim M" devices from "Electromedical Products International, Inc." Fifty percent of the devices provided active stimulation with a current of 100 µA and 0.5 Hz, while the remainder served as sham stimulators without any current emission. Patients applied daily 60-min CES to the auricular lobules, along with a 3-min TENS of the tongue, over a 28-day period. To monitor in-home stimulation, we employed a tracking system, and patients were required to document the execution and effects of the stimulation in their pain diary daily.

Design

At the initial appointment, subjects were extensively briefed on the study procedure, potential side effects, and risks of CES in a medical consultation. After assessing the inclusion and exclusion criteria and obtaining written consent, subjects received an introduction to CES stimulation and were guided through a self-administered trial stimulation. Furthermore, at the baseline (day 0) and the end of the study (day 28), patients completed the following questionnaires: The Pittsburgh Sleep Quality Index (PSQI) was utilized for sleep assessment, the Oral Health Impact Profile (OHIP-14) served as an oral health evaluation, and for the assessment of somatic symptoms, the Somatic Symptom Module of the Patient Health Questionnaire (PHQ) was employed. To evaluate anxiety and depression, the following questionnaires were utilized: the Patient Health Questionnaire for Depression (PHQ-D), Hamilton Rating Scale for Depression (HAMD), Hamilton Anxiety Rating Scale (HAMA), and Hospital Anxiety and Depression Scale (HADS). The study duration was 4 weeks (28 days) per subject. A paper diary was used daily to characterize pain. The reported daily maximum pain score on the NRS before stimulation served for subsequent evaluations of the stimulation's impact on pain, which is the primary outcome of this study. Additionally, interference, pain-amplifying and alleviating factors, accompanying symptoms, and medication usage were documented. Furthermore, the diary recorded details about the stimulation, including its effects and side effects. After 1 week (Day 7), a follow-up appointment was conducted to inquire about the subjects' use of CES and address any questions they might have had. Due to the COVID-19 pandemic, this appointment was conducted via telephone. After the 4-week study period, a final evaluation meeting took place to assess the stimulation, review the pain diary, and readminister the questionnaires. The study timeline is visualized in Figure 1.

Outcomes

The primary outcome of the study was to explore therapeutic effects of CES on pain in patients with BMS, in comparison to sham stimulation. As a secondary outcome, the study investigated its effects on sleep quality and mental health.

Statistical analyses

The SPSS version 27 statistical package for Microsoft Windows was used to analyze the data (28). Qualitative variables were represented by their absolute (n) and relative (%) frequencies, mean and standard deviation. Homogeneity of the study groups on day 0 (baseline) in their variables was tested with t-tests. Simple linear regression was used to evaluate the association between duration of stimulation (measured in days) and pain intensity (measured in the NRS score). Changes of scores a two-way ANOVA with repeated measures was used to examine the interaction of time (baseline and day 28) and group (real stimulation and sham stimulation). To

compare the rate of responders Fisher's exact test was used. A probability of less than $p \leq 0.05$ was regarded as significant.

Blinding

Blinding was carried out by the company and was only disclosed to the clinical staff upon completion of the study for data analysis. The devices shared identical appearances and controls, rendering them indistinguishable externally.

Ethical aspects

The research was conducted in accordance with the declaration of Helsinki and approved by the Ethics committee of the University Medical Center Rostock (A2020-0138). All study participants were provided with written information about the study procedure prior to inclusion in the study and gave their informed consent before participating in the study.

Pseudonymization was implemented.

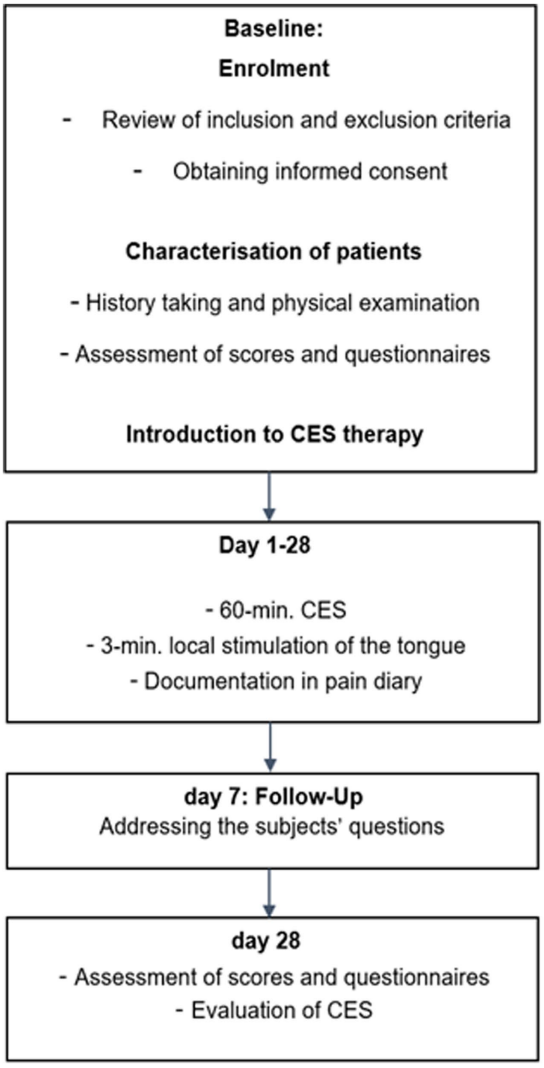

FIGURE 1
Study timeline.

Results

The process of patient recruitment is shown in Figure 2. At the onset of recruitment, there were 101 potential study participants with BMS. Out of these, 22 patients met the inclusion criteria and none of them discontinued the study. The average age of the entire group was 64 years, with 77% of the patients being female. Demographic and clinical characteristics of patients are summarized in Table 1.

Pain

Pain was mostly described as a burning sensation in the tongue, with a moderate intensity ($M \pm SD = 4.50 \pm 2.3$). Nineteen out of the 22 patients reported daily pain localization in their headache diaries, with the tongue being the most frequently affected location (63%, $n = 12$). During patient history assessments, all 22 patients described their pain as "burning." There were no significant differences between the active and sham groups. The most frequently mentioned accompanying symptoms were xerostomia, taste disturbances, and sensory distortions. Most frequent pain triggers reported by patients included spicy, acidic, hot, sweet and cold food and stress. The most frequently mentioned pain-relieving factors were chewing gum, mouth rinses food and fluid intake (Supplementary Tables S1, S2). Simple linear regression showed that the period of stimulation significantly predicted decrease in the intensity of pain in the active group [$\beta = -0.036$; $t(26) = -7.219$; $p < 0.00$] as in the sham group [$\beta = -0.026$; $t(26) = -2.56$; $p < 0.017$]. The results are visualized in Figure 3 and summarized in Table 2. An identification of responders and non-responders was conducted. Using the applied cut-off of 30%

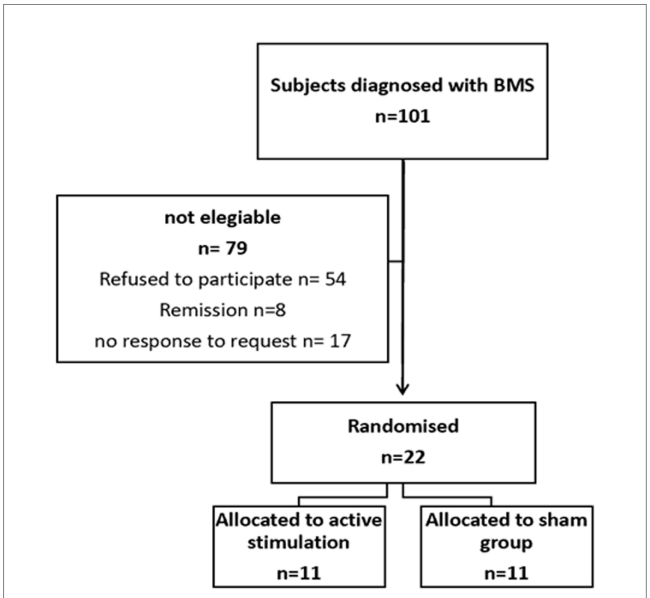

FIGURE 2
Enrolment of patients.

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TABLE 1 Demographic and clinical characteristics of patients.

Characteristics		Stimulation group (n = 11)	Sham group (n = 11)	Total (n = 22)
Sex female, (%)		85.7	88.9	87.5
Age in y, mean (SD)		63.09 ± 13.69	63.09 ± 8.71	63.09 ± 2.3
Duration of illness in years, mean (SD)		5.95 ± 7.29	6.20 ± 5.63	6.07 ± 1.35
Medication, (%)	Pregabalin	9.1	0	4.5
	NSAR for facial pain	0	18.2	9.1
	Antidepressant medication	18.2	0	9.1
Oral and maxillofacial disorders, (%)	None	81.8	72.7	68.2
	HO dental surgery	9.1	27.3	18.2
	Craniomandibular dysfunction	9.1	0	4.5
Neurological disorder (%)	None	63.6	72.7	68.2
	Episodic migraine	27.3	9.1	18.2
	Tinnitus	9.1	9.1	9.1
	HO stroke	0	9.1	4.5
Diagnosed psychiatric disorders, (%)	None	81.8	90.9	86.4
	Depression	18.2	0	9.1
	Somatic symptom disorder	0	9.1	4.5
Metabolic disorders, (%)	Morbus Fabry	9.1	0	4.5
	Hypothyroidism	0	9.1	4.5
Rheumatic diseases, (%)	Rheumatoid arthritis	0	9.1	4.5
	CREST-syndrome	9.1	0	4.5
Cardiovascular diseases, (%)	Arterial hypertension	36.4	63.6	50
Musculoskeletal disorders, (%)	Spinal stenosis	9.1	18.2	13.6
	Herniated disc	9.1	9.1	9.1
	Leg length discrepancy	9.1	0	4.5
	Osteoarthritis	9.1	0	4.5
Gastrointestinal disorders, (%)	HO gastritis	0	27.3	13.6
	Gastroesophageal reflux	18.2	0	9.1
Gynecological Comorbidities, (%)	HO carcinoma	0	18.2	9.1
	HO hysterectomy	18.2	0	9.1
Chemotherapy, (%)	HO chemotherapy	0	9.1	4.5

HO, "history of".

pain reduction at the end of the stimulation period, both the active and sham groups had 36% responders ($n = 4$) (Fisher's Exact Test, $p = 1.00$).

Psychiatric comorbidities

Patients had a high prevalence of psychiatric comorbidities. The prevalence of somatic symptoms was high. 45% ($n = 10$) of the subjects had mild somatic symptoms, 18% ($n = 4$) moderate somatic symptoms and 23% ($n = 5$) severe somatic symptoms. In the overall study population, a statistically significant decrease in the somatic symptom disorder scores over the study period [$F(1, 20) = 4.91$; $p = 0.039$; $\eta^2 = 0.20$] was observed. However, no significant difference was observed between the active and sham stimulation [$F(1, 20) = 0.24$; $p = 0.628$; $\eta^2 = 0.01$] Applying the official cut-offs, 41% ($n = 9$) had a mild anxiety severity, 14% ($n = 3$) a moderate anxiety severity, and one patient had severe anxiety symptoms. No statistically significant change in the anxiety scores was observed over the study period [$F(1, 20) = 0.86$; $p = 0.364$; $\eta^2 = 0.04$]. 41% ($n = 9$) of the subjects were mild depressed and 18% ($n = 4$) were moderate depressed. No statistically significant change of depression was observed over the study period [$F(1, 20) = 0.80$; $p = 0.381$; $\eta^2 = 004$]. There was no statistically significant difference between the groups at the baseline for the assessed scores.

Sleeping disorders

Compared to the general population the sleeping quality was poorer. According to the general cut-off. Only 23% ($N = 5$) had a good

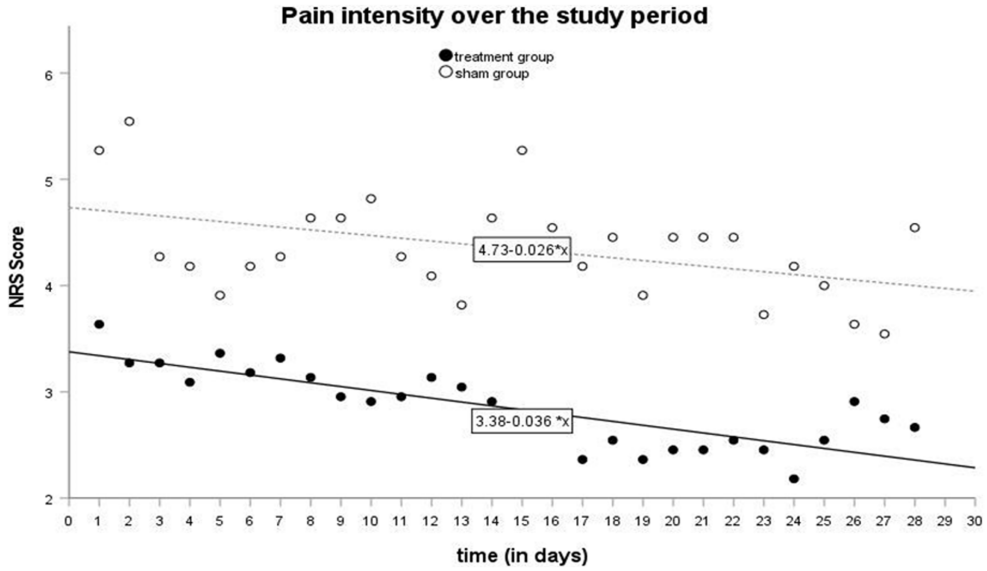

FIGURE 3
Pain intensity over the study period.

TABLE 2 Regression analyses summary (Association between duration of stimulation and pain intensity).

	Stimulation group			Sham group		
	Unstandardized		Standardized	Unstandardized		Standardized
	B	SE	Beta	B	SE	
Constant	3.377***	0.084		4.734***	0.170	
Day	−0.036***	0.005	−0.817***	−0.026**	0.010	−0.449**
R^2	0.667			0.201		
Adj. R^2	0.654			0.171**		
F (df 1; 26)	52.110***			6.552		

**$p < 0.05$; ***$p < 0.001$.

sleeping quality, 50% ($N = 11$) had a bad sleeping quality and 27% ($N = 6$) have a clinically relevant sleep disorder. The subjects in the active group had a better sleeping quality at baseline [$t(20) = -2.75$; $p = 0.012$]. The sleeping quality statistically significant improved in both groups [$F(1, 20) = 13.21$, $p < 0.05$; $\eta^2 = 0.40$]. However, there was no difference between the active and the sham group [$F(1, 20) = 3.06$; $p = 0.095$; $\eta^2 = 0.13$].

Oral health

The examined BMS patients had poor oral health-related quality of life. There was no statistically significant difference between the groups. The values were at the 80th percentile or higher for all three categories of dental status. There was no statistically significant improvement in oral health in both groups.

Patient's evaluation

The results in the evaluation regarding improvements in pain, sleep quality, psychological well-being, and overall improvement ranged between categories (3) "no change" and (4) "mild improvement" in both groups. There were no statistically significant differences between the groups in any of these variables. The patients were "neither nor" and "moderately satisfied" with CES. Consequently, only 28% of both the sham and active groups would recommend CES as a treatment option.

Tolerability and safety

None of the patients reported severe adverse events during TENS or CES. Stimulation was never discontinued due to side effects. The most common side effect was localized tingling.

Discussion

CES represents a non-invasive treatment option with a low likelihood of severe adverse events. Over the study period, both groups experienced a significant reduction in pain. However, superiority of active stimulation over sham stimulation could not be demonstrated. Other studies have shown a significant reduction in

pain intensity through CES in chronic pain syndromes, such as fibromyalgia or pain in Parkinson's disease (15, 29, 30). TENS as well has demonstrated efficacy in individuals (21), neuropathic pain after spinal cord injury (22) and various types of headaches in clinical studies (23–27). As TENS and CES share similarities in their application, mechanisms, and effects, there is a potential for a synergistic analgesic effect. Additionally, there could be an additional local effect through the TENS stimulation directly on the tongue, where the main symptoms of BMS are located. However, in our study, the patients' evaluation at the end of the study period indicates that the modest improvements were not significant enough to create a subjective sense of improvement for the majority of the patients. Many BMS patients had a long history of unsuccessful treatments, leading to a high burden of disease and therefore high hope for an improvement. When this improvement does not occur in the expected intensity, it can reinforce the already felt frustration. It is known that BMS patients tend to catastrophize (31). Catastrophizing has been defined as an exaggerated negative orientation toward pain stimuli and pain experience (32). It affects the modulation of pain stimulus, the way patients cope with their pain, and the response to the treatment (33). These aspects could have been a reason that the patients did not perceiving little changes and evaluated the stimulation rather negative. The subjects for the study were recruited via the Headache Centre and the Department of Oral and Maxillofacial Surgery at Rostock University Medical Centre, so that a selected clientele was probably included in the study. The patients were often severely affected and had remained refractory to previous treatment attempts.

Another factor that influenced the results is the placebo effect, which is often particularly strong in patients with pain and can pose a methodological problem in the control group, especially in stimulation studies. In other BMS studies, a significant placebo effect has been reported, ranging from 15 to 75% (34). Barcley et al. conducted a 5-week randomized, double-blind, placebo-controlled study to evaluate the efficacy of CES for various anxiety disorders and comorbid depression. Patients in the active group received 60 min of stimulation over the course of 5 weeks, and their symptoms were assessed using the HAMA and HAMD. They found a significant decrease of anxiety and comorbid depression scores in the active group. However, a significant increase of 28% in anxiety scores was also observed in the sham group. The authors attributed this result to the placebo effect (11).

Also in chronic migraine, another chronic pain condition with a similar spectrum of especially psychiatric comorbidities, a substantial placebo effect is often observed. The reported placebo effect in the acute treatment of migraine attacks is up to 47% and in migraine prophylaxis usually between 20 and 40% (35).

The choice of sham stimulation can pose a methodological problem, as shown in the study by Straube et al. who investigated the efficacy of transcutaneous stimulation of the auricular branch of the vagus nerve in chronic migraine patients. Active stimulation with a 1 Hz frequency was used in the control group, which surprisingly proved to be more effective than the stimulation at 25 Hz in the active group. The authors initially expected the 25 Hz stimulation to be more effective, and the 1 Hz frequency was primarily planned for blinding purposes only. It remains unclear whether this result was due to a placebo effect or if the frequency was already high enough to induce a therapeutic effect (36). Although we chose inactive devices for the control group to avoid this effect in our study, including a non-intervention group would have provided additional information for both studies. As it helps to evaluate whether the stimulation process itself induced the reduction in pain intensity or a placebo effect. As a secondary endpoint, our study investigated the impact of CES on psychiatric comorbidities and sleep. At the baseline a greater number of patients in the active group were utilizing antidepressants and pregabalin. Nevertheless, considering the limited potential for neuromodulation devices to interfere with concurrent treatments or associated comorbidities, this is expected to have a relatively modest effect (10, 37, 38). Despite the presence of high psychosomatic comorbidity in our study population, there was no significant decrease in depression and anxiety scores between the beginning and end of the study either. This differs from numerous other studies that have described CES as a good treatment option for psychiatric conditions (10, 39, 40). However, contradictory and heterogeneous results are also described in the literature. In a Cochrane Review, O'Connell et al. concluded that the evidence was insufficient to support the use of CES for depression due to the low quality of the studies (41). The FDA also reached a similar conclusion in December 2019 stating that effectiveness of CES for the treatment of depression was "unclear." They noted significant limitations in the quality of available clinical studies and a lack of high evidence results regarding the use of CES in patients with depression or sleep disorders (42). In summary, the evidence regarding the effectiveness of CES for psychiatric conditions is heterogeneous and does not allow a definitive judgment. Kirsch and Gilula conclude in a meta-analysis on the use of CES for insomnia that CES is an excellent treatment option for patients with insomnia. The review examined 20 studies using CES for the treatment of patients with primary insomnia, as well as with insomnia occurring as a comorbidity with psychiatric and pain-related disorders (39). We observed an improvement in sleep quality in some patients. However, in comparison to other studies, the observed effect was small, and no advantage of active stimulation over sham stimulation could be observed.

Limitations

As the study was designed as a pilot study, we considered the sample size of 22 as sufficient given the difficult recruiting during the COVID19 pandemic. Nevertheless, this small sample size limits the interpretation of the results. This is a common problem in studies with CES, so the literature on the effects of CES is dominated by small studies with unclear risk of bias (41, 42). The study was carried out by the Headache Centre Rostock in collaboration with the Department of Oral, Maxillofacial, and Plastic Surgery in Rostock. The University Medical Centre Rostock serves as care provider for the region, and these centers serve as the primary points of contact and consultation for BMS patients. However, as the BMS is often a non-diagnosed syndrome, it was a rather small number of subjects which was eligible for the study ($n = 101$). To aim for a larger patient population, it would be necessary to either screen for BMS patients regionally in smaller centers such as dental practices or cooperate with other centers.

The study's design was created similarly to other related studies regarding stimulation parameter to enhance comparability. The stimulation intensity of 0.5 Hz and 100 μA has been employed in numerous other studies (11, 29, 43). At this current intensity, 1 h of application is recommended, as was the case in the present study (43). The sham devices had the identical appearance, and it is not possible to distinguish from the active devices. Stimulation at the intensities used is below the threshold of perception, so that the participants should not be able to differentiate between active and sham conditions (41, 44). Patients could have been asked at the end of the study which study group they believed they were in. This could have provided insight into whether the sham stimulation provided adequate blinding. A possible reason for the small observed effect could be that the chosen study period of 4 weeks was too short. It appears that the impact of stimulation on pain intensity accumulates over time. While there was no indication of a short-term effect immediately after stimulation, both groups experienced a significant reduction in pain over the study period. Furthermore, considering that the stimulation resulted in a greater reduction of pain in the active group compared to the passive group, an extended study period could reveal a significant difference. This is supported by the observation that individuals with depression and sleep disorders exhibit a slower response to CES compared to the overall study population of patients with psychological disorders. Assessment points at three and 6 weeks of study duration have been recommended (10). A study by Holubec states that CES has a positive cumulative effect on refractory patients in patients with a variety of pain-related disorders (45). Our study did not have a follow-up session after the stimulation. Scheduling another appointment a month after the end of the study would provide additional information to evaluate long-term effects.

Conclusion

This study aimed to investigate the therapeutic effectiveness of CES as an adjunct therapy in patients with BMS compared to sham stimulation. According to our study results, CES is a low-risk and easily applicable therapeutic option that led to an improvement in symptoms and reduced the burden of the disease in some BMS patients. Over the study period, both groups experienced a significant reduction in pain intensity, somatic symptoms and an improvement in sleep quality. Superiority of active stimulation over sham stimulation could not be demonstrated. To prove the high effectiveness of CES, further studies with strong evidence are necessary. Studies exploring the ethology of BMS are needed to develop therapeutic approaches, as well as clinical trials aimed at devising improved treatment strategies for BMS.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the University Medical Centre Rostock. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AP: Data curation, Formal analysis, Investigation, Writing – original draft. TH: Formal analysis, Writing – review & editing. JL: Formal analysis, Writing – review & editing. BM: Formal analysis, Writing – review & editing. PK: Formal analysis, Writing – review & editing. TJ: Conceptualization, Formal analysis, Writing – review & editing. FR: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

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Conflict of interest

All authors are employees of the University Medical Centre Rostock. PK served on advisory boards and/or as speaker for Allergan, Novartis, Teva and Lilly. TJ served on advisory boards and/or as speaker for Abbvie, Allergan, Autonomic Technologies, Desitin, Grünenthal, Hormosan, Novartis, Lilly, Lundbeck Pfizer, Sanofi and Teva. FR served on advisory boards and/or as speaker for Allergan/Abbvie, Novartis, Teva, Ipsen, Lilly, Lundbeck, Hormosan.

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Evaluating the efficacy and acceptability of vagus nerve stimulation for fibromyalgia: a PRISMA-compliant protocol for a systematic review and meta-analysis

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Background: Fibromyalgia has imposed substantial burdens on patients' health and well-being, yet effective therapeutic options for this condition remain limited. Recently, vagus nerve stimulation (VNS) has emerged as a promising therapy for fibromyalgia. Nonetheless, despite the increasing number of randomized clinical trials (RCTs), current evidence remains inconclusive. Therefore, this protocol of a systematic review and meta-analysis aims to synthesize the existing evidence to clarify the efficacy and acceptability of VNS for treating fibromyalgia.

Methods: A comprehensive search for eligible RCTs will be conducted across nine bibliographic databases, namely PubMed, Cochrane Library, Embase, AMED, PsycINFO, PEDro, Chinese BioMedical Literature Database, Chinese National Knowledge Infrastructure, and Wangfang database. Data obtained from the included studies will be synthesized quantitively using RevMan 5.4.1 for meta-analyses. The methodological soundness of included RCTs will be assessed via the Cochrane's updated risk of bias tool (version 2.0). Additionally, sensitivity analyses, publication bias assessment, and subgroup analyses will be conducted as appropriate. Finally, we will utilize the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to evaluate the certainty for the body of evidence.

Conclusion: The findings of our study are anticipated to ascertain the efficacy and acceptability of VNS as a promising treatment option for fibromyalgia. This will not only fill current research gap but also identify potential areas for future research. The findings will provide essential guidance for evidence-based treatment decisions for fibromyalgia, benefiting both patients and clinicians.

KEYWORDS

fibromyalgia, vagus nerve stimulation, protocol, efficacy, acceptability

1 Introduction

Fibromyalgia stands as a predominant chronic pain condition, characterized by widespread pain, fatigue, sleep disturbances, cognitive dysfunction, and depression (1). Its pathogenesis is linked to central sensitization, in addition to factors such as inflammation, genetics, and psychosocial influences (2). The prevalence of fibromyalgia exhibits significant geographical disparities, with rates ranging from under 1% in Denmark to 2.4% in Spain, and from 2.0 to 3.3% in North America (3). Furthermore, the condition shows a distinct gender difference, being more prevalent among women than men, and it also demonstrates an increasing trend with advancing age.

Pharmacological interventions, such as duloxetine and pregabalin, are frequently utilized in the management of fibromyalgia, providing pain relief and enhancing overall patient functioning (4). Nonetheless, pharmacotherapy for fibromyalgia can have certain side effects associated with medication. Additionally, given that fibromyalgia is a complex condition with both physical and psychological components, patients can be benefit from non-pharmacological approaches such as mindfulness meditation, body awareness therapies, and exercise therapy (5), which address various facets of the disorder and improve overall well-being. These non-pharmacological therapies can potentially reduce the polypharmacy burden, provide symptom relief with fewer side effects compared to medication, and improve overall well-being. Furthermore, non-pharmacological treatments allow patients to actively manage their condition, influencing lifestyle factors like stress levels, and when combined with pharmacological interventions, may provide additional benefits for patients. However, despite the numerous available therapies, a noteworthy proportion of patients exhibit a lack of active response to them. To date, there has been a lack of therapies with widely recognized efficacy for fibromyalgia. As a result, there is an urgent need for alternative therapies that offer favorable efficacy, safety, and good tolerance (6). Vagus nerve stimulation (VNS) has emerged as a promising technique in the field of neuromodulation. It is indicated for the treatment of various diseases across multiple systems, encompassing neurological conditions (e.g., headache, migraine, tinnitus), psychological disorders (e.g., depression, anxiety, insomnia), cardiovascular diseases (e.g., hypertension, heart failure), and gastrointestinal disorders (e.g., inflammatory bowel disease, functional dyspepsia) (7). Notably, the Food and Drug Administration (FDA) granted approval for VNS in the treatment of refractory epilepsy in 1997 and resistant depression in 2005. The application of VNS can be broadly categorized into two forms: invasive, which involves the implantation of stimulating electrodes at the cervical branch of the vagus nerve, and noninvasive, which employs transcutaneous modalities. When electrical stimulation is specifically applied to the auricular branch of the vagus nerve that is distributed in the concha or the lower half of the back ear, it is referred to as transcutaneous auricular vagus nerve stimulation (ta-VNS) (8, 9). ta-VNS has demonstrated a comparable modulatory effect to the invasive vagus nerve stimulation (i-VNS), while exhibiting a more favorable safety profile and ease of operation (10). In recent decades, VNS has emerged as a promising new approach for treating various kinds of chronic pain conditions such as fibromyalgia, as it has been shown to reduce pain by modulating descending serotonergic and noradrenergic neurons (11). These neurons play a pivotal role in central sensitization, a process closely correlated with the pathogenesis of fibromyalgia.

1.1 The feasibility and significance of conducting this study

To note, the feasibility and significance of conducting this systematic review (SR) and meta-analysis can be highlighted as follows. In recent years, there has been a notable rise in clinical trials, including randomized controlled trials (RCTs), aimed at investigating the therapeutic effect of VNS on fibromyalgia. For example, Lange et al. (12) conducted a trial to explore the efficacy and tolerance of i-VNS in patients with fibromyalgia. The results demonstrated a favorable efficacy and tolerance to i-VNS treatment. Another RCT (13) conducted in 2020 investigated the efficacy of ta-VNS in combination with exercise on 60 patients with fibromyalgia, ultimately leading to significantly reduced pain intensity. However, the comparison between the treatment group, which received ta-VNS combined with exercise, and the control group, which solely underwent exercise, revealed no statistically significant between-group differences. In addition, a more recent RCT (14) published in 2022 sought to compare the therapeutic effects of ta-VNS, sham ta-VNS, and meditation-based diaphragmatic breathing for treating fibromyalgia. The results of this RCT revealed significant inter-group differences in overall fibromyalgia severity, while it did not manifest noteworthy differences in average pain intensity across different groups. Furthermore, there are several ongoing RCTs or trials (15–17) with upcoming results to be published. Despite the increasing number of trials in this field, however, the current body of literature exhibits a dearth of accessible SRs and meta-analyses concerning the efficacy and acceptability of VNS for fibromyalgia treatment, thus hindering the establishment of definitive conclusions. Consequently, our study aims to address this research gap by contributing valuable insights in this area. Moreover, the publication of the aforementioned trials makes it feasible to perform our study because it is expected to incorporate a sufficient number of eligible trials into the SR and meta-analysis. As discussed above, the significance and feasibility of this SR and meta-analysis are well-founded.

1.2 Research objective

Since that the review question for our SR and meta-analysis is whether VNS is effective for fibromyalgia with favorable acceptability, the objective of our study is to systematically synthesize the evidence concerning the efficacy and acceptability of VNS in fibromyalgia.

2 Methods

Our present study protocol is carefully designed and reported based on the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) (18) (as shown in Supplementary material).

2.1 Prospective registration

This reported protocol is specified in advance and registered in the International Prospective Register of Systematic Reviews

(PROSPERO) platform in advance with the identification number CRD42023449232.

2.2 Eligibility criteria for included studies

The criteria for the inclusion of eligible studies are meticulously designed according to the "*PICOS*" (i.e.; *P* for participants, *I* for interventions, *C* for controls, *O* for outcome measures, and *S* for study designs) framework.

2.2.1 Participants

The eligibility criteria for participants are adults (aged >18 years) who have a definite diagnosis of fibromyalgia using one of the widely accepted criteria built by the American College of Rheumatology [versions published in 1990 (19), 2010 (20) or 2016 (21)].

2.2.2 Interventions

Eligible interventions will be restricted to VNS, which is performed via placement of the vagus nerve stimulator. As the efficacy of VNS for fibromyalgia is undetermined, the intervention group's eligibility criteria will be limited to the use of VNS alone. VNS combined with other active interventions will not be considered in this context. Alone No limitations will be imposed on the types (e.g., invasive, or noninvasive VNS), stimulator models, and stimulus parameters of VNS.

2.2.3 Comparisons

1. No intervention or waiting list control;
2. Placebo/sham controls (e.g., sham VNS, placebo medication).

2.2.4 Outcome measures

Drawing from references to similar SRs and meta-analysis studies in this field (22–24), our study focuses on several key outcome measures. These measures include pain intensity, fatigue, sleep quality, psychological disorders, quality of life, and patient acceptability. To be considered for inclusion in our study, a study must report at least one of the above-mentioned outcome measures.

2.2.4.1 Primary outcome

The primary outcome is pain intensity measured by the Visual Analog Scale (VAS) and/or other validated instruments such as Numeric Rating Scale (NRS), Verbal Rating Scale (VRS), Brief Pain Inventory (BPI), and short-form McGill Pain Questionnaire (SF/MPQ).

2.2.4.2 Secondary outcomes

2.2.4.2.1 Fatigue

Fatigue associated with fibromyalgia can be measured by standardized scales, such as Multidimensional Fatigue Inventory (MFI), Fatigue Severity Scale, and Multidimensional Assessment of Fatigue Global Index.

2.2.4.2.2 Sleep quality

The assessment of sleep quality can be effectively accomplished using self-reported scales that have demonstrated both reliability and validity (e.g., the Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index (ISI)).

2.2.4.2.3 Psychological disorders

Psychological disorders (e.g., depression, anxiety) associated with fibromyalgia can be measured by standardized questionnaires, for examples, Beck Depression Inventory (BDI) and Hamilton Depression Scale (HAMD) for evaluating depression, and Self-Assessment Scale for Anxiety (SAS) for evaluating anxiety.

2.2.4.2.4 Quality of Life (QoL)

QoL can be evaluated by multiple standardized scales, such as the Fibromyalgia Impact Questionnaire (FIQ), the General Health Questionnaire (GHQ), and the Short Form 36 Health Survey (SF-36).

2.2.4.2.5 Patient acceptability

Patient acceptability is characterized by the number of discontinuations attributed to adverse reactions associated with VNS or the control treatment. This outcome will be quantified by the proportion of participants who withdraw from the trial for any reason, relative to the total number of patients initially randomly assigned to each group.

2.2.5 Study designs

The eligible type of studies will be restricted to RCTs. Additionally, only studies published in English and Chinese language will be included due to the research team's inability to finance translation services for other foreign languages. Studies will be excluded if they are non-RCTs, trials without a control group, utilize comparators that not included in the above predetermine list, or contain fewer than five participants in any treatment arm.

2.3 Identification of eligible studies and search strategy

2.3.1 Identification of studies via databases and registry platforms

A comprehensive search will be performed across the subsequent bibliographic databases: PubMed, Cochrane Library, Embase, AMED, PsycINFO, PEDro, Chinese BioMedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), and Wangfang database. Potentially eligible publications in these databases will be searched from inception to 31 December, 2023. Additionally, an add-on search will be conducted by thoroughly searching five prominent clinical trial registry platforms: the ClinicalTrials.gov registry, the International Clinical Trial Registration Platform (ICTRP), the Chinese Clinical Trial Registry, the Australian New Zealand Clinical Trials Registry (ANZCTR), and the ISRCTN registry. Our aim is to identify ongoing trials containing unpublished data relevant to this research topic. We will then contact the principal investigators of these ongoing trials via email to request the most recent data.

To ensure a comprehensive search for eligible studies, we will employ a well-established and rigorous search strategy. This strategy will include a combination of subject headings, such as medical topic heading words (MeSH) for PubMed, and relevant free text terms related to fibromyalgia, vagus nerve stimulation, and randomized controlled trials. Our planned search will not be limited by terms relating to the types of control interventions used, thereby ensuring the inclusion of all relevant studies comparing the effectiveness of VNS therapy against any standard treatment or management option for fibromyalgia.

For the search strategy in PubMed, a detailed illustration is provided in Table 1. Adapting this search strategy to the remaining bibliographic databases will entail substituting MeSH terms with relevant subject headings (when available), while maintaining consistency with the use of relevant free text terms. The detailed search strategies for the other databases were provided in the Supplementary material.

TABLE 1 Search strategy in PubMed.

No.	Search items
#1	Randomized controlled trial [Publication type]
#2	Controlled clinical trial [Publication type]
#3	Random* [Title/Abstract]
#4	Clinical trials [MeSH]
#5	Randomly [Title/Abstract]
#6	RCT [Title/Abstract]
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	Humans [MeSH]
#9	#7 AND #8
#10	Fibromyalgia [MeSH] OR Fatigue Syndrome, Chronic [MeSH]
#11	Fibromyalgia*[Title/Abstract] OR Muscular Rheumatism [Title/Abstract] OR Fibrositis [Title/Abstract] OR Diffuse Myofascial Pain Syndrome [Title/Abstract]
#12	#10 OR #11
#13	Vagus Nerve Stimulation [MeSH] OR Vagus Nerve [MeSH]
#14	VNS [Title/Abstract] OR taVNS [Title/Abstract] OR ta-VNS [Title/Abstract] OR iVNS [Title/Abstract] OR vagus nerve stimulation [Title/Abstract]
#15	#13 OR #14
#16	#9 AND #12 AND #15

2.3.2 Identification of studies through supplementary approaches

To expand the potential pool of studies, we will conduct thorough examinations of the reference lists of all identified publications to supplement any additional eligible studies. Furthermore, we will perform comprehensive searches and browse through relevant associations, institutions, and preprint servers to uncover any supplementary trials. Specifically, we will include preprint studies from reputable platforms such as Research Square,[1] medRxiv,[2] and Arxiv.[3] Furthermore, we will explore grey literature, which includes conference proceedings, academic dissertations, and government reports, as potential sources of valuable information. The incorporation of these supplementary approaches is intended to enhance the comprehensiveness and robustness of our study selection process.

2.4 Data acquisition and analysis

2.4.1 Study selection process

The inclusion and exclusion criteria will be applied to determine potential eligible studies by screening the titles and abstracts of corresponding papers initially, followed by a full-text screening by two independent reviewers. Should discrepancies arise, a third senior reviewer will arbitrate such conflicts. The illustration outlining the procedure for study selection is presented in the PRISMA flowchart (Figure 1).

2.4.2 Data collection and management

Upon inclusion of all eligible studies, two independent extractors will use a standardized extraction form to collect relevant data and information. The extracted data will be carefully cross-checked for accuracy. The standardized extraction form will mainly encompass demographic and clinical characteristics, including study design, details of the study population, types of VNS (e.g., invasive, noninvasive), stimulation parameters of VNS (e.g., stimulation frequency, pulses, intensity), types of comparator interventions, treatment frequency and durations, outcome measurements, and other pertinent details. For continuous data in each group of the original trial, the mean value and standard deviation (SD) will be extracted along with the total number of participants. When continuous data are reported as median (range) and/or median (interquartile range (IQR)), we first contact the study authors to request the mean (SD) data. If no reply is obtained from the authors, we will adopt the preferred method described by Wan et al. (25) to convert median, IQR, and range values into mean (SD), which is based on a sample size-dependent extension of the formula for approximating the SD using IQR or range values. For dichotomous data, the number of respondents and the total number of participants in each category will be recorded.

In addition, assuming that crossover RCTs are included in the review, we will only extract and analyze the preliminary results from the two groups prior to the crossover by referencing to related studies. In addition, data obtained from three-arm RCTs included in the meta-analysis will undergo processing. This will involve the division of the common group found within multi-arm trials, allowing for a pairwise meta-analysis approach, which is a widely recognized method (26). Any discrepancies that may arise during the selection of RCTs and data extraction will be resolved through discussion or arbitration, facilitated by a senior researcher.

2.4.3 Handling of missing data

In cases where essential data is not accessible within the original publication of the included trial, we will contact the corresponding author of the original study via email and make reasonable requests for the relevant data.

2.4.4 Assessment of the methodological quality of included studies

To evaluate the methodological quality of each RCT, two independent raters will use the Cochrane's updated risk of bias (ROB) tool (version 2.0) (27). The ROB assessment will focus on five critical aspects: (1) randomization process, (2) handling of missing data for outcomes, (3) deviations from intended interventions, (4) outcome assessment, and (5) selection of study results. Each ROB item will

1 www.researchsquare.com/
2 www.medrxiv.org/
3 www.arxiv.org/

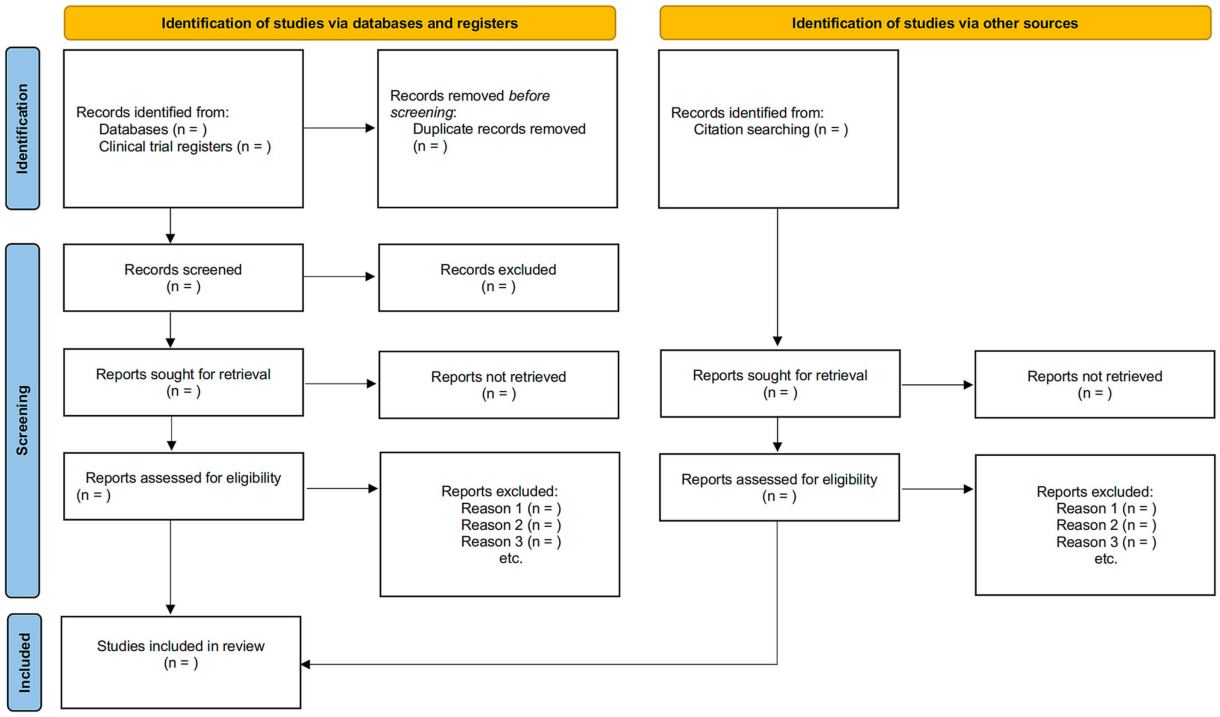

FIGURE 1
Flow diagram of study selection.

be categorized as "low," "high" or "some concerns" (27). Additionally, an overall ROB rating for each study will be assigned as "low" (indicating low ROB for all items), "some concerns" (indicating some concerns in at least one item), or "high" (indicating high ROB for at least one item or some concerns for various items). In case of any discrepancies between the two raters, they will be resolved through negotiations with a senior reviewer.

2.4.5 Treatment effect measures

To combine and analyze treatment effect data, we will utilize the meta-analysis statistical program RevMan Version 5.4.1. For continuous data, we will compute the weighted mean difference or standardized mean difference, accompanied by their corresponding 95% confidence intervals (CI). Dichotomous data will be analyzed using the risk ratio with the corresponding 95% CI.

2.4.6 Evaluation of heterogeneity across studies

When evaluate the heterogeneity across the included studies, we will employ the Cochran Q-test and I2 statistic, which expresses the percentage of total variability attributed to between-study heterogeneity. If the Q-test yields a p-value greater than 0.10 and the I2-value is below 50%, indicating an acceptable level of heterogeneity, a fixed-effect model will be adopted for the quantitative analysis of pooled data (28). However, if the Q-test's p-value is equal to or less than 0.10 and the I2-value is 50% or higher, indicating significant heterogeneity, the random-effect model will be employed (28). Furthermore, when applicable, subgroup analyses will be conducted to investigate potential sources of significant heterogeneity.

2.4.7 Data synthesis

Data synthesis using meta-analysis (i.e., quantitative analysis) will be undertaken in the RevMan software (Version 5.4.1). Notably, a descriptive qualitative description (i.e., qualitative analysis) of the findings will be provided if the clinical and methodological heterogeneity makes it impractical to conduct the meta-analysis.

2.4.8 Subgroup analysis

When applicable, we will conduct subgroup analyses to investigate possible sources of significant heterogeneity based on the following characteristics of the original studies.

1. Variations in stimuli parameters (e.g., stimulation frequency, pulses, duration) of ta-VNS.
2. Different measurement timepoints for primary outcomes (e.g., short-term effect vs. long-term effect).

2.4.9 Sensitivity analysis

To ensure the rigor of the meta-analysis results and assess the impact of individual studies on the overall effect size, a sensitivity analysis will be performed using the established leave-one-out approach. If inconsistent results are identified during sensitivity analysis, the results of the corresponding meta-analyses will be interpreted with great caution.

2.4.10 Assessment of certainty of evidence

The certainty of evidence produced by this SR and meta-analysis will be independently evaluated by two raters using the Grading of

Recommendation, Assessment, Development, and Evaluation (GRADE) framework (29). Various factors, such as research constraints, inconsistent results, indirectness of evidence, reporting bias, and imprecision, will be taken into consideration when determining the certainty of evidence. To ensure accuracy, the outcomes of the GRADE evaluation are subject to verification, with the resolution of any discrepancies being carried out by a senior researcher.

2.4.11 Evaluation of publication Bias

To investigate potential publication bias and the influence of studies with small sample sizes, we will employ a funnel plot. For meta-analysis results with more than 10 trials included, we will assess the asymmetry of the funnel plot using Begg's and Egger's tests (28). A *p*-value less than 0.05 in these tests will indicate a significant level of publication bias.

2.5 Patient and public involvement

Patients or the public will not be involved in the development of the research topic, methodology design, data collection, outcome measurements, or data analysis of this study. Consequently, the study participants will not receive the dissemination of the study's results.

3 Discussions

Drawing from previous literature search, our study reports the first SR and meta-analysis protocol regarding efficacy and safety of VNS on fibromyalgia, which is an important topic for clinical practice. As a neuromodulation technique with significant application value, VNS is frequently used for a variety of diseases, mainly including neurological disorders, pain conditions, and gastrointestinal disorders (30). Regarding the relevant mechanisms of action, VNS has the capacity to modulate vagal activity and neuro-immune communication, thereby achieving analgesic effects in addition to ameliorating neurological disorders, as indicated by findings from both human and animal studies (11). In addition, VNS exerts its influence on numerous brain regions involved in pain processing, thus presenting a promising avenue for pain modulation. Furthermore, the anti-inflammatory properties of VNS may also contribute significantly to its pain-inhibitory effects. Therefore, VNS has been increasing utilized to treat a wide range of diseases, such as chronic pain conditions (11, 31), encompassing fibromyalgia (14), visceral pain (32), rheumatoid arthritis (33), trigeminal allodynia (34), and migraine (35, 36). To note, clinical trials (12–14) published in recent years reveal that patients with fibromyalgia can benefit from VNS, thereby indicating that VNS may be a promising therapy for fibromyalgia.

However, despite the increasing number of published studies and ongoing clinical trials in this field, it is noteworthy that the therapeutic effect and acceptability of VNS in the treatment of fibromyalgia remain inconclusive due to the lack of published SR and meta-analysis. Therefore, there is a need for conducting a SR and meta-analysis study to comprehensively examine the evidence and determine the effectiveness and safety of VNS for fibromyalgia. Considering the research gaps, we have meticulously designed the current PRISMA-compliant protocol to provide a thorough outline of the rationale, feasibility, and methodological procedures for conducting the subsequent SR and meta-analysis on this clinically significant topic.

3.1 Strengths of the current study

First, our study addresses the challenge posed by the lack of well acknowledged therapies for fibromyalgia, both pharmacological and non-pharmacological. Consequently, fibromyalgia remains a difficult disease to treat. Therefore, establishing robust evidence on the efficacy and patient acceptability of VNS for fibromyalgia will offer valuable guidance to clinicians, patients, and policymakers. This evidence will help determine whether VNS, as a stand-alone treatment or an adjunct, could be a viable therapeutic approach for treating fibromyalgia, thereby enhancing current treatment strategies. Based on comprehensive literature search in advance, to the best of our understanding, our study is the first SR and meta-analysis protocol that aims to synthesize evidence regarding the efficacy and acceptability of VNS in alleviating fibromyalgia, following a comprehensive literature search.

Second, our investigation will assess the quality of evidence through the utilization of the GRADE methodology (29). The outcomes of the systematic review will captivate a wide-ranging readership, encompassing individuals diagnosed with fibromyalgia, healthcare practitioners involved in its management, and insurers/compensation boards. The results and findings derived from our study will contribute to the refinement of evidence-based management of fibromyalgia and identify essential areas warranting further investigation.

Third, this protocol has been meticulously developed in adherence to the authoritative PRISMA-P guidelines (18) and is prospectively registered in the validated PROSPERO platform. These measures ensure the overall methodological quality of the subsequent completed SR and meta-analysis, enhance research transparency, and minimize potential performance bias (37).

3.2 Limitations

First, the limited affordability of translation services for various languages restricts the publication language to Chinese and English. This constraint might introduce a selection bias in the inclusion of studies. Second, given that there is currently no consensus on the optimal treatment protocols for VNS, such as stimulus sites and parameters. The varied treatment approaches utilized in the included trials may increase the level of heterogeneity, potentially hindering the effectiveness of quantitative analysis. In such situations, if appropriate, an alternative approach using descriptive qualitative accounts of the findings will be considered.

4 Conclusion

This protocol outlines the rationale, feasibility and methodology for a SR and meta-analysis that intends to synthesize the existing evidence pertaining to the use of VNS in the treatment of fibromyalgia. The findings are expected to ascertain the efficacy and acceptability of VNS in alleviating fibromyalgia, which will not only clarify the current state of evidence but also highlight any existing gaps. Ultimately, these findings will provide valuable insights that assist both patients and

clinicians in making well-informed and appropriate treatment decisions for fibromyalgia.

Author contributions

YC: Investigation, Writing – original draft. YZ: Writing – original draft. YF: Writing – original draft. HH: Methodology, Writing – review & editing. XL: Writing – review & editing. LF: Conceptualization, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1367295/full#supplementary-material

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Glossary

ACR	American College of Rheumatology
BDI	Beck Depression Inventory
BPI	Brief Pain Inventory
CI	Confidence Interval
FDA	Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
GHQ	General Health Questionnaire
GRADE	Grading of Recommendation, Assessment, Development, and Evaluation
HAMD	Hamilton Depression Scale
IQR	Interquartile Range
i-VNS	Invasive Vagus Nerve Stimulation
ISI	Insomnia Severity Index
MeSH	Medical Subject Headings
MFI	Multidimensional Fatigue Inventory
NRS	Numeric Rating Scale
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality of Life
RCT	Randomized Controlled Trial
ROB	Risk of Bias
SAS	Self-Assessment Scale for Anxiety
SD	Standard Deviation
SF-36	Short Form 36 Health Survey
SF/MPQ	Short-form McGill Pain Questionnaire
SR	Systematic Review
ta-VNS	Transcutaneous Auricular Vagus Nerve Stimulation
VAS	Visual Analog Scale
VNS	Vagus Nerve Stimulation
VRS	Verbal Rating Scale

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A role of NLRP3 and MMP9 in migraine progression: a systematic review of translational study

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Background: Migraines affect one billion individuals globally, with a higher occurrence among young adults and women. A significant survey in the United States indicated that 17.1% of women and 5.6% of men suffer from migraines. This study seeks to investigate the potential connection between NLRP3 and MMP9 in migraine pathology.

Methods: The research involved searching databases such as PubMed, Scopus, Science Direct, Google Scholar, and Proquest, with the search concluding on March 31, 2024. Following PRISMA guidelines, PICO data were collected, focusing exclusively on animal models induced by Nitroglycerine (10 mg/kg), while excluding clinical studies.

Results: The study, originally registered in Prospero Reg. No. CRD42022355893, conducted bias analysis using SYRCLE's RoB tool and evaluated author consensus using GraphPad v9.5.1. Out of 7,359 search results, 22 papers met the inclusion criteria. Inter-rater reliability among reviewers was assessed using Cohen's kappa statistics.

Conclusion: This review summarizes 22 preclinical studies on Nitroglycerin (NTG), NLRP3, MMP9, and related biomarkers in migraine. They reveal that NTG, especially at 10 mg/kg, consistently induces migraine-like symptoms in rodents by activating NLRP3 inflammasome and stimulating proinflammatory molecule production.

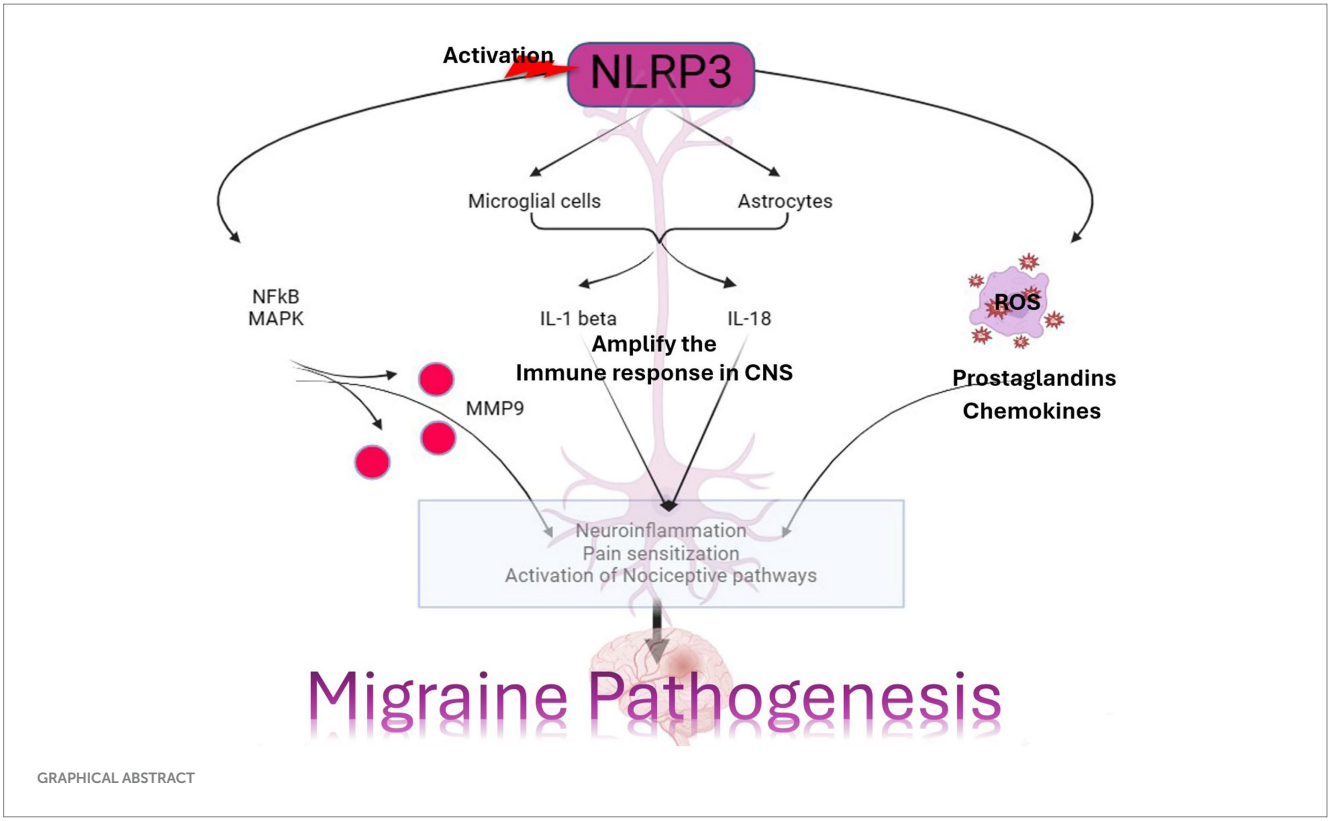
Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, CRD42022355893.

KEYWORDS

NLRP3, MMP9, migraine, IL1β, P2X7R, P2X4, IL1-β, IL-18

1 Introduction

One of the most common causes for outpatient visits to general neurologists is migraine, a prevalent and incapacitating neurological condition. Lifestyle changes are a cornerstone of treatment in addition to pharmaceutical therapy (1). Scientists have yet to find a medication that treats migraine for ten decades. They started targeting different biomarkers such as NFkB (2–4), interleukins (5–7), serotonin (8–11), etc. which was released immensely in the



GRAPHICAL ABSTRACT

migraineurs but unable to find a way to cure. Then the treatment for migraine has changed dramatically as a result of medications that target the CGRP pathway (12–14). Numerous articles have provided evidence for the efficacy of monoclonal antibodies targeting CGRP or its receptor in preventing difficult-to-treat migraines (15–19). A trial of intravenous eptinezumab in individuals with 2–4 prior failed efforts at preventive therapy was conducted in 2022 to supplement this work (20–22). During the 12-week double-blind observation period, a single infusion of 300 mg eptinezumab significantly reduced the number of monthly migraine attack days compared to the placebo group (23–25). Nowadays, researchers are especially targeting NLRP3 inflammasomes (26–30) which has a robust connection to migraine and predicting MMP9 additionally playing a major role in the migraine attack (31–33).

Neurological diseases, whether fatal or non-fatal, constitute a significant portion of the non-communicable disease burden in India (34). According to the 2019 Global Burden of Disease study (GBD2019), migraine was reported as the second leading cause of disability, especially among women under the age of 50. Out of 357 publications primarily from high-income countries, the estimated global prevalence of active headache disorders was 52.0% (with a 95% confidence interval of 48.9–55.4). Specifically, the prevalence of migraine was estimated at 14.0% (with a confidence interval of 12.9–15.2), tension-type headache (TTH) at 26.0% (with a confidence interval of 22.7–29.5), and other severe headache disorders (H15+) at 4.6% (with a confidence interval of 3.9–5.5) (35). These estimates aligned with the figures for migraine and tension-type headache (TTH) reported in GBD2019, the most recent available data, but they indicated a higher prevalence of headaches in the general population. Specifically, on a daily basis, 15.8% of the global population experiences headaches (35, 36). A statistical report from 2019 found that headache disorders, including conditions like migraine and tension-type headaches, were the most common neurological conditions, affecting approximately 488 million individuals in India (with a 95% uncertainty interval ranging from 449 to 527 million) (37). Regardless of regional differences, the issue of headaches is a global concern, affecting people of various ages, ethnicities, income levels, and geographic locations. Between half to three-quarters of individuals aged 18 to 65 worldwide experienced a headache in the past year, with 30% or more reporting migraine of the two main categories of headache disorders, migraine has the most significant impact on overall neurological health, contributing the highest share of Disability-adjusted life years (DALYs) (38). The DALYs associated with migraine significantly surpass those linked to tension-type headaches. Between 1990 and 2019, India saw an increase in the raw prevalence and DALY rate of headache disorders, while the age-standardized prevalence and DALY rate remained relatively stable. In 2019, it was observed that females between the ages of 35 and 59 had a higher prevalence of migraine compared to males in the same age group (39).

The prevalence of this condition increases with age, peaking between 40 and 44 years, and then gradually decreases in both men and women. The proportion of non-communicable neurological disorders was 4.0% (with a 95% uncertainty interval of 3.2–5.0) in 1990, doubling to 8.2% (with an interval of 6.6–10.2) by 2019. Projections indicate that this percentage is expected to climb to 16.5% by 2040. Migraine, a widespread neurological disorder, stands as the second most significant contributor to years lived with disability globally and ranks among the top twenty most disabling conditions worldwide (36, 40–42). Migraine is a severe neurological condition diagnosed through clinical criteria (43). Many individuals are unable to work due to migraines, which are complex neurological events lasting for several hours or even extending over multiple days. The

TABLE 1 Inclusion and Exclusion criteria.

Aspects of research	Inclusion	Exclusion
Population	Rodents	Non-Rodents
Interventions	New strategies with the express purpose of alleviating migraine symptoms in preclinical studies. NLRP3 and MMP9 biomarkers and other proinflammatory molecules are involved in it.	Migraine trails in clinical point of view.
Induction model	Nitroglycerine inducing model	Other than the nitroglycerine induction animal model; Comorbities related to the Nitroglycerine induction model such as Cardiovascular, Endocrine, and Psychiatric disorders.
Language	English	Non-English
Outcome	Any	Other than rats and mice
Comparators	Any	Other than rats and mice

most common type of migraines is those without an aura (44). As a result, it is estimated to affect hundreds of millions annually (45). The underlying processes in migraine pathophysiology have a significant genetic component and involve the activation of pain pathways associated with the trigeminovascular system (46–51). This systematic study is motivated by the exploration of the roles of NLRP3 and MMP9 in the onset of migraine attacks. After identifying, evaluating, and consolidating research results, a thorough examination of relevant preclinical studies is essential to establish the reliability and potential applicability of the data in future research. This hypothesis sets the stage for establishing a robust connection between NLRP3 and MMP9 in the context of migraines.

2 Methods

Three authors independently evaluated the inclusion and exclusion criteria to reduce the chance of excluding pertinent records and determine whether the studies were eligible. After removing duplicate entries, the title, and abstract of the remaining records were evaluated in the first screening. The analysis included NLRP3 and MMP9 biomarker studies assessing the relationship with the progression of chronic migraine pathology through pain pathways. No limitations on the length of the survey, its follow-up, or the date of publication have been imposed. The study excluded *in vitro* and *in vivo* animal experiments, narrative or systematic reviews, meta-analyses, abstracts, proceedings, conference communications, editorials, and book chapters. Additionally, publications that were either unavailable in full text/not published in English were excluded, as indicated in Table 1. This systematic review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta Analysis Protocols (PRISMA-P). The review followed the Population, Intervention, Comparison, and Outcome strategy (52). The following were the PICO requirements for inclusion.

Population: All species of rats and mice; there are no restrictions for selection of age and gender.

Intervention: Nitroglycerin-inducing animal models were explicitly focused on in this study. The role of biomarkers such as NLRP3 and MMP9 are scrutinized in all the studies of migraine.

Comparison: The non-clinical model of Nitroglycerine induction will be included, but groups with comorbidities will be excluded from the analysis.

Outcome: Behavioral test, Sensory sensitivity testing, von Frey Testing, Thermal Withdrawal Latency Test, Paw Licking Time Test, Gelatin gel zymography, Light/dark test, Von Frey test, Hot plate test, Orofacial formalin test, immunohistochemistry, Histopathology, Immunofluorescence staining, Flow Cytometry, qRT PCR will be included in this review. Different Outcomes will be excluded from scrutiny if they have no bearing on the development of migraine. Inclusion was not restricted to a specific period, and only original research published in English and reviewed by academic peers was considered.

2.1 Search strategy

We conducted a literature search by consulting the most pertinent scientific databases, including PubMed, Science Direct, Scopus, Google Scholar, and Proquest. There were no limitations on the publication date. The search encompassed records matching the specified search terms from the inception of these databases up to March 31, 2024, which was the date of the last search. To initiate the review, we primarily used Pub Med,[1] a search engine managed by the National Center for Biotechnology Information of the US National Library of Medicine, under the National Institutes of Health. Filters on PubMed were utilized to narrow the results down to human clinical trials and literature available in English. The results were not restricted by publication date, and the last search was performed on March 31, 2024. We employed the search terms (NLRP3 AND Migraine), (MMP9 AND Migraine), (Preclinical AND Migraine), (Migraine), and (Herbal treatment AND Migraine) across the PubMed, Science Direct, Google Scholar, Proquest, and Scopus search platforms.

2.2 Data retrieval

In this process, one reviewer (RR) collected data from each study, which encompassed information such as the animal strain, weight, route of administration (ROA), dose, and the specific biomarkers addressed in the study. This data was then documented in an Excel Sheet for the purpose of data management. Subsequently, three reviewers (ASS, AS and RR) cross-validated the gathered information to ensure its coherence and relevance.

1 https://pubmed.ncbi.nlm.nih.gov/

2.3 Risk of bias

Using the Systematic Review Centre for Laboratory Animal Experimentation risk of bias (SYRCLE's RoB) method (53–55), five reviewers (IK, CV, RR, ASS, and AS) conducted individual assessments of bias risk for all 22 studies. This assessment questionnaire comprises ten categories associated with six types of bias, evaluating the methodological quality of preclinical studies. These categories encompass elements like sequence generation, baseline characteristics, allocation concealment, random housing, random outcome assessment, incomplete outcome data, selective outcome reporting, and other factors, such as drug pooling, funder influence, design-specific bias risk, unit of analysis errors, and replacement of dropouts from the original population. Each study's risk of bias was evaluated by all reviewers using the designations 'yes', 'no,' and 'unclear' to denote high risk, low risk, and insufficient information to determine the risk of bias, respectively. Any disparities in these assessments were resolved through discussion among the reviewers or by reaching a consensus. The author agreement is assessed based on kappa values with reference values of less than zero No agreement; 0.00–0.20 Slight agreement; 0.21–0.40 Fair agreement; 0.41–0.60 Moderate agreement; 0.61–0.80 Substantial agreement; 0.81–1.000 Almost perfect agreement. The level of agreement was quantified using kappa, employing the GraphPad by Dotmatics tool.[2]

2.4 Data analysis

This review was officially registered with PROSPERO under the reference CRD42022355893. We conducted a thorough examination of the literature to ascertain the extent and prevalence of the utilization of particular concepts, objectives, and correlated outcome measures in preclinical trials focused on migraine treatments. The methodology protocol adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (56), which offer consensus-based standards for developing and carrying out high-quality systematic literature reviews. The PRISMA checklist provides guidelines for various stages of conducting a literature search and review. This includes specifying eligibility criteria for published papers, determining the dataset for the search, formulating search terms, establishing a standardized review process for identified publications, implementing record tracking and data management systems, outlining the data to be extracted from each publication meeting inclusion criteria, and devising a strategy for data extraction from qualifying publications.

3 Results

3.1 Study selection

The database search yielded 7,359 results, with 47 records from PubMed, 323 from Science Direct, 803 from Scopus, 6,180 from Google Scholar, and 6 from Proquest. Initially, 737 titles were screened, and after eliminating duplicates, book chapters, other than NTG induction model, clinical studies, and conducting abstract screening, at last 22 remained. All of the studies that were included adhered to ethical guidelines and received approval from the relevant institutional bodies. The characteristics and outcomes of these selected studies are listed in Table 2. Various animal species were represented among the rodents in the study, with the Nitroglycerin (10 mg/kg, b.wt) model being the most frequently employed for inducing migraine-related conditions, and it was the primary focus. The timeline of the systematic review is presented in Figure 1.

3.2 Population

Albino Sprague Dawley rats and mice, CD1 mice, Wistar rats, Knockout mutant mice, Neonatal Mice, and C57BL6/J mice were included, and other than these were excluded from this study. Of these 22 studies, 9 studies used C57BL6/J mice; 6—Sprague Dawley rats studies; 3—CD1 mice studies; Wistar rats-2; Knockout mutant mice-1; Neonatal mouse-1 study for pharmacological evaluation. They used both genders for the study, and mostly Nitroglycerin (10 mg/kg, b.wt, i.p) chemical induction model was selected and utilized to create migraine-like conditions.

3.3 Intervention

By decreasing microglial and NLRP3 inflammasome activity, TREM1 regulation demonstrates potential as a therapy approach for chronic migraine. Through stimulating the Nrf2 pathway, which in turn decreases oxidative stress and neuroinflammation, NBP lessens the severity of migraines. One possible mechanism by which Wuzhuyu Decoction reduces inflammation and oxidative stress in migraine sufferers is via activating the NRF2 pathway. A possible treatment target in chronic migraine could be AMPK activation, which lowers neuroinflammation. UA has the ability to reduce migraine symptoms by reducing mitochondrial dysfunction in different parts of the brain. Vestibular dysfunction and increased fibrinogen levels are the results of NTG-induced migraines in rats. Possible migraine treatment targets include the trigeminal nucleus caudalis (TNC), which shows increased expression of PACAP and PAC1R. One novel approach to studying migraine in rats is the use of postauricular injection. In mice that have peripheral hypersensitivity caused by NTG, acupuncture at the GV16 acupoint alleviates mechanical and cold allodynia. RUT alleviates migraine symptoms by triggering the antioxidant mechanism of Nrf2. Possible relief from migraine symptoms may be achieved through the inhibition of the NGF/TRPV1/COX-2 pathway by Shaoyao Gancao Decoction. A possible therapeutic target could be the suppression of PACAP/PAC1R, since repeated intranasal PACAP treatments in CM rats cause hyperalgesia. The fact that perampanel blocks PACAP expression suggests it may be useful in treating migraines. It has been suggested that PAR2 could be a therapeutic target for migraines, as its activation and IL-6 signaling could prime NO donors. Metabolite and target influences on MXFD's efficacy in migraine treatment provide light on areas for future investigation. Novel migraine therapy techniques may be available via BAY-117082's modulation of the Erk/CREB/Akt pathways. One mechanism by which W146 reduces chronic

2 https://www.graphpad.com/quickcalcs/kappa1/?K=3

TABLE 2 Characteristics of the included studies and a summary of the outcome.

Author/ Year	Cell line/ Animal Strain and weight	Induction	ROA/Dose	Biomarkers/ Receptors/Cell culture	Endpoint	Outcome
Sun et al. (57)	C57BL/6 J Male 20-30 g BV2 cells	NTG induced	i.p 10 mg/kg	cfos, CGRP, p-65, NLRP3, Caspase-1, IL-1β, IL-18, GFAP, TREM-1, NeuN, Iba	Behavioral assessment Western blot Immunofluorescence	It shows that TREM1 regulates microglial and NLRP3 inflammasome activity via modulating the NF-κB signaling pathway. Furthermore, TREM1 was linked to CGRP and c-fos expression, contributing to central sensitization. These discoveries offer new insights into CM mechanisms, suggesting that targeting TREM1 may be a feasible treatment option.
Liu et al. (58)	C57BL/6 J Male 20-30 g	NTG induced	i.p 10 mg/kg	CGRP, cFOs, SOD, MDA, ROS intensity, iNOS, IL-6, IL-1β, TNF-α, Nrf2, HO-1, NQO1,	Light/dark test, Von frey test Elevated plus maze	Dl-3-n-butylphthalide (NBP) significantly reduced the severity of migraines in mice that were caused by NOG. Therapeutic results were achieved by lowering oxidative stress and neuroinflammation via activating the Nrf2 signaling pathway, which in turn reduced nociceptive hypersensitivity and central sensitization. As a result, NBP shows promise as a migraine prevention treatment.
Xu et al. (59)	Mice	NTG induced	i.p 10 mg/kg	ROS, MDA, SOD, NrF2, HO1, NQO1, MZF1	Behavior tests and immunofluorescence assay	Wuzhuyu Decoction down-regulated PGK1 via MZF1, activating the NRF2 pathway.
Lu et al. (60)	C57BL/6 J Mice Male 20-30 g	NTG induced	i.p 10 mg/kg	ATP, ADP AMP, IL-1β, IL-4, IL-6, IL-10, TNF-α, IFN-γ, CGRP, AMPK, PAMPK, UHRF1, iNOS, Arg1, Iba1, NFkB, P65, and GM-CSF	ELISA The Luminex liquid suspension chip assay Immunohistochemistry	Their findings strongly suggests that AMPK plays a crucial role in central sensitization of chronic migraine (CM), especially in cases of aberrant energy metabolism. AMPK activation reduces neuroinflammation in NTG-induced CM mice via polarizing microglia in M2. AMPK activity modulation may aid in treating CM by targeting central sensitization processes.
Xie et al. (61)	C57BL/6 J Mice Male 21-32 g	NTG induced	i.p 10 mg/kg	AT, MRC complex-I, Fundc1, Fis1, Mid49, OPA1, PGC1α, TFAM, CHOP, HSP10, MDA	Behavioral test, von-Frey filaments, a hot plate, and a light–dark box, Light-aversive test, qPCR, ELISA, TEM,	In the thalamus, hypothalamus, periaqueductal grey, trigeminal ganglio, and trigeminocervical complex, respectively, 529, 109, 163, 152, and 419 differentially expressed proteins were found using proteomics profiling of the CM model. Significant alterations in region-specific brain circuits indicated mitochondrial dysfunction in the thalamus. UA intervention had a modest attenuating effect on NTG-induced mitochondrial structural damage, malfunction, and homeostatic dysregulation.
Zhang et al. (62)	SPF-grade Wistar rats 250-300 g	NTG induced	i.p 10 mg/kg	Fibrinogen, Tail lift index, Negative geotaxis, Air righting reflex, vestibular dysfunction ratings	Behavioral tests ELISA	Their findings demonstrated that rats subjected to NTG-induced chronic migraines exhibited decreased vestibular function. After several injections of NTG, the fibrinogen levels rose. The rats used to study migraines showed no changes in mechanical hyperalgesia (either worsening or improving) or vestibular dysfunction (either improving or worsening) after defibrinogenation.
Zhang et al. (62)	Male SD Rats 210-235 g	NTG induced	i.p 10 mg/kg	pCREB, PACAP, PAC1R, ERK, BDNF, cFos	Behavioral test Immunofluroscence staining Western blot TEM	Overall, the research work found to be the expression of PACAP and PAC1R in TNC was elevated after repeated treatment of NTG to rats. In addition, via modifying NTG-induced synaptic plasticity via the ERK/CREB/BDNF pathway, PACAP6-38, a selective PAC1R antagonist, reduced chronic cephalic allodynia and inhibited the augmentation of neuronal activity. Inhibiting PACAP/PAC1R could be a new therapeutic target for migraine based on our findings.

(Continued)

TABLE 2 (Continued)

Author/ Year	Cell line/ Animal Strain and weight	Induction	ROA/Dose	Biomarkers/ Receptors/Cell culture	Endpoint	Outcome
Qi et al. (63)	Wistar rats Male 200-250 g	NTG induced	i.p 10 mg/kg	–	ABR Latency	The postauricular nitroglycerin injection is safer and more effective than intraperitoneal injection for migraine modeling in rats. Postauricular nitroglycerin injection damages rats hearing function more. The migraine model rat caused by nitroglycerin postauricular injection may represent a new cochlear migraine model.
Kim et al. (64)	C57BL/6 Male	NTG induced	i.p 10 mg/kg	cFos expression; cold allodynia measurements in the hindpaws and facial region	Immunohistochemistry	When repeatedly stimulated at the GV16 acupoint, mice with NTG-induced peripheral hypersensitivity and high TNC c-Fos expression can reduce hindlimb and face mechanical and cold allodynia. DBV injections at GV16 activate alpha-2 adrenoceptors, not endogenous opioid receptors. Based on this study, chemotherapeutic acupuncture with Diluted Bee Venom at GV16 may help migraine patients with peripheral discomfort.
Xu et al. (65)	C57BL/6 mice Male 7 weeks old	NTG induced PC12 cell line	i.p 10 mg/kg	ROS, c-Fos, NeuN, PTEN, NQO1, PGK1, SOD, MDA, and NRF2	Behavioral tests Cell viability assay Western blot	Their study demonstrated that RUT reduced oxidative stress and relieved migraine symptoms by blocking PGK1 activity with PTEN and activating the Nrf2 antioxidant mechanism. Based on these results, RUT, a natural medicine, may be a good choice for migraine treatment.
Luo et al. (66)	SD rats	NTG induced	i.p 10 mg/kg	COX-2, PGE2, CGRP, ERK, SRC, TRPV1	Elisa, rtPCR, Western blot	Shaoyao Gancao Decoction considerably inhibits the NGF/TRPV1/COX-2 signaling pathway, which is responsible for central hyperalgesia migraine. This indicates that the molecular mechanism by which SGD alleviates migraine symptoms might be associated with the central hyperalgesia neurotransmitter, which controls the pathophysiology of migraine.
Zhang et al. (62)	SD rats Male 200–250 g	NTG induced	i.p 10 mg/kg	c-Fos, CGRP, PACAP, PAC1, PKA and ERK	Von Frey filaments, and hot plate tests, Immunofluorescence, Western blot	Their investigation showed that repeated intranasal PACAP treatments caused mechanical and thermal hyperalgesia like NTG injections. The impact of PACAP on migraine attacks involves PAC1 receptor internalization and PKA and ERK signaling pathways. This is the first research to show that inhibiting PACAP-induced PAC1 receptor internalization improves hyperalgesia in CM rats by restricting ERK signaling. PACAP-induced trigeminal vascular activation requires further study to determine the process and uncover additional targets that modulate PAC1 receptor internalization with specificity.
Zhai et al. (67)	SD rats 230–250 g Male	NTG induced	50 μg/kg and 100 μg/kg perampanel	PKC PLC PKA CREB PACAP	ELISA Western blot	Perampanel inhibited PACAP expression in an *in vitro* research by inhibiting the cAMP/PKA/CREB pathway. However, the mechanism by which perampanel affects the cAMP/PKA/CREB pathway is complex and uncertain. Studying the protective benefits of perampanel against diseases like migraine can shed light on the causes of nervous system problems and aid in developing effective treatments.
Mason et al. (68)	ICR mice PAR2KO mice Male and female 5–8 weeks	NTG induced	10 μL /g	IL6	Mechanical hypersensitivity and grimace assays Facial hypersensitivity Mouse grimace scale	They demonstrate that PAR2 activation and IL-6 signaling can prime a NO donor through different methods. Targeting IL-6 in people is currently being tested, but its efficacy in migraine has yet to be determined. This study, together with previous research, strongly suggests that PAR2 may be a promising therapeutic target for migraine.

(Continued)

TABLE 2 (Continued)

Author/ Year	Cell line/ Animal Strain and weight	Induction	ROA/Dose	Biomarkers/ Receptors/Cell culture	Endpoint	Outcome
Ge et al. (69)	SD rats Male 200 ± 10 g	NTG induced	i.p 10 mg/kg	CGRP cfos	Immunohistochemistry Behavioral tests	The integrated approach combining harmacodynamics, metabolomics, and network pharmacology to understand the impact and mechanism of MXFD on migraine. Our integrated analysis revealed two differentially expressed metabolites, 5-MIAA and DCA, and nine targets, including MAOB, MAOA, ADRB1, ADRB2, ADRB3, ADORA2A, ADORA2B, DRD5, and HTR4. MXFD's effectiveness in treating migraine is significantly impacted by these metabolites and targets. This research provides useful data for exploring the mechanisms behind MXFD's therapeutic effects.
A. Filippone et al. (27)	CD1 female and male mice 25-30 g	NTG induced migraine model	i.p 10 mg/kg	NLRP3 IL-18 IL-1β TNF-α NGF BDNF NT-3	Light/dark test, Von frey test, Hot plate test, Orofacial formalin test, ELISA, Immunofluorescence, RT-qPCR, and Histological analysis	Neuronal damage; IL-18, IL-1β, and TNF-α protein expressions; mRNA expressions of these proteins; Nerve growth factor (NGF), Brain-derived neurotropic factor (BDNF), and Neurotrophin-3 (NT3) expressions were dramatically decreased when treated with BAY-117082 at 5 mg/kg and 10 mg/kg. These report suggesting that it significantly modulated Erk/CREB/Akt pathways and could be considered novel strategy therapeutics for migraine treatment.
Pan et al. (70)	C57BL6/J mice 20-25 g	NTG induced	i.p 10 mg/kg	S1PR1 STAT3	Behavioral test qRT-PCR Western blot Immunofluorescence staining	W146 (3-amino-4-(3-hexylphenylamino)-4-oxobutylphosphonic acid) could alleviate chronic NTG induced hypersensitivity and reduce the expression of CGRP, pSTAT3 and c-fos in the Trigeminocervical complex by blocking S1PR1 activity.
Aral et al. (31)	Neonatal mouse	GTN induced	–	CRLR/CGRPR1 MMP9	qPCR, Perl's histochemistry, Immunofluorescence staining and ELISA.	Elevation of nitric oxide which has been demonstrated to have a role in the production of inflammation such as MMP9 and CGRPR1 may regulate cellular iron traffic; hence, different cells and mislocalization of iron within the cell may contribute to migraine pathophysiology via diverse molecular mechanisms.
Ting et al. (71)	C57BL/6 mice 20-25 g	NTG induced migraine model	i.p 10 mg/kg	IL-1β IL-18 CGRP NLRP3	Behavioral tests Rota-rod test Western blot qRT-PCR Immunofuorescence staining	BoNT/A suppressed the expression of the NLRP3 protein and the pro-inflammatory cytokine IL-1β in the TNC produced by NTG, and it may regulate the activity of microglia in the TNC through modulating CGRP. It is possible to interact with microglia, which controls the release of inflammatory factors but, BoNT/A therapy had no effect on LPS-induced pro-inflammatory factor release in astroglia.
Wang et al. (72)	Mice 20 ± 2 g Rat 200-266 g	NTG induced migraine model	i.p 10 mg/kg	CGRP Substance P CCK 5-HT COX-2 CB1R	ELISA Immunohistochemical analysis	. Hejie Zhitong prescription decreases the production of neurotransmitters linked with nociceptive transmission, including as 5-HT, CGRP, and CCK, which may be connected to its overexpression of CB1R and downregulation of COX-2.
He et al. (28)	Male C57BL/6 mice 8–12 weeks old 18-25 g	NTG induced migraine model	i.p 10 mg/kg	c-Fos CGRP p-ERK NLRP3 IL-1β	Sensory sensitivity testing, Western blot, qRT-PCR and Immunofuorescence staining	Both NLRP3 and IL-1 inhibition alleviated hyperalgesia and decreased the increase in biomarkers such as p-ERK, c-Fos and CGRP associated with central sensitization of CM in the TNC. The NLRP3 inflammasome may be a target for controlling CM-associated pain, and inhibiting it may represent a novel therapeutic rationale and technique for migraine treatment.

(Continued)

TABLE 2 (Continued)

Author/ Year	Cell line/ Animal Strain and weight	Induction	ROA/Dose	Biomarkers/ Receptors/Cell culture	Endpoint	Outcome
Kim et al. (73)	Male Sprague Dawley rats 270-300 g	GTN	i.v 10 μg/kg	COX-2 TNF-α MMP9	Western blot analysis and Immunohistochemistry	Proinflammatory mediators such as COX-2, TNF-α, and MMP9 play a role in the NO-mediated migraine pathogenesis cascade. Further research into these inflammatory mediators in the various transcription factor pathways may have pharmacological implications for new migraine therapies.

NLRP, Nod like receptor; IL-Interleukin; MMP, Matrix metalloproteinase; TNF, Tumor necrotic factor; BDNF, Brain derived neurotropic factor; NO, Nitric oxide; RAGE, Receptor for advanced glycation end product; COX, Cyclooxygenase; HMGB, High mobility group box; MAPK, Mitogen activated protein kinase; NFkB, Nuclear factor kappa B; TIMP, Tissue inhibitor of metalloproteinase; ERK, Extracellular signal-regulated kinase; CGRP, Calcitonin gene related peptide; CCK, Cholecystokinin; 5-HT, Serotonin; Iba, Ionized calcium binding adaptor molecule; ROS, Reactive oxygen species; TXNIP, Thioredoxin-interacting protein; TRPA, Transient receptor potential ankyrin; P2X4, P2X purinoceptor 4; P2X7R, P2X purinoceptor 7 receptor; S1PR1, Sphingosine-1-phosphate receptor 1; STAT, Signal transducer and activator of transcription; CXCL1, The chemokine (C-X-C motif) ligand 1; CCL2, chemokine (C-C motif) ligand 2; NGF, Nerve growth factor; NT3, Neurotrophin-3; i.p, Intraperitoneal; s.c, Subcutaneous; i.v, intravenous; p.o, Per oral; NTG, Nitroglycerin; GTN, Glyceryl trinitrate; CCI, Chronic constriction injury; LPS, Lipopolysaccharide; CSD, Cortical spreading depression.

NTG-induced hypersensitivity is via inhibiting S1PR1 activity. An increase in nitric oxide levels may control the pathogenesis of migraines through a variety of molecular pathways. BoNT/A may have a therapeutic function in migraines by reducing the expression of NLRP3 and IL-1β. By influencing neurotransmitter synthesis and the expression of CB1R and COX-2, Hejie Zhitong, when prescribed, may reduce migraine symptoms. A potential new approach to treating migraines could be to inhibit NLRP3, which would lessen hyperalgesia and central sensitization. It has been suggested that proinflammatory mediators such as COX-2, TNF-α, and MMP9 could be viable pharmaceutical targets in the development of migraines caused by NO.

3.4 Comparison

The comparison of findings across the 22 studies underscores the complexity of migraine pathophysiology and highlights the diverse approaches to intervention and treatment. Many studies focus on specific molecular pathways implicated in migraine pathophysiology, such as neuroinflammation (57, 60, 65), oxidative stress (58, 59, 61), and mitochondrial dysfunction (61, 65). These studies suggest that targeting these pathways could offer therapeutic benefits for migraine patients. Various pharmacological agents are explored across the studies, including natural compounds (58, 65), traditional Chinese medicines (59, 66), and novel drugs (62, 67). These interventions aim to modulate molecular targets associated with migraine pathogenesis, highlighting the potential of diverse treatment modalities. Studies utilize different animal models of migraine induction, including NTG-induced models (57, 62, 68, 71), GTN-induced models (31, 73), and others. Variations in animal species, strains, and induction methods contribute to the diversity of findings and insights into migraine mechanisms. Behavioral tests are commonly employed to evaluate migraine symptoms and treatment outcomes across studies, including assessments of mechanical hypersensitivity (59, 61), light aversion (61), and vestibular function (62). These assessments provide valuable insights into the efficacy of interventions in alleviating migraine-associated symptoms. Studies investigate a range of molecular targets implicated in migraine pathogenesis, such as CGRP (58, 64), NLRP3 inflammasome (57, 71), and PACAP/PAC1R signaling (62). Targeting these specific molecules offers potential avenues for developing novel migraine therapies. While the specific mechanisms vary, many interventions exert their therapeutic effects by modulating key signaling pathways associated with migraine, including the NF-κB pathway (57), Nrf2 antioxidant pathway (58, 65), and ERK/CREB/BDNF pathway (62). Understanding these mechanisms provides insights into the underlying biology of migraine and informs the development of targeted therapies. Migraine is one of several neurological illnesses studied using C57BL/6 mice in preclinical settings. Researchers frequently opt to use pre-existing models because they allow them to make use of prior knowledge and procedures, which in turn makes it easier to analyze data and compare it to other studies. Although there is not a foolproof mouse model of migraine because the condition is complex, some mouse strains, such C57BL/6, can experience migraine-like symptoms in response to certain environmental factors. Behavioral abnormalities, nociceptive reactions, and neurochemical changes similar to migraine patients may be among these symptoms. There is a gender difference in migraine prevalence, with women experiencing more attacks than men. To get a full view of the pathogenesis and treatment responses to migraines, it is essential to research both sexes. Researchers may be able to simplify trial design by minimizing any confounding effects due to hormonal fluctuations in females or study sex-specific differences in antimigraine activity by focusing on male mice in this circumstance. Migraine sensitivity and intensity are both affected by hormonal changes, especially changes in estrogen levels. Because male mice do not experience these hormonal changes, researchers can use them to their advantage when designing experiments to determine the effectiveness of antimigraine drugs.

3.5 Outcome

Across the research included in this review, a variety of outcome measures were observed, such as behavioral tests ($n = 9$; 40.09%) (30, 70, 74–76), Sensory sensitivity testing (28), von Frey Testing (27, 77), Light/dark test (27), Von frey test (27). To check the specific biomarker estimation ELISA ($n = 8$; 36.36%) (30, 31, 72, 74, 75, 77–79), Western blot analysis ($n = 9$; 40.09%) (28, 70, 73–75, 79–83), immunohistochemistry ($n = 4$; 18.18%) (72, 73, 75, 77, 78, 81, 82),

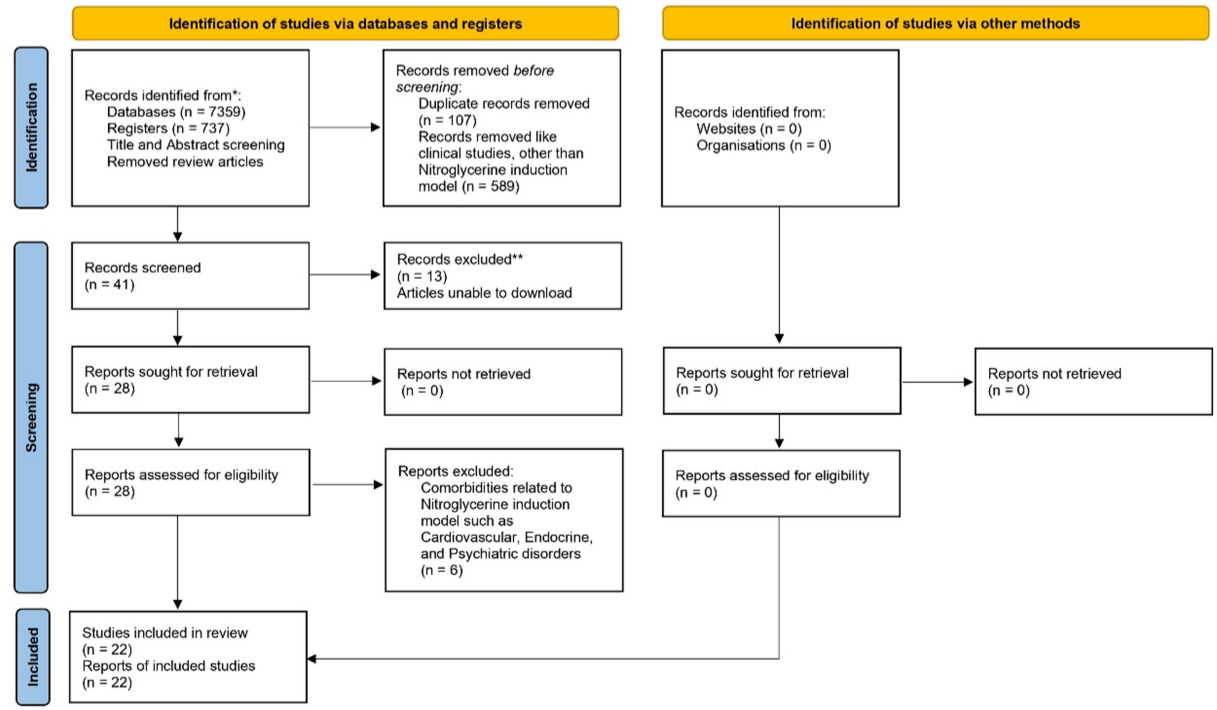


FIGURE 1
Schematic representation of article screening.

Histopathology (27), Immunofuorescence staining ($n = 9$; 40.09%) (27, 28, 30, 31, 70, 76, 78), and for gene expression used qRT PCR ($n = 7$; 31.81%) (27, 28, 31, 70, 74, 77, 78, 80, 81, 83). The majority of researchers, around 60–70%, neglect to validate their experiments using behavioral tests, Western blotting, Immunofluorescence, and Immunohistochemistry, despite these tests being crucial for experimental validation.

The systematic review reveals a significant association between NLRP3 and MMP9 expression levels and migraine progression. Elevated levels of both NLRP3 and MMP9 are consistently observed in migraine patients compared to controls, suggesting their potential involvement in the pathophysiology of the condition. Furthermore, the review highlights the inflammatory cascade initiated by NLRP3 activation and subsequent MMP9 release as a potential mechanism underlying migraine pathogenesis. These findings underscore the importance of targeting NLRP3 and MMP9 pathways for the development of novel therapeutic strategies aimed at mitigating migraine progression and improving patient outcomes.

3.6 Risk of bias

The results of the risk of bias evaluation, conducted using SYRCLE's RoB tool, are summarized in Figure 2. Notably, there was a high risk of selection-bias, performance-bias, and detection-bias identified in the assessed studies. While all studies addressed sequence generation and allocation concealment, clarity regarding random grouping was absent in nine of them. Most studies adequately presented baseline characteristics, although three studies lacked clarity in this regard. All included studies explicitly reported random housing of animals. For the assessment of random outcome, 12 studies exhibited some degree of clarity, while it remained unclear in two studies. In most instances, there were efforts to blind investigators during behavioral outcome assessment, and histological examination was consistently blinded across all 22 studies. An overall unclear risk of bias was found in the category of attrition bias. While all studies reported complete outcome data, they did not offer clear explanations for the reasons behind or methods for handling missing data. To assess the interrater reliability among the reviewers, Cohen's kappa statistics were employed. To ensure impartiality in the study, Mrs. Pavithra, who was blinded to it, was randomly assigned the selection of a subset of studies for evaluation. The kappa test was utilized to gauge the degree of agreement and potential discrepancies among the reviewers.

Kappa tests were carried out among all reviewers to validate the consistency between their assessments, revealing a substantial level of agreement. Specifically, the actual kappa score between RR and IK was calculated at 1.000 (SE of kappa = 0.000; 95% CI: 1.000–1.000; weighted kappa = 1.000), while the score between IK and CV was 0.741 (SE of kappa = 0.168; 95% CI: 0.412–1.000; weighted kappa = 0.763). CV and AS demonstrated a score of 0.745 (SE of kappa = 0.171; 95% CI: 0.570–1.000; weighted kappa = 0.836), AS and RR had a score of 0.685 (SE of kappa = 0.198; 95% CI: 0.410–1.000; weighted kappa = 0.774), AS and ASS scored 0.763 (SE of kappa = 0.150; 95% CI: 0.468–1.000; weighted kappa = 0.696), RR and CV scored 0.770 (SE of kappa = 0.217; 95% CI: 0.345–1.000; weighted kappa = 0.781), RR and AS scored 0.767 (SE of kappa = 0.214; 95% CI: 0.348–1.000; weighted kappa = 0.774), IK and AS showed a score of

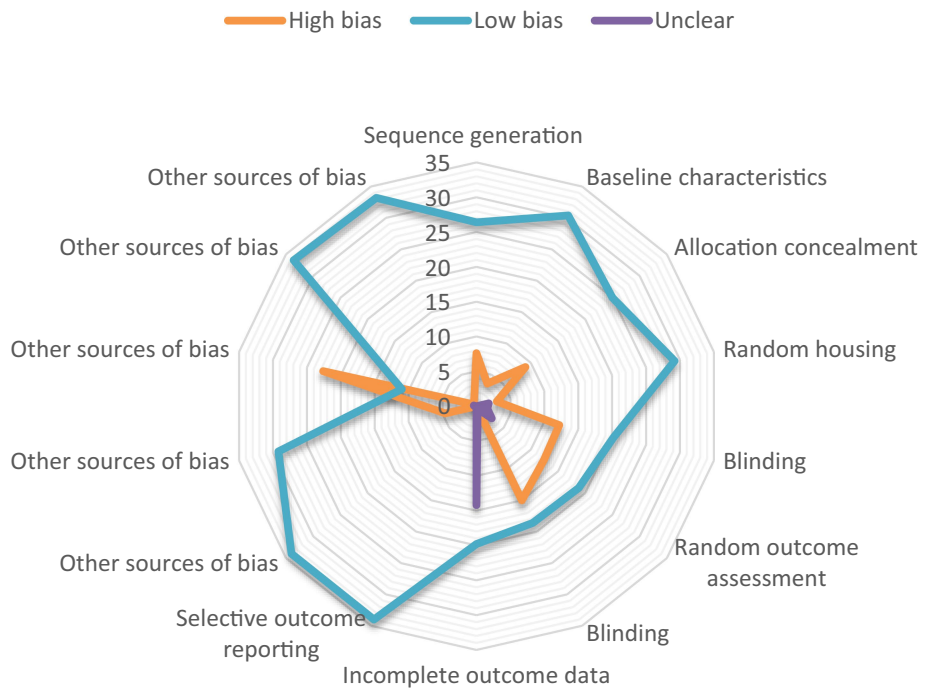


FIGURE 2
The risk of bias was analysed for all the authors. The proportion of studies with a high risk of bias categorised as 'Yes' is indicated in orange. The blue colour represents the proportion of studies with a low risk of bias labelled as 'No,' while the purple colour represents the proportion of study with an unclear response to the stated issue.

0.641 (SE of kappa = 0.319; 95% CI: 0.015–1.000; weighted kappa = 0.650), RR and ASS showed a score of 0.841 (SE of kappa = 0.137; 95% CI: 0.572–1.000; weighted kappa = 0.708), IK and ASS showed a score of 0.803 (SE of kappa = 0.160; 95% CI: 0.490–1.000; weighted kappa = 0.632), CV and ASS showed a score of 0.853 (SE of kappa = 0.140; 95% CI: 0.579–1.000; weighted kappa = 0.865). Analysis of the data reveals consistent agreement among most author pairs, with some demonstrating substantial agreement, such as IK-CV (Kappa = 0.763), CV-AS (Kappa = 0.774), RR-CV (Kappa = 0.781), and RR-AS (Kappa = 0.774). However, there are instances of only fair to moderate agreement, as seen in IK-AS (Kappa = 0.65) and IK-ASS (Kappa = 0.632). Notably, the agreement between CV and ASS authors stands out with almost perfect agreement (Kappa = 0.865), contrasting the fair to moderate agreements found elsewhere. The majority of the studies included in this systematic review exhibited medium to high methodological quality, as evaluated by SYRCLE's RoB tool. The statistical representation of the quality assessment is provided in Figure 3.

3.7 Quality assessment

We meticulously reviewed and assessed all reports using the standard checklist provided by SYRCLE's-RoB tool. Cohen's-kappa statistic was employed to ascertain the agreement between two/more raters. Among the 22 studies, it was noted that 8 of them incorporated a random component in the sequence-generation processes, whereas only 9 studies are employed C57/BL6 mice weighing between 20 and 25 g; the remaining studies used a variety of weight ranges for evaluation. The issue of investigator blinding was insufficiently addressed in all the studies, and allocation concealment was not blinded in 2 of them. Nearly all studies mentioned the random housing of animals, and 1 study provided clear documentation of blinding the outcome assessors. All the studies were ensured the random assignment of animal outcome evaluation. However, two studies inadequately addressed the handling of incomplete outcome data. There was a general lack of documentation regarding other potential causes of bias including medication dropouts, pooling, unit of analysis errors, design specific bias, and conflicts of interest.

4 Discussion

All 22 preclinical investigations suggested that based on the different behavioral tests, biochemical parameters, histological and immunohistochemistry reports revealed that Nitroglycerine has the capacity to damage the neuronal cells, over expression of NLRP3, Brain derived neurotrophic factor (BDNF), Nerve growth factor (NGF), RIPK1 activation, neuroinflammation, cognitive impairment, NFkB, TXNIP, ADAR3, p-ERK, c-Fos, HMGB1 and Neurotrophin-3 (NT3) may be responsible for the migraine attack. After extensive literature reviews and discussions, we concluded that the NTG-inducing model (10 mg/kg) is the most suitable for inducing the production of NLRP3, MMP9, and other proinflammatory molecules

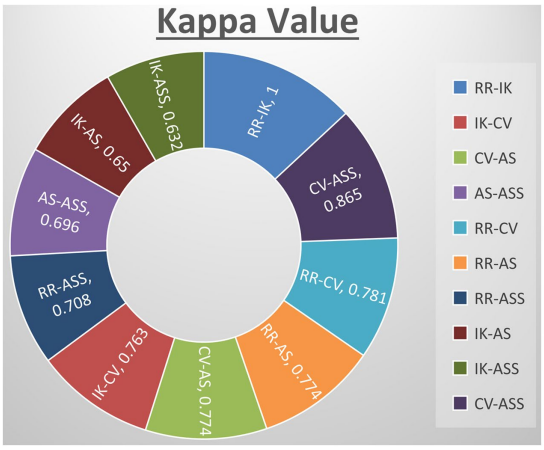


FIGURE 3
Quantify agreement by kappa value of all authors. RR-KI and VC-SA reported perfect agreement and rest others showed substantial agreement.

in rodents, making it widely accepted as a universal animal model for studying migraines. Elevated levels of nitric oxide, which have been associated with neuroinflammation, might regulate the movement of cellular iron. As a result, variations in iron distribution within cells could contribute to migraine pathophysiology through diverse molecular mechanisms. Brain-derived neurotrophic factor (BDNF) is linked to the modulation of pain and central sensitization. There is a growing suspicion of BDNF's involvement in the pathophysiology of migraine and cluster headaches, primarily because of its established interaction with calcitonin gene-related peptide (84). From a clinical perspective, there is a need for increased research emphasis on NLRP3 and BDNF, as this may offer more effective solutions for migraine treatment. Studies have revealed that female mice are more susceptible to migraine compared to male mice. Through the induction of NTG (10 mg/kg) injection, researchers have observed that the end products of the NLRP3 inflammasome, specifically cytokines, elevate neurotrophic factors that play a crucial role in the pathological processes associated with the progression of migraines. Their critical findings indicate that NLRP3 is capability to mature IL1-β and is involved in the production of IL-10. Elevated levels of neurotrophic factors, particularly BDNF, may also influence NTG through the CREB/Erk/Akt pathways (27, 28, 30, 70, 75, 82). In the context of a neuropathic pain model, S1PR1 on glial cells influenced various downstream signaling pathways, including the MAPK pathways and the NLRP3 inflammasomes (85–87). S1PR1 signaling enhances the production of IL-1β by upregulating NLRP3 (70, 88–90). Wang, Yuan, and their research team provided scientific evidence indicating that the expression of the NLRP3 protein occurs in a specific manner via the P2X7R and P2X4 receptors (30, 75). These receptors can be potential targets for impeding the generation of proinflammatory molecules via NLRP3 inflammasomes in the brain, potentially aiding in the treatment of migraines (30, 75, 91). However, Fan et al. discovered that NFκB primarily plays a critical role in activating NLRP3 via TRPA1 (80). Kimono and their research team made an intriguing observation that the activation of the NLRP3 inflammasome is prompted by elevated levels of reactive oxygen species (ROS) (92). The stimulation of NLRP3 inflammasomes was linked with elevated levels of IL1β and IL18 in the brain, potentially contributing to neuroinflammation (82). An intriguing discovery is that the modulation of NLRP3-IL1β signaling plays an important role in the transition from acute to chronic neuroinflammation is represented in Figure 4, particularly driven by brain microglia. Upon activation of the Trigeminal nerve system pathway, microglia release an array of chemokines, cytokines, as well as free radicals including nitric oxide and reactive oxygen species. Nevertheless, further investigation into brain microglia is necessary to advance therapy (76). Excessively active microglia can potentially lead to neuroinflammation and tissue damage. Interestingly, both PAMP s and DAMP s are implicated in the process of neuroinflammation (93–95). PAMP s initiate the priming signaling molecule for the NLRP3inflammasome, while DAMP s serve as the second signaling molecule, fostering neuro inflammation and enabling the transmission of pain signal from primary to higher centers (79, 96). TXNIP NLRP3 plays a critical role in microglia mediated neuroinflammation. The buildup of NLRP3 leads to increased caspase1 activation and maturation (97–99). Consequently, caspase1 has the capacity to cleave pro-IL1β and pro-IL18, amplifying the proinflammatory response (78, 100–102). The Li et al. explored the presence of ADARs genes in various human tissues, which exhibit a specific down-regulation of the NLRP3 inflammasome. This discovery could potentially be identified as a novel target for migraine treatment (83, 103). MMP9 is typically regarded as an inflammatory mediator (104). Elevated MMP9 levels intensify the interconnected inflammatory processes involving CCL2 and CXCL1 (105). MMP9 is among the biomarkers that might serve as an alternative therapeutic target to disrupt BBB integrity in astrocytes, and its role in migraine pathogenesis is of significant importance to explore (31, 106–109). Several key discoveries from this systematic review were emphasized, notably the association between PX7R, RIPK, P2X4 receptor activation, NLRP3, and MMP9 in the genesis of migraines. The interconnected relationship between NLRP3 and MMP9 was depicted in Figure 5. Concentrating on these markers could offer potential solutions to alleviate the ongoing challenges faced by individuals dealing with migraines.

Activation of NLRP3 and upregulation of MMP9 contribute to neuroinflammation, which is increasingly recognized as a key factor in migraine pathogenesis. Neuroinflammation can sensitize trigeminal nociceptive pathways, leading to the generation and propagation of migraine pain. MMP9-mediated disruption of the blood–brain barrier can facilitate the entry of inflammatory cells and molecules into the brain parenchyma, exacerbating neuroinflammation and promoting migraine attacks. Both NLRP3 activation and MMP9 upregulation have been implicated in the sensitization of pain pathways, enhancing the perception of pain associated with migraine attacks and potentially contributing to the development of chronic migraine. Cortical spreading depression (CSD), a wave of neuronal depolarization followed by suppression of neuronal activity, is believed to underlie the aura phase of migraine (110). NLRP3 inflammasome activation and MMP9-mediated neuroinflammation may modulate the susceptibility to CSD, influencing the frequency and severity of migraine attacks. The roles of NLRP3 and MMP9 in migraine pathophysiology not only sheds light on the underlying mechanisms of the disease but also identifies potential therapeutic targets. Targeting these molecules or their downstream pathways could offer new strategies for the treatment and management of migraine, particularly in patients who do not respond to currently available therapies.

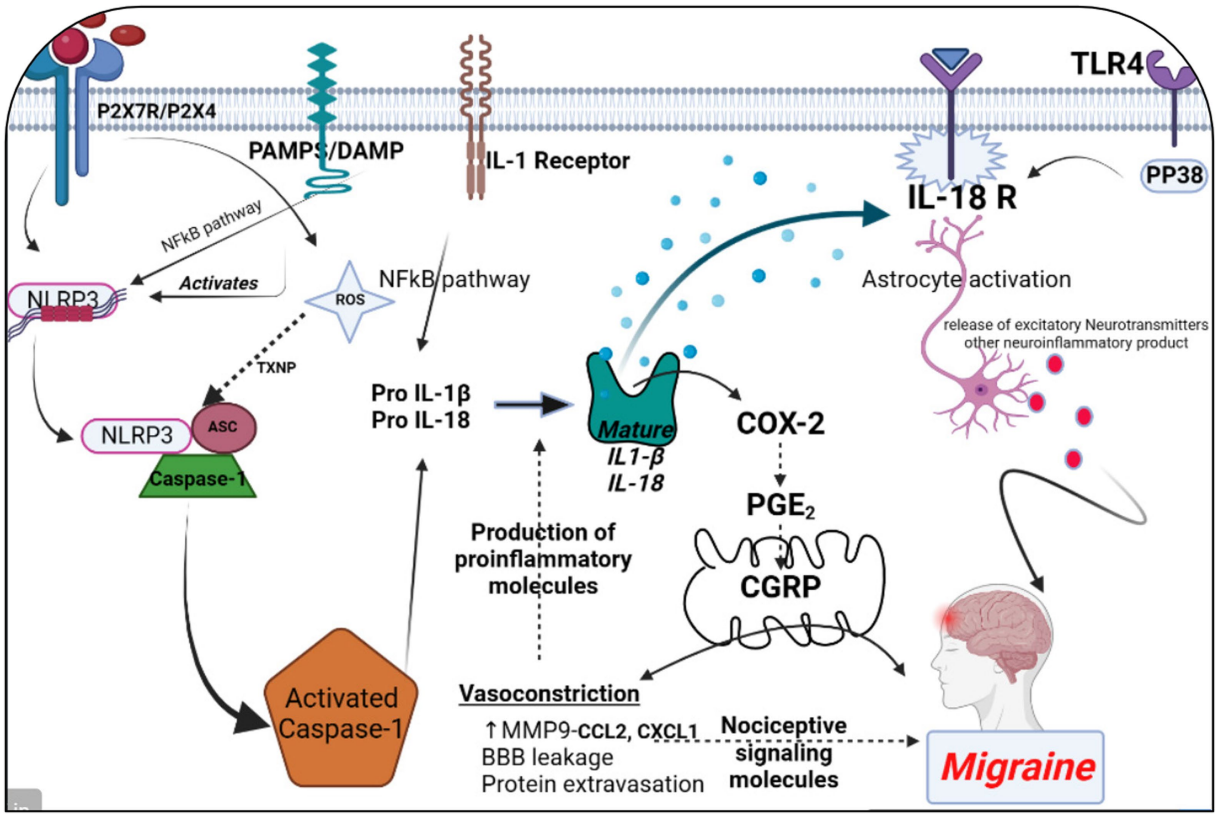


FIGURE 4
The significance of NLRP3 and MMP9 in the context of a migraine episode involves the generation and refinement of proinflammatory signaling molecules through various receptors, including P2X7R, P2X4, PAMPs or DAMP, TLR4, IL-1β, and IL-18 receptor activation. This process triggers the release of CGRP, leading to vasoconstriction by enhancing the maturation of IL-1β. Simultaneously, an elevation in MMP9 levels results in blood–brain barrier permeability and the leakage of proteins due to vasoconstriction. This phenomenon contributes to the further production of proinflammatory molecules. Additionally, astrocyte activation plays a pivotal role in the release of excitatory neurotransmitters and other neuroinflammatory substances within the brain, collectively contributing to the onset of a migraine attack. The figure was created with BioRender.com.

Treatment with TREM1 modulation in C57BL/6J male mice and BV2 cells revealed potential therapeutic insights for chronic migraine, while interventions including Dl-3-n-butylphthalide (NBP), Wuzhuyu Decoction, AMPK activator, UA, and RUT demonstrated varied mechanisms in reducing migraine severity and neuroinflammation across different mouse models and cell lines. SYRCLE's RoB tool was used by reviewers IK, RR, ASS, CV, and AS to thoroughly assess all the studies included in the analysis. The majority of these studies effectively reported critical aspects such as sequence generation, allocation concealment, baseline characteristics, blinding, animal housing, randomization of outcome assessment, and comprehensive outcome data, which enhanced the reliability of their findings. However, it's worth noting that a few studies failed to provide adequate details regarding blinding and the proper execution of outcome assessment randomization ($n = 14$).

Several factors led us to conclude that nitroglycerin models alone would be sufficient for our purposes. To begin, nitroglycerin-induced migraine models have shown to be a reliable way to replicate migraine symptoms in the lab, making them a popular choice for migraine studies. An effective tool for studying the biology of migraines and assessing possible treatments, this model has undergone thorough characterization and validation in clinical and preclinical investigations. The second benefit of nitroglycerin-induced migraine models is that they can reproduce both the acute and chronic phases of migraine, including the onset of headaches, pain sensitization, and the emergence of migraine-related symptoms like photophobia and nausea. Since nitroglycerin models capture all the hallmarks of migraine pathophysiology, they are ideal for investigating different facets of this condition and evaluating potential new treatments. We are aware that there are additional models for migraines; for example, the cortical spreading depression model and animal models that include inflammatory mediators or other migraine triggers, such as CGRP, and we have incorporated these into our exclusion criteria. In our work, we found that nitroglycerin models allowed us to examine migraine mechanisms in a clear and concentrated manner.

Taking over-the-counter pain relievers like ibuprofen or acetaminophen frequently for headache relief can lead to medication overuse headaches or rebound headaches. This phenomenon occurs when the body becomes dependent on the medication, and headaches recur as the medication wears off (111). Overuse of certain medications can disrupt the body's natural pain-regulating systems and lead to increased sensitivity to pain, perpetuating a cycle of headaches. Studies have shown that individuals with obesity are more likely to experience migraines compared to those with a healthy weight. For instance, a person

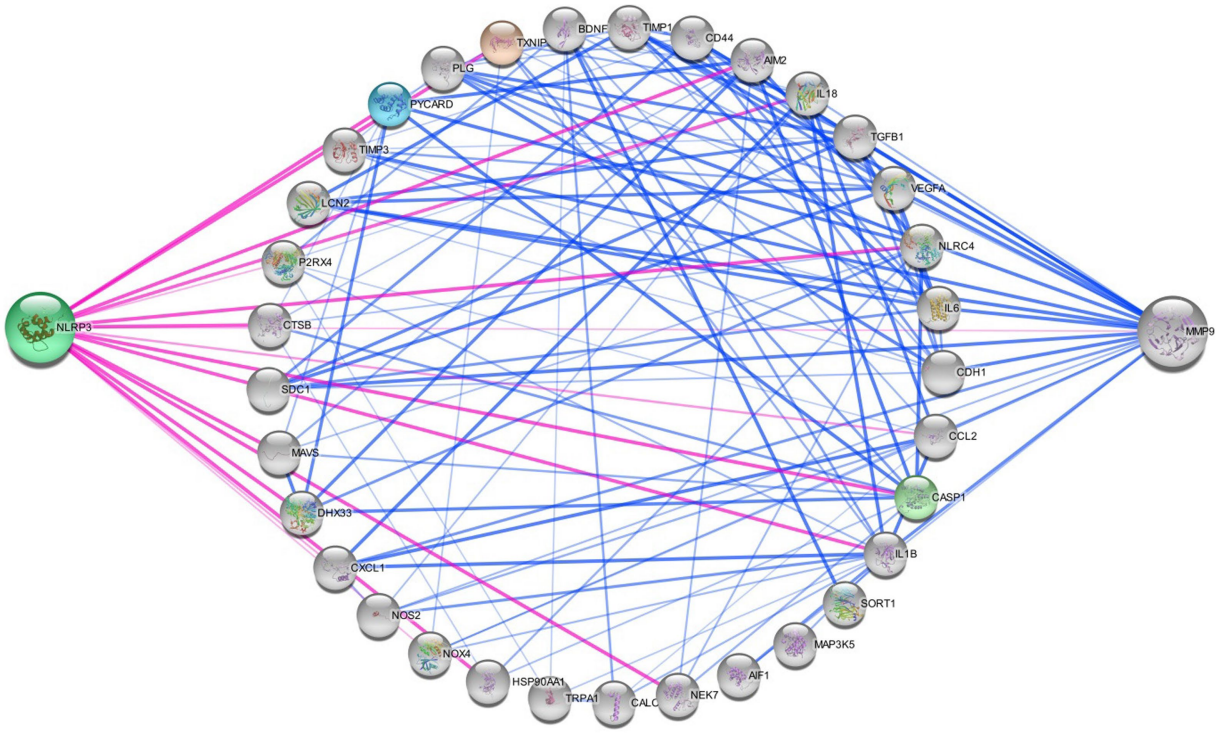


FIGURE 5
Networking of migraine targets. The figure illustrating that the different proteins interlinked with NLRP3 and MMP9 in migraine attack. There are different connecting targets of NLRP3 and MMP9 are analysed by protein–protein interaction in string database that NOX4, IL1B, P2RX4, NOS2, IL18, CCL2, TRPA1, CALCA, MAP 3 K5, TXNIP etc. are connected to migraine progression.

who is obese may have a higher likelihood of experiencing migraines triggered by hormonal changes associated with adipose tissue (112). The exact mechanisms linking obesity and migraines are not fully understood, but factors such as inflammation, adipose tissue-derived hormones, and metabolic changes may play a role in migraine development and progression. Individuals with obstructive sleep apnea may experience frequent interruptions in breathing during sleep, leading to oxygen desaturation and fragmented sleep patterns. These disruptions can trigger migraines or make existing migraines worse (113). Sleep disturbances like snoring and sleep apnea can alter neurotransmitter levels, increase inflammation, and affect the regulation of pain pathways, all of which may contribute to migraine susceptibility. A person who sustains a concussion in a car accident may develop post-traumatic headaches, which can evolve into chronic migraines over time (114). Traumatic brain injuries can cause structural and functional changes in the brain, including alterations in neuronal excitability, neurotransmitter levels, and pain processing pathways, all of which may contribute to the development and progression of migraines. Individuals who have experienced physical or sexual abuse may have a higher prevalence of migraines compared to those who have not experienced such trauma. The chronic stress associated with trauma can contribute to changes in brain chemistry and increase the risk of developing migraines (115). Traumatic experiences can lead to persistent alterations in stress response systems, neurotransmitter function, and emotional regulation, which may increase vulnerability to migraine attacks. Hypothyroidism, characterized by an underactive thyroid gland, can lead to hormonal imbalances that may influence migraine development. For instance, fluctuations in thyroid hormone levels can affect serotonin levels in the brain, which are implicated in migraine pathophysiology (116). Thyroid hormones play a role in regulating metabolism, neurotransmitter function, and vascular tone, all of which can impact migraine susceptibility and severity. Iron deficiency anemia, a common type of anemia, can result in reduced oxygen delivery to tissues, including the brain, which may trigger migraines or exacerbate existing headaches (117). Iron is essential for the synthesis of neurotransmitters and the maintenance of healthy blood vessels. Iron deficiency can lead to alterations in brain function and vascular reactivity, increasing the risk of migraine attacks. Individuals with anxiety or depression are more likely to experience migraines compared to those without these mental health conditions. Stress, dysregulated neurotransmitter levels, and altered pain processing pathways associated with anxiety and depression can contribute to migraine susceptibility and severity (118). Anxiety and depression are associated with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, increased inflammation, and changes in serotonin and noradrenaline levels, all of which may influence migraine pathophysiology. Chronic tension-type headaches or frequent episodic headaches may precede the onset of chronic migraines in some individuals. Over time, these headaches may become more frequent and severe, transitioning into chronic migraines (119). Frequent headaches, regardless of their specific type, can lead to sensitization of pain

pathways and alterations in pain processing mechanisms, increasing the likelihood of developing chronic migraines.

5 Limitations

5.1 Excluded papers

Several papers were omitted from consideration due to restricted access, as their complete texts were not freely available. This selective exclusion could potentially introduce publication bias and influence the outcomes of the review. It underscores the critical importance of comprehensive literature access to mitigate bias in systematic reviews.

5.2 Pooling of statistical data

The utilization of diverse animal models across the included studies precluded the feasibility of conducting a meta-analysis. This limitation notably impacts the robustness of quantitative synthesis. Emphasizing the value of narrative synthesis within the context of varied study designs is imperative. We will delve into the implications of the inability to amalgamate statistical data, thus ensuring a thorough understanding.

5.3 Sample size constraints

We acknowledge the constraint posed by the sample sizes within our included studies. A larger sample size could undoubtedly offer a more exhaustive comprehension of the subject matter. The necessity for forthcoming studies with expanded sample sizes to corroborate and generalize our findings will be duly emphasized.

5.4 Preclinical emphasis and translatability

Our focus primarily rests on preclinical investigations employing animal models, which may not fully encapsulate the intricate nature of migraine in humans. We recognize the inherent limitations in extrapolating findings from animal studies to human physiology. Hence, we underscore the imperative for translational research to bridge this gap and address the challenges in clinical applicability.

5.5 Gender bias consideration

The potential presence of gender bias in preclinical studies warrants attention and consideration, particularly concerning its ramifications on the generalizability of findings. We will thoroughly explore the issue of gender bias in preclinical research and its implications for comprehending migraine pathophysiology across diverse gender populations.

These adaptations and expansions within our discussion aim to enrich the critical appraisal of our research and augment the depth of understanding within the field of migraine progression. We greatly value your constructive feedback, which serves to refine the quality and relevance of our manuscript.

6 Highlights

This study delves into the potential roles of NLRP3 and MMP9 as biomarkers in the pathophysiology of migraine, shedding light on the underlying mechanisms of this complex neurological disorder. The study rigorously evaluates the methodological quality of 22 preclinical studies, enhancing the reliability of the findings and offering a robust foundation for further research in this field. It highlights the interconnected relationships between NLRP3, MMP9, and various other biomarkers, providing a comprehensive overview of their potential contributions to migraine attacks. The study provides valuable insights into the preclinical aspects of migraine, emphasizing the need for further research to bridge the gap between animal models and clinical applications. The study underscores the necessity for continued research in both preclinical and clinical settings to better understand the complex mechanisms of migraine and develop more effective treatments. The study touches on the gender bias observed in migraine susceptibility, emphasizing the importance of considering gender specific factors in future research and treatment strategies. The study transparently acknowledges its limitations, including small sample size, potential selection bias, and publication bias, ensuring a balanced interpretation of the findings. By identifying potential biomarkers and their roles in migraine, this study contributes to the ongoing efforts to improve migraine management and therapy, ultimately benefiting individuals worldwide who experience this disabling condition.

7 Conclusion and future perspective

In conclusion, this systematic review significantly advances our understanding of the intricate relationship between NLRP3 and MMP9 and their potential implications in the pathophysiology of migraine. Drawing insights from a comprehensive analysis of 22 preclinical studies utilizing specific animal models, this review sheds light on the interconnected pathways involving NLRP3 and MMP9, offering valuable clues to their involvement in migraine attacks. While the study's rigorous evaluation of method quality and comprehensive analysis of biomarkers and behavioral tests enhance its credibility, several limitations warrant consideration. These include potential biases such as selection bias, small sample sizes, publication bias, and gender bias, which may affect the generalizability of the findings. Moreover, the reliance on animal models, while informative, may not fully capture the complexity of migraine in humans, limiting the direct applicability of the results to clinical practice. Despite these limitations, this review underscores the urgent need for further research, both in preclinical and clinical settings, to unravel the roles of NLRP3 and MMP9 in migraine pathogenesis comprehensively. Addressing the identified limitations and diversifying the scope of animal models and human studies are imperative steps toward bridging the translational gap between preclinical insights and clinical applications. In the pursuit of improved migraine management and therapy, ongoing investigations into specific biomarkers and their interplay hold immense promise. Future research endeavors should strive to transcend the confines of animal models, embracing a holistic approach that integrates preclinical findings with clinical observations. By doing so, we can aspire to develop more effective treatments and interventions, offering relief to the millions worldwide burdened by

this debilitating neurovascular disorder. Future research should aim to bridge the gap between preclinical findings and clinical applications, ultimately benefiting the millions of individuals worldwide who suffers from this debilitating neurovascular disorder.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

RR: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Data curation, Methodology. AS: Investigation, Writing – review & editing, Conceptualization, Data curation, Methodology, Writing – original draft. SA: Data curation, Methodology, Writing – original draft. VC: Formal analysis, Investigation, Supervision, Validation, Visualization, Writing – review & editing. KI: Formal analysis, Investigation, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

NLRP3	Nod like receptor-3
MMP9	Matrix metalloproteinase 9
DALY	Disability-adjusted life years
RIPK1	Receptor interaction protein kinase
TNF	Tumor necrotic factor
BDNF	Brain derived neurotropic factor
NO	Nitric oxide
RAGE	Receptor for advanced glycation end product
COX	Cyclooxygenase
HMGB	High mobility group box
MAPK	Mitogen activated protein kinase
NFkB	Nuclear factor kappa B
TIMP	Tissue inhibitor of metalloproteinase
ERK	Extracellular signal-regulated kinase
CGRP	Calcitonin gene related peptide
CCK	Cholecystokinin
5-HT	Serotonin
Iba	Ionized calcium binding adaptor molecule
ROS	Reactive oxygen species
TXNIP	Thioredoxin-interacting protein
TRPA	Transient receptor potential ankyrin
P2X4	P2X purinoceptor 4
P2X7R	P2X purinoceptor 7 receptor
S1PR1	Sphingosine-1-phosphate receptor 1
STAT	Signal transducer and activator of transcription
CXCL1	The chemokine (C-X-C motif) ligand 1
CCL2	Chemokine (C-C motif) ligand 2
NGF	Nerve growth factor
NT3	Neurotrophin-3
NTG	Nitroglycerin
GTN	Glyceryl trinitrate
CCI	Chronic constriction injury
LPS	Lipopo lysaccharide
CSD	Cortical spreading depression

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Vortioxetine treatment for neuropathic pain in major depressive disorder: a three-month prospective study

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Introduction and objective: Several studies revealed the therapeutic potential of vortioxetine (Vo) for pain. In this context, we aimed to evaluate the efficacy of Vo as a safe and tolerable novel pharmacologic agent in treating neuropathic pain (NP) in patients with major depressive disorder (MDD).

Materials and methods: The population of this cross-sectional prospective study consisted of all consecutive patients who were newly diagnosed with MDD by a neurology doctor at a psychiatric clinic and had NP for at least 6 months. All patients included in the sample were started on Vo treatment at 10 mg/day. They were assessed with Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Self-Reported Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS), Douleur Neuropathique 4 Questions (DN4), Montreal Cognitive Assessment (MoCA), and Neuropathic Pain Impact on Quality of Life (NePIQoL) at the beginning of treatment and during the follow visits conducted at the end of the first, second and third months of the treatment. During these follow-up visits, patients were also queried about any side effects of Vo.

Results: The mean age of 50 patients included in the sample, 76% of whom were female, was 45.8 ± 11.2 years. There was a significant reduction in patients' NP complaints based on DN4 and S-LANNS, the subscales of NePIQoL, and significant improvement in MoCA. There was a significant reduction in patients' NP complaints based on DN4 and S-LANNS scores and a significant improvement in scores of the subscales of NePIQoL and MoCA.

Conclusion: The study's findings indicate that Vo, with its multiple mechanisms of action, can effectively treat NP independently of its mood-stabilizing effect. Future indication studies for Vo are needed to establish Vo's efficacy in treating NP.

KEYWORDS

neuropathic pain, major depressive disorder, vortioxetine, Beck Depression Inventory, Beck Anxiety Inventory, cognitive function, quality of life, pain measurement

Introduction

Chronic pain is a devastating clinical situation characterized by persistent or recurrent pain lasting more than 3 months (1). There are a variety of chronic pain conditions with different etiologies, including neuropathic, visceral, musculoskeletal, and cancer-related pain (2). Patients with chronic pain often simultaneously experience depression associated with the

stressful state of chronic pain. Reduced pain threshold, increased pain perception, more pronounced functional limitations, and worse analgesic response are common denominators of patients with chronic pain complicated by depression (1).

Vortioxetine (Vo) is a novel antidepressant with a multimodal mechanism of action (1–3). Vo, the chemical formula of which is 1-[2-(2,4-dimethyl phenyl sulfanyl)-phenyl]-piperazine, is a bis-aryl sulfanyl amine compound. Vo, like many other antidepressants, inhibits the serotonin transporter and, at the same time, modulates the activity of 5-Histamine (5-HT) receptors (2). With its antidepressant and anxiolytic effects, Vo is frequently used in the treatment of major depressive disorder (MDD) (4). Vo's multimodal mechanisms of action enable it also to be used as a sleep modulator. Vo can also be used as a painkiller medication by reducing hyperalgesia and increasing analgesia (1, 2).

Vo has a better safety profile than other antidepressants due to a lower incidence of side effects such as weight gain, sexual dysfunction, and cardiovascular side effects, as well as more consistent procognitive effects (3). These advantages benefit specific patient groups, such as those with higher comorbidities and cognitive disorders (1–3).

Neuropathic pain (NP) is a highly complex chronic condition with perceptual and emotional components, affecting 7 to 10% of the population and often accompanied by anxiety, depression, or sleep disorders (2, 5, 6). Therefore, treatment approaches that consider mood and sleep disorders have come to the fore in treating NP (7).

In light of this information, we aimed to evaluate the efficacy of Vo as a safe and tolerable novel pharmacologic agent in treating NP in patients with MDD.

Materials and methods

Study design

This study was designed as a cross-sectional, prospective study. The study protocol was approved by the Hitit University School of Medicine Ethics Committee (2023-139). The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies[1] and the ethical considerations outlined in the Declaration of Helsinki. Written informed consent was obtained beforehand from the patients included in the study.

Population and sample

The study population consisted of all consecutive patients newly diagnosed with MDD by a neurology doctor at a psychiatric clinic who had an NP for at least 6 months. MDD diagnosis was based on the diagnostic criteria outlined in the Diagnostic and Statistical Manual for Mental Disorders Fifth Edition (DSM-5) (8). Patients with polyneuropathy, entrapment neuropathy, and infective metabolic diseases that could cause NP and a patient with dizziness and not responding to medical treatment were excluded from the study. In the end, the study sample consisted of 50 patients. All patients included in the sample were started on Vo treatment at 10 mg/day. They were assessed with Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Self-Reported Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS), Douleur Neuropathique 4 Questions (DN4), Montreal Cognitive Assessment (MoCA), and Neuropathic Pain Impact on Quality of Life (NePIQoL) at the beginning of treatment and during the follow visits conducted at the end of the first, second and third months of the treatment. During these follow-up visits, patients were also queried about any side effects of Vo.

Statistical analysis

The collected data were statistically analyzed using SPSS 26.0 (Statistical Product and Service Solutions for Windows, Version 26.0, IBM Corp., Armonk, NY, US, 2019) software package. Descriptive statistics were expressed as mean ± standard deviation and percentage values. The change in measurements over time was analyzed using the repeated analysis of variance (ANOVA) test. Differences in measurements conducted at different times were analyzed using the independent *t*-test between two groups and the one-way ANOVA test between three or more groups. Pearson's correlation test was used to analyze the relationships between the measurements.

The significance of the findings obtained from repeated measurements was determined by Tukey's method for multiple comparisons. In cases where the assumptions of normal distribution and repeated measures ANOVA were not met, the Friedman test was used to analyze the changes over time. Multiple comparisons of measurements found to be significant in the Friedman test were performed using the Durbin-Conover test. Probability (p) statistics of ≤ 0.05 were deemed to indicate statistical significance.

Results

The mean age of 50 patients included in the sample, 76% of whom were female, was 45.8 ± 11.2 years. Most patients were secondary school graduates (64%) and married (72%). The sociodemographic and clinical characteristics of the patients included in the sample are given in Table 1.

As side effects of Vo, nausea was observed in six patients, dizziness in two patients, headache in one patient, diarrhea in one patient, and constipation in one patient during the three-month follow-up period, most of which occurred in the first 2 weeks after starting the treatment.

A significant gradual increase in mean MoCA score over the course of the follow-up period compared to baseline revealed that Vo had a significant positive effect on patients' cognitive function (25.6 ± 3 vs. 23.1 ± 4.3, $p < 0.001$) (Table 2; Figure 1A).

The significant gradual decrease in mean BDI score over the course of the follow-up period compared to baseline revealed that Vo significantly reduced patients' depression severity (26.9 ± 10.7 vs. 41.7 ± 6.4, $p < 0.001$, Figure 1B). Similarly, a significant decrease in median BAI score at the end of the follow-up period compared to baseline revealed that Vo significantly reduced patients' anxiety severity ($p < 0.001$) (Table 2; Figure 1C). There was also a significant gradual decrease in the median S-LANNS score over the course of the follow-up period and a significant decrease in median DN4 at the end of the follow-up period compared to baseline ($p < 0.001$ for both cases) (Table 2; Figures 1D,E). The mean total NePIQoL score and mean

1 www.strobestatement.org

NePIQoL subscale scores increased significantly over the course of the follow-up period compared to baseline ($p < 0.001$; Table 2; Figure 1F).

The changes in patients' scores obtained from the assessment tools are shown in Figures 1A–F.

The mean BDI score of male patients was significantly higher than that of female patients ($p = 0.042$). There was no significant difference in other measurements between gender groups ($p > 0.05$; Table 3). There was also no significant difference in baseline mean BDI score between groups created based on marital status, i.e., married, single, and divorced ($p = 0.057$). On the other hand, there were significant differences between marital status groups in mean BDI scores assessed at the first-, second-, and third-month follow-up visits ($p < 0.05$; Table 3).

There were significant differences in mean BDI scores assessed at baseline and first-month follow-up visits between groups created based on educational status, i.e., middle school graduates, high school graduates, and university graduates ($p < 0.039$ and $p = 0.014$). Patients with higher educational statuses had significantly higher baseline BDI scores assessed at baseline and first-month follow-up visits than those with lower educational statuses (Table 3).

The mean total NePIQoL score was significantly higher in patients over 55 than those younger than 55 ($p = 0.009$; Table 4).

Analysis of the assessments conducted during the third-month follow-up visit revealed that the mean BDI score had a strong positive correlation with mean BAI score ($r = 0.682$) and a strong negative correlation with mean total NePIQoL score ($r = -0.710$; Table 5).

TABLE 1 Sociodemographic and clinical characteristics of the patients.

	Overall ($n = 50$)
Age (year)†	45.8 ± 11.2
Age groups‡	
<55 years	38 (76.0)
≥55 years	12 (24.0)
Gender‡	
Female	37 (74.0)
Male	13 (26.0)
Education level‡	
Secondary school	32 (64.0)
High school	10 (20.0)
Bachelor/master	8 (16.0)
Marital status‡	
Married	36 (72.0)
Single	7 (14.0)
Divorced	7 (14.0)
Hypertension‡	4 (8.0)

†Mean ± Standard Deviation, ‡*n* (%).

Discussion

It is known that symptoms of depression and anxiety frequently occur in patients with chronic pain, as in patients with chronic diseases. Depression is the most common psychological complication and comorbid condition in patients with chronic pain. Depression accompanying chronic pain causes a decrease in pain threshold, an increase in nociceptive sensitivity, further functional limitations, and reduces the patient's response to analgesia. There may also be a reciprocal relationship between chronic pain and anxiety and/or depression. It has been reported in the literature that pain and depression interact and that depression plays a role in the development and maintenance of chronic symptoms (9).

Although a wide variety of antidepressant medications are available for use, Vo differs from other antidepressant drugs in its combination of pharmacological properties (10). Vo's mechanisms of action include increasing 5-HT levels by inhibiting the serotonin transporter. Thus, Vo offers an advantage compared to other antidepressants in that it has lower therapeutic dose ranges of 5–20 mg. In addition, Vo produces twice as much serotonin through 5HT receptors by different mechanisms, including antagonism of 5HTD1, 5HT3, and 5HT7, agonism of 5HT1A, and partial agonism of 5HT1B (11). Thus, Vo treatment is less likely to cause emotional blunting and

TABLE 2 Changes in the assessment scores over the study period.

	Baseline	Month 1	Month 2	Month 3	*p*-value
MoCA score†	23.1 ± 4.3	23.4 ± 4.4	24.6 ± 4.0	25.6 ± 3.4	**<0.001***
Beck depression Scale score†	41.7 ± 6.4	37.0 ± 5.2	32.1 ± 9.0	26.9 ± 10.7	**<0.001***
Beck anxiety scale score§	26.0 [8.0–58.0]	20.0 [8.0–51.0]	23.0 [8.0–50.0]	18.0 [6.0–44.0]	**<0.001****
S-LANSS score§	17.0 [13.0–24.0]	16.0 [13.0–23.0]	14.0 [10.0–23.0]	13.0 [9.0–23.0]	**<0.001****
DN4 score§	7.5 [5.0–10.0]	7.0 [5.0–10.0]	6.0 [4.0–10.0]	6.0 [4.0–10.0]	**<0.001****
NePIQoL score†	105.4 ± 13.5	111.0 ± 13.6	121.3 ± 23.1	136.7 ± 35.9	**<0.001***
Symptoms§	20.0 [13.0–33.0]	21.0 [14.0–33.0]	24.0 [14.0–40.0]	30.0 [12.0–43.0]	**<0.001****
Relationship§	13.0 [7.0–18.0]	13.5 [7.0–20.0]	15.0 [7.0–20.0]	16.0 [8.0–20.0]	**<0.001****
Daily activities†	35.3 ± 7.7	36.5 ± 7.3	39.6 ± 9.5	44.0 ± 13.7	**<0.001***
Psychological effects§	18.0 [8.0–27.0]	19.0 [8.0–29.0]	21.0 [8.0–36.0]	29.0 [8.0–40.0]	**<0.001****
Personal care†	19.0 ± 4.8	19.6 ± 5.0	21.5 ± 5.6	23.2 ± 5.7	**<0.001***

MoCA, Montreal cognitive assessment test; S-LANSS, Self-Leeds Assessment of Neuropathic Symptoms and Signs; DN-4, Douleur Neuropathique 4 Questions; NePIQoL, Neuropathic pain quality of life questionnaire. *Repeated Measures ANOVA. **Friedman Test. †Mean ± Standard Deviation. §Mean (minimum-maximum score). Bold to indicate values that are statistically significant.

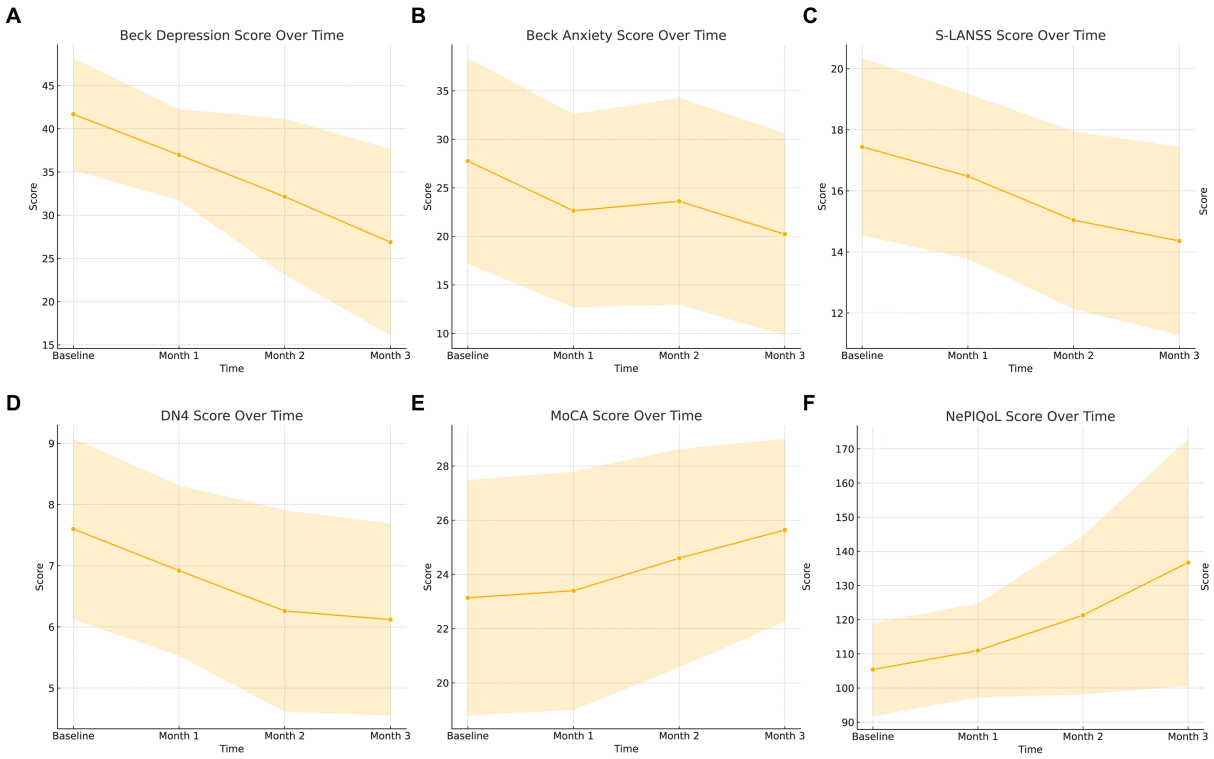

FIGURE 1
(A–F) Graphical summary of the questionnaires used in the study. MoCA, Montreal cognitive assessment test; S-LANSS, Self-Leeds Assessment of Neuropathic Symptoms and Signs; DN-4, Douleur Neuropathique 4 Questions; NePIQoL, Neuropathic pain quality of life questionnaire.

TABLE 3 **Comparison of the beck depression scale scores obtained at different times in terms of gender, marital status, and educational status.**

	Time/category	Women	Men		*p*-values
Beck depression scale	Baseline	36.11 ± 4.88	39.46 ± 5.56		**0.042***
	Month 1	32.68 ± 5.80	34.54 ± 7.47		0.062*
	Month 2	31.84 ± 8.98	33.00 ± 9.29		0.692*
	Month 3	27.54 ± 11.46	25.00 ± 8.29		0.467*
	Time/category	Married	Single	Divorcee	*p*-values
	Baseline	40.58 ± 6.02	46.86 ± 5.96	42.14 ± 7.20	0.057**
	Month 1	35.97 ± 4.83	43.29 ± 4.57	35.86 ± 3.44	**0.001****
	Month 2	30.50 ± 7.14	42.86 ± 10.78	29.86 ± 9.44	**0.002****
	Month 3	24.31 ± 8.41	40.00 ± 10.58	27.00 ± 13.06	**0.001****
	Time/category	Secondary school	High school	Bachelor/master	*p*-values
	Baseline	40.50 ± 5.53	41.30 ± 6.09	46.88 ± 8.29	**0.039****
	Month 1	35.88 ± 4.58	36.70 ± 4.83	41.75 ± 6.02	**0.014****
	Month 2	30.69 ± 8.63	33.80 ± 9.27	35.88 ± 9.73	0.283**
	Month 3	26.53 ± 10.85	28.30 ± 11.81	26.50 ± 9.89	0.900**

*Independent Samples T-Test. **One-Way ANOVA test. Bold to indicate values that are statistically significant.

is more efficacious in reducing anhedonia. Furthermore, various pharmacodynamic properties of Vo are more likely to be associated with higher antidepressive, antianxious, and procognitive effectiveness with potentially less weight gain (10). These advantages might be indicative of Vo in patients suffering from chronic pain.

We conducted our study evaluating the efficacy of Vo in patients with chronic NP, with reference to several studies in the literature in terms of Vo's therapeutic potential for pain (12, 13). In addition to its agonist and antagonist effects on HT receptors, Vo exhibits antidepressant, procognitive, sleep-regulating, and anti-inflammatory

TABLE 4 Comparison of the total NePIQoL scores according to the age groups.

Measurement	<55	≥55	*p*-value
Total NePIQoL score	131.21 ± 38.37	154.17 ± 19.14	**0.009***

NePIQoL, Neuropathic pain quality of life questionnaire. Bold to indicate values that are statistically significant. *$p < 0.05$.

TABLE 5 Correlation analysis of the scores of the scales at the third month follow-up examination.

		Beck depression scale	Beck anxiety scale	MoCA	NePIQoL
Beck depression scale	*r*	1	0.682**	−0.223	−0.710**
	p	–	<0.001	0.120	<0.001
Beck anxiety scale	*r*		1	−0.142	−0.589**
	p		–	0.326	<0.001
MoCA	*r*			1	0.303*
	p			–	0.032
NePIQoL	*r*				1
	p				–

MoCA, Montreal cognitive assessment test; NePIQoL, Neuropathic pain quality of life questionnaire; *$p < 0.05$; **$p < 0.01$.

activities through its impact on interleukin 4 (IL-4) and brain-derived neurotrophic factor (BDNF).

Vo is a novel pharmacologic agent with procognitive efficacy independent of mood improvement (14). Beyond its effect on serotonin transport, Vo accelerates the desensitization and disinhibition caused by the release of 5-HT. The antagonism of another receptor, 5-HT7, also plays a role in mood improvement by increasing serotonergic transmission (15, 16). It has been reported in the literature that Vo shows cognitive enhancing properties with improvements in different functions in humans (17–19). Decreased gabaergic transmission in the prefrontal cortex and hippocampus due to 5-HT3 receptor blockade, increased glutamatergic neurotransmission, and increased glutamate, acetylcholine, histamine, dopamine, and noradrenaline in the same regions with 5-HT1 receptor partial agonism were reportedly responsible for the positive effect of Vo in cognition. The antagonism of 5-HT7 increases acetylcholine and noradrenaline levels in the medial prefrontal region cortex. The enhancing effect on noradrenergic neurotransmission is also associated with the stimulation of 5-HT1A and the blockade of 5-HT3 receptors. These mechanisms of action of Vo support its efficacy in neuroplasticity (11, 20–22). Vo also affects the synaptic neuroplasticity of the brain by playing a role in neurogenesis by creating functional synapses, increasing BDNF levels and dendritic branching, and in dendritic spine maturation with mitochondrial support in the dentate gyrus of the hippocampus (23, 24). It has been reported that Vo induces the maturation of neurons by acting on dendrites (25). In our study, patients' MoCA scores indicated cognitive improvement starting from the second follow-up visit. As a matter of fact, according to the results of a meta-analysis conducted in 2022, both 10 and 20 mg/day Vo doses positively affected cognitive symptoms in MDD patients (26).

Several hypotheses have been proposed in the literature regarding the basic mechanisms underlying the effect of Vo on pain. Accordingly, the blockade of serotonin transport by Vo, the increase of neurotransmitters such as noradrenaline and 5-HTin central and peripheral nervous system synapses, and its direct effect on receptor activity that can modulate pain transmission may explain the impact of Vo on pain (27, 28). In addition to its immunomodulatory, antioxidant, and anti-inflammatory effects, Vo is considered potentially effective in chronic pain by increasing BDNF levels (29, 30). Vo inhibits neuroinflammation and increases neurogenesis and neuroplasticity via 5-HT2b and 5-HT7 receptors (31).

The starting dose of Vo is 10 mg per day, but its 5 and 20 mg doses are also effective. The 20 mg dose of Vo has been associated with a more significant clinical response (32, 33). Many studies have found Vo is highly tolerable and more effective in MDD than many other antidepressant medications (34, 35). Vo also has a reducing effect on the anxiety levels that accompany MDD (36). It has been determined that the 8-week Vo treatment improved sleep quality and reduced sleep disorders. Vo has been shown to improve non-rapid eye movement (REM) sleep through its 5-HT receptor effects, increase slow-wave sleep, and improve sleep quality by suppressing REM sleep (37). Similarly, our patients' NePIQoL scores indicated a statistically significant improvement in sleep-related problems with Vo treatment. The increase in NePIQoL scores as a result of the 10 mg/day Vo treatment we administered to all 50 patients for 3 months was significantly correlated with the decrease in their depression and anxiety-related complaints. In an experimental study, the effect of Vo on pain appeared after 7 days and gradually increased. Similarly, we observed a decrease in the pain complaints of many of our patients as of the end of the first month of treatment (28). Case series in the literature on Vo suggests that Vo may also have a positive effect on mood and restless legs syndrome symptoms through its activity on dopamine and gamma-aminobutyric acid (GABA) (38).

In today's clinical practice, neurologists and physiotherapists widely use duloxetine, venlafaxine, and amitriptyline to treat various pain syndromes, including fibromyalgia and migraine (39). However, due to their side effect profiles, their use is limited, especially in elderly patients. Compared to these medications, Vo is a more effective and better-tolerated antidepressant at doses of 5–20 mg/day in individuals over 55 years of age, considering comorbid conditions. Similarly, our findings show that Vo can be used effectively and safely in patients over 55. Common side effects of Vo include nausea, headache, dizziness, and itching, while rare side effects include gastrointestinal disorders, insomnia, nasopharyngitis, dry mouth, urticaria, and suicidal ideation. No clinically significant impact of Vo treatment on vital signs, electrocardiogram values, liver enzymes, or body weight has been reported (40, 41). In our study, no patient discontinued medication or was excluded from the study due to side effects, except for one patient who was voluntarily excluded from the study due to persistent dizziness. The findings of this study support the clinical findings reported in the literature regarding the efficacy of Vo on NP (28, 42). In a study conducted on diabetic rats, Yucel et al. (43) showed that Vo, in addition to its neutral activity on glycemic control, significantly improved diabetes-induced hyperalgesia and allodynia responses without affecting motor coordination. Todorovic et al. (44) demonstrated the potential usefulness of Vo's analgesic effect in treating inflammatory pain. Vo has been reported to be safe and

tolerable at doses of 5 mg to 20 mg, and the most common side effects are nausea, headache, and diarrhea, in order of frequency (45).

Our study's primary limitations are its small sample size, lack of a control group, lack of comparison with other antidepressants, and its single-center design. In our study, patients were not blinded to treatment and knew they were receiving Vo. Patients' awareness that they were using Vo may have contributed to significant positive results obtained at 3-month follow-up due to positive expectations. Therefore, there is a need for future long-term, large-scale clinical studies featuring a double-blind design to reduce this potential bias. In addition, given its multimodal effect on serotonergic and other neurotransmitter systems, it is also necessary to consider Vo's potential impact on other types of pain. Nevertheless, the beneficial effects of Vo on different pain conditions, such as osteoarthritis and phantom limb pain, have not yet been adequately studied. Therefore, future studies should also address the efficacy of Vo in various pain syndromes.

Depression is a multifactorial and clinical process with varying severity and symptoms. Chronic pain may inherently predispose individuals to psychiatric symptoms. Although these intertwined conditions are challenging to diagnose and treat, the doctor and the patient must overcome this process. Many animal, preclinical, and clinical studies have proven that some antidepressants show antinociceptive and analgesic effects and can be used in chronic pain. The goal of clinicians is to suppress many symptoms with a single tolerable medication for pain or MDD.

The mechanisms of action of each antidepressant or new active substance and their usefulness in relieving pain need to be investigated with both animal and human models. In this context, Vo emerges as a novel treatment option with proven tolerability and efficacy, attracting increasing attention. As with many molecules, clinical studies are needed to establish new indications for Vo, which started its journey as an antidepressant.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Ethics statement

The studies involving humans were approved by Hitit University Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SE: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AE: Funding acquisition, Methodology, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Aberrant functional connectivity in anterior cingulate gyrus subregions in migraine without aura patients

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Background: The anterior cingulate gyrus (ACG) is an important regulatory region for pain-related information. However, the ACG is composed of subregions with different functions. The mechanisms underlying the brain networks of different subregions of the ACG in patients with migraine without aura (MwoA) are currently unclear.

Methods: In the current study, resting-state functional magnetic resonance imaging (rsfMRI) and functional connectivity (FC) were used to investigate the functional characteristics of ACG subregions in MwoA patients. The study included 17 healthy volunteers and 28 MwoA patients. The FC calculation was based on rsfMRI data from a 3 T MRI scanner. The brain networks of the ACG subregions were compared using a general linear model to see if there were any differences between the two groups. Spearman correlation analysis was used to examine the correlation between FC values in abnormal brain regions and clinical variables.

Results: Compared with healthy subjects, MwoA patients showed decreased FC between left subgenual ACG and left middle cingulate gyrus and right middle temporal gyrus. Meanwhile, MwoA patients also showed increased FC between pregenual ACG and right angular gyrus and increased FC between right pregenual ACG and right superior occipital gyrus. The FC values between pregenual ACG and right superior occipital gyrus were significantly positively correlated with the visual analogue scale.

Conclusion: Disturbances of FC between ACG subregions and default model network and visual cortex may play a key role in neuropathological features, perception and affection of MwoA. The current study provides further insights into the complex scenario of MwoA mechanisms.

KEYWORDS

migraine without aura, anterior cingulate gyrus, functional connectivity, functional magnetic resonance imaging, resting state

1 Introduction

Migraine is a neurological disorder characterised by paroxysmal unilateral throbbing headache and autonomic nervous system dysfunction. The prevalence of migraine is 10–15% of the population and represents a significant personal and social burden (1). Migraine without aura (MwoA) is one of the most common types of migraine and is characterised by unilateral or bilateral frontotemporal pain with recurrent throbbing episodes. The headaches may be accompanied by nausea, vomiting, scalp tenderness and other unpleasant symptoms, and if the attacks are frequent, they can seriously interfere with daily life and work (2).

The anterior cingulate gyrus (ACG) is part of the limbic system and a component of the medial nociceptive system (3). A large number of functional magnetic resonance imaging (fMRI) studies have shown functional abnormalities in the ACG in migraineurs, such as amplitude of low-frequency fluctuations, regional homogeneity, and functional connectivity (4). A meta-analysis shows an association between reduced grey matter density in the right ACG and migraine attack frequency (5). Improvement in migraine frequency, intensity and disability in migraineurs after 3 months of long-term treatment is associated with increased Gamma-aminobutyric acid + macromolecules (GABA+) levels in the ACG (6). After thermal pain stimulation, the anterior cingulate gyrus was significantly activated in migraineurs compared to healthy controls (HCs) (7).

However, the ACG is composed of cytoarchitecturally distinct subdomains that serve multiple functions. According to the different corresponding functions, the ACG can be divided into different subregions, including the pregenual anterior cingulate gyrus (pgACG), the subgenual anterior cingulate gyrus (sgACG) and the supracallosal anterior cingulate gyrus (srACG) (8). The pgACG was more strongly connected to the default mode network (DMN) in patients with low back pain, and there was a positive correlation between clinical pain and the strength of the DMN connection (9). After receiving noxious and non-noxious hot and cold stimuli and finger movement tasks, healthy subjects showed different partial activation of the ACG. Non-noxious heat stimulation activated the anterior part of the ACG, noxious heat-related activation activated the ventral part of the ACG and motor-related activation activated the posterior part of the ACG (10).

The above studies showed that there were functional abnormalities with different characteristics in the ACG subregions of migraine patients, especially functional network abnormalities (4, 9). Functional connectivity, defined as the time-dependent pattern of neuronal activation in anatomically separated brain regions, had been widely used to reveal the overall organisation of functional communication in brain networks (4, 9). To our knowledge, brain network characterisation of ACG subregions in migraineurs is still lacking. In the current study, we hypothesised that different subregions of the ACG in MwoA patients have their own specific brain network patterns. We used resting state fMRI (rsfMRI) and the functional connectivity (FC) method to investigate changes in the brain networks of different subregions of the ACG in MwoA patients. We hypothesised that there is abnormal functional connectivity between ACG subregions and visual, cognitively relevant brain regions in migraineurs compared to healthy controls.

2 Methods

2.1 Participants

Between March 2014 and October 2014, 28 right-handed MwoA patients and 17 age- and sex-matched right-handed HCs were recruited for this study. The diagnosis of definite MwoA was made according to the criteria of the International Headache Society (11) by two neurologists specialising in headache disorders who were blinded to the MRI and neuropsychological findings. The following requirements had to be met by the patients: (a) the right hand must be used as the usual hand; (b) the patient must be over the age of 18; (c) the patient must have experienced migraine symptoms for more than 6 months; (d) the patient must have experienced headache attacks at least twice a month (as confirmed by the patient's self-reports prior to the study); and (e) patients had no headache attacks during the fMRI scan and had not taken any acute migraine medication for at least 3 days prior to the scan. Exclusion criteria included headache attacks in the 3 days prior to the scan, on the day of the scan, or in the 3 days after the scan; history of substance abuse or prophylactic drug use; psychotic disorder; contraindications to MRI scanning; female subjects who were pregnant or menstruating. The control subjects were recruited from the local community and had no history of neurological disease. They did not have migraines or headaches and were not taking any medication. This study was approved by our university's institutional review board. All participants gave written informed consent before undergoing the procedure.

2.2 MRI scan

Images were acquired on a 3.0 Tesla magnetic resonance imaging scanner (Achieva X-series, Philips Medical, Best, the Netherlands). Functional images were acquired axially using a gradient-echo planar imaging sequence as follows: repetition time (TR) = 2,000 ms; echo time (TE) = 30 ms; slice = 35; thickness = 4 mm; gap = 0 mm; field of view (FOV) = 240 mm × 240 mm; acquisition matrix = 80 × 80; flip angle (FA) = 90°. fMRI sequences took 8 min. We instructed patients to remain still and close their eyes during image acquisition.

2.3 Data processing

Data preprocessing was performed using SPM12[1] and the Resting State fMRI Data Analysis Toolkit+V1.25 (RESTplus V1.25)[2] (12). The preprocessing steps were as follows: the first 10 volumes were discarded to allow the signal to reach equilibrium, corrected for slice time and head motion, spatially normalised to Montreal Neurological Institute (MNI) space using EPI template, and resampled to a resolution of $3 \times 3 \times 3\,mm^3$, smoothed with an isotropic Gaussian kernel (full width at half maximum = 6 mm) to reduce registration errors, linear trend removal and temporal band-pass filtering

1 http://www.fil.ion.ucl.ac.uk/spm

2 http://www.restfmri.net

(0.01–0.08 Hz) to remove high-frequency noise and physiological signals. Finally, interference was further removed from the resulting images by regressing out the head motion parameters (Friston 24 model), cerebrospinal fluid signal and white matter signal. Subjects with head movements greater than 2.0 mm translational or 2.0° rotational in any direction were excluded.

2.4 Resting-state functional connectivity analysis

Using an atlas-based approach, six individual ACG subregion seeds (three per hemisphere) were generated for each participant in the AAL3 template (13) (Figure 1). Pearson correlation coefficients were calculated between mean seed time series and other whole-brain voxel time series. The resulting values were transformed to z-values using Fisher's z-transformation to improve normality (14).

2.5 Statistical analysis

The Mann–Whitney U-test was used to compare the age and education of the two groups to determine whether or not there was a difference in applied mathematics. Chi-square was used to compare the gender composition of the two groups.

We performed statistical analysis using RESTplus V1.25. The normal distribution of the fMRI signal was determined using the Jarque-Bera test. We used a one-sample t-test to observe the functional connectivity mapping of the ACG subregions of the two groups. A general linear model was performed on individual FC maps that were voxel-by-voxel-normalised between the two groups. To reduce the influence of confounding variables in the statistical analysis, we regressed the mean relative change in head movement, age, and sex as covariates in the statistical analysis. For multiple comparisons, the resulting statistical map was set to $p < 0.05$ (AlphaSim corrected for multiple comparisons, with individual combined p-values for voxels <0.001 with cluster size > 16 voxels). To investigate the association between FC value and clinical outcome in MwoA patients, a spearman correlation between the Z value of abnormal brain regions and clinical outcome of MwoA patients was performed in a voxel system. The statistical threshold was set at $p < 0.05$.

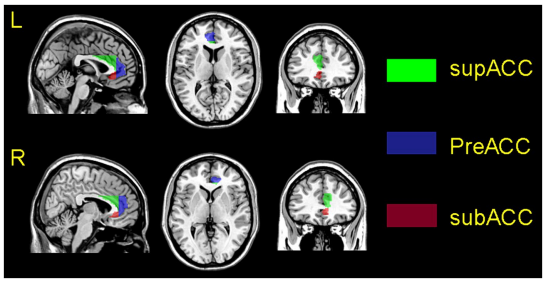

FIGURE 1
Schematic representation of the positioning of the ACG subregions, superimposed on the ch2 template. The upper picture shows the left side of the ACG, the bottom picture shows the right side of the ACG. The subgenual anterior cingulate gyrus is marked in orange; the pregenual anterior cingulate gyrus is marked in blue, and supracallosal anterior cingulate gyrus is marked in green.

3 Results

3.1 Neuropsychological results

There were no significant differences in age ($t = -0.270$, $p = 0.7873$), gender distribution ($\chi 2 = 2$, $p = 0.3431$), or years of education ($t = 0.973$, $p = 0.2030$) between the two groups. Details of the demographic data and associated tests are shown in Table 1.

3.2 Altered FC of ACG subregions in MwoA patients

The results of the one-sample t-test revealed, compared to HCs, MwoA patients showed reduced functional connectivity between the subgenual ACG with the default mode network, ventral attention network, and somatomotor network. MwoA patients showed enhanced functional connectivity between the pregenual ACG with the default mode network and frontoparietal network. MwoA patients showed enhanced functional connectivity between the supracallosal ACG with the default mode network (Figure 2).

Compared to HCs, MwoA patients showed decreased FC between left subgenual ACG and left middle cingulate gyrus (MCG) and right middle temporal gyrus (MTG). Meanwhile, MwoA patients also showed increased FC between pregenual ACG and right angular gyrus (AG) and increased FC between right pregenual ACG and right superior occipital gyrus (SOG; Figure 3; Table 2).

TABLE 1 Demographics and neuropsychological data.

	MwoA	Median	Q25	Q75	IQR	HCs	t/χ^2	p-value
Gender, n (M/F)	28(22/6)	-				17(11/6)	2	0.3431
Age, years	35.6 ± 9.9	38.5	27.5	43	15.5	36.5 ± 8.9	−0.270	0.7873
Education (years)	13 ± 4	15	9	16	7	15 ± 4	0.973	0.2030
Duration (years)	9 ± 7	6.75	3	14.5	11.5	-	-	-
Frequency (d/m)	4.7 ± 7.7	2.5	1.62	3.12	1.6	-	-	-
VAS score	6.85 ± 1.3	6.75	5.25	7.25	2.25	-	-	-

Data represent mean ± SD. Data were analysed using independent-samples t-tests. MwoA, Migraine without aura; HCs, Healthy controls; d/m, day per month; VAS, visual analogue scale; Q25, 25% quantile; Q75, 75% quantile; IQR, interquartile range.

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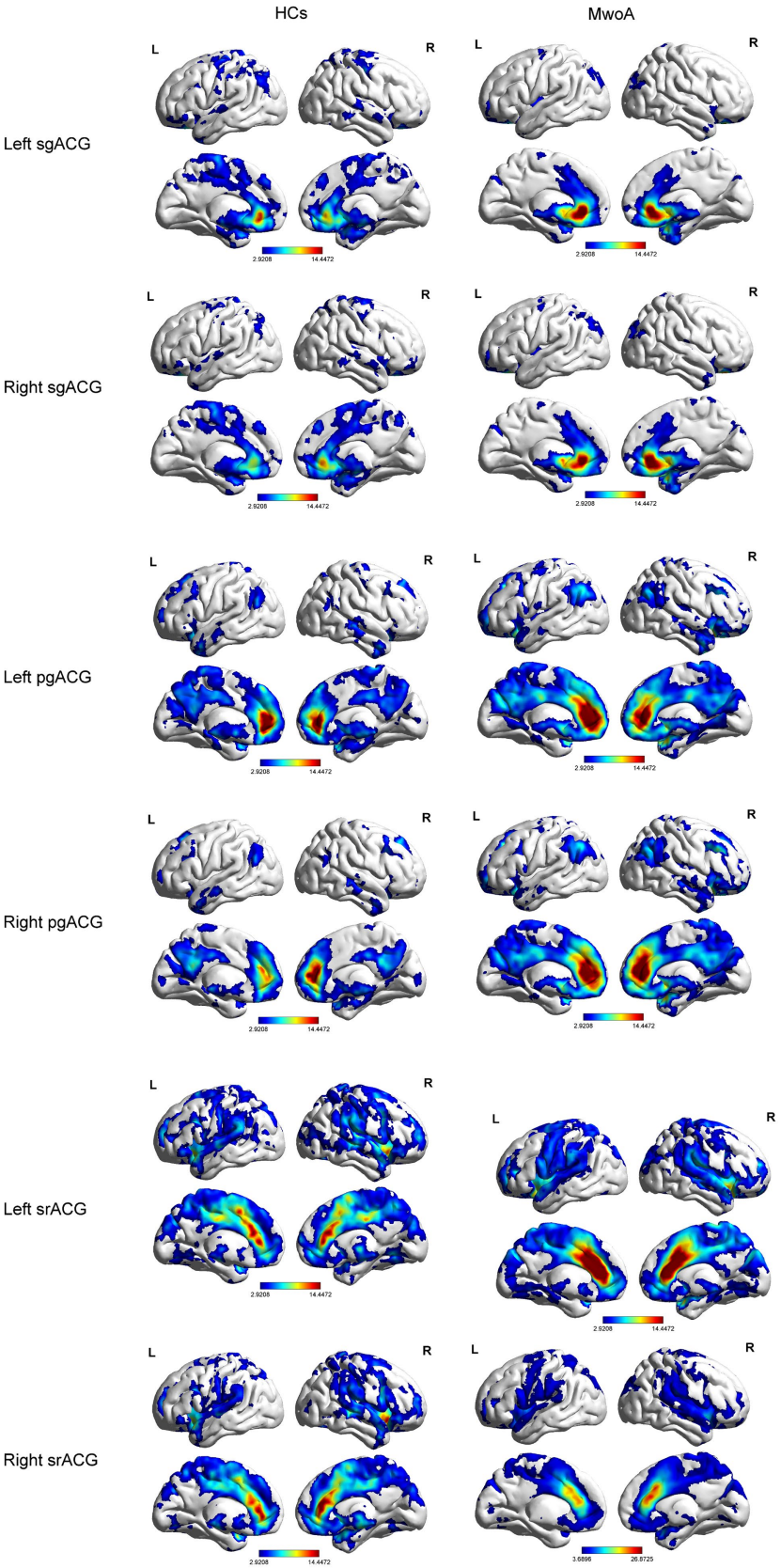

FIGURE 2
Functional connection mapping of the anterior cingulate subregions. pgACG, pregenual anterior cingulate gyrus; sgACG, subgenual anterior cingulate gyrus; srACG, supracallosal anterior cingulate gyrus.

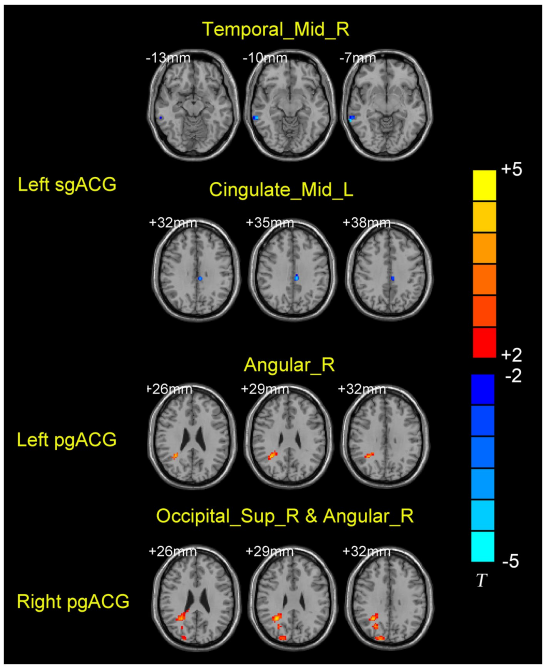

FIGURE 3
Brain regions with significantly different FC values with ACG subregions in the MwoA group compared with the HCs group.

3.3 Relationships between FC values and clinical variables

The FC values between pgACG and right SOG were significantly positively correlated with the visual analogue scale ($r = 0.4446$, $p = 0.0178$). The FC values between pgACG and right AG were positively correlated with disease duration ($r = 0.4947$, $p = 0.0074$; Figure 4).

4 Discussion

In the current study, we investigated changes in the brain networks of the ACG subregions in MwoA patients. Compared to HCs, MwoA patients showed decreased FC between left subgenual ACG and left middle cingulate gyrus and right middle temporal gyrus. Meanwhile, MwoA patients also showed increased FC between pregenual ACG and right angular and increased FC between right pregenual ACG and right occipital gyrus. Abnormal brain regions are mainly located in the default mode network (DMN) and the visual cortex.

Our results show an unusual FC between the left sgACG and the left MCG and right MTG. The sgACG plays an important role in pain-related emotional behaviour. After active transcranial direct current stimulation, patients with chronic neuropathic pain showed a significant decrease in pain scores and increased metabolism in the sgACG and insula (15). Activation of sgACG in chronic cluster headache patients using transcranial direct current stimulation improved their clinical symptoms (16). The Mulligan manoeuvre can improve pain levels by modulating the function of the frontal lobe and middle temporal gyrus related brain regions in patients with cervicogenic headache, and has a moderating effect on pain-related negative emotions (17). Meta-analysis showed that pain-related anxiety is characterised by neural activation in the inferior frontal gyrus, medial superior frontal gyrus, postcentral gyrus, MTG, parieto-occipital sulcus and striatum (18). Compared with healthy controls, migraineurs showed increased regional homogeneity scores in the bilateral thalamus, right insula and right MTG (19). Our findings suggest that MwoA patients have abnormalities in emotion-related brain networks.

Our results show an increased FC between the pgACG and the AG and right SOG. PgACG segregate representations of rewarding, positively affective (pleasant) stimuli (8). Painful touch can activate pregenual ACGs in HCs (20). A small increase in 5-Hydroxytryptamine (5-HT) levels leads to increased activation of the pgACG, suggesting that activation of the pgACG may also be increased during migraine attacks, a process that may be associated with sudden increases in 5-HT levels (21). Compared with the HCs, the neurovascular coupling function of SOG and AG in patients with chronic migraine was abnormal, and it was negatively correlated with headache frequency and positively correlated with health status (22). The angular gyrus is the visual language centre and impaired function can lead to dyslexia (23). Migraine is a factor in aphasia (24). The occipital lobe is the main brain area for visual perception and is also responsible for visual language processing (25). HCs showed increased activity in the left SOG and left AG during artificial grammar learning (26). MwoA patients also showed abnormal efficient connections from the middle occipital gyrus to the right periaqueductal grey (27). Our results suggest a compensatory mechanism in visual language processing in MwoA patients.

The abnormal brain areas suggested by our results are mostly located in the DMN. When pain persists beyond healing and becomes chronic, pain-related somatosensory cortical activity may become functionally linked to the DMN of self-representation, i.e., it becomes an intrinsic part of self-perception (28). The default mode network has been proposed as a biomarker for several chronic pain conditions. The default mode network FC is influenced by negative emotions and may be related to the emotional dimension of pain in patients with chronic pain (29). MwoA patients also show reduced FC in the prefrontal and temporal regions of the DMN (30). It is not only the pain pathway but also migraine that leads to emotional changes in MwoA patients, which has a broader impact on brain function in MwoA patients.

Several limitations should be considered when interpreting the current results. First, multi-site and large sample data are needed to validate the reliability of the results of this study. Second, because the current study used a cross-sectional design, it investigated differences in the ACG brain network between MwoA and HCs. However, whether and how these ACG brain network abnormalities exist in the onset and development of MwoA needs to be further observed in longitudinal studies in the future. Third, diffusion imaging can be used to explore the mechanisms of white matter microstructure in the ACG subregions. Finally, our results revealed abnormalities in brain regions related to mood and vision, but we did not obtain clinical scales for mood and vision in this study, and we were unable to further explore the neural mechanisms of the brain regions associated with MwoA patients.

5 Conclusion

We investigated the FC of ACG subregions in MwoA patients using resting-state functional MRI and the FC method. Compared to

TABLE 2 Brain regions with significantly different FC values with ACG subregions in the MwoA group compared with the HCs group.

Brain regions	Voxels	BA	MNI coordinates			*T* value	*p*-value
			x	y	z		
Left sgACG							
Temporal_Mid_R	23	21	69	−42	−6	−4.6144	<0.001
Cingulum_Mid_L	19	23	−6	−30	36	−4.5804	<0.001
Left pgACG							
Angular_R	48	39	40	−53	28	5.1178	<0.001
Right pgACG							
Angular_R	79	40	33	−49	40	5.5695	<0.001
Occipital_Sup_R	33	19	18	−90	33	4.5178	<0.001

MwoA, Migraine without aura; HCs, Healthy controls; MNI, Montreal Neurological Institute; BA, Brodmann area.

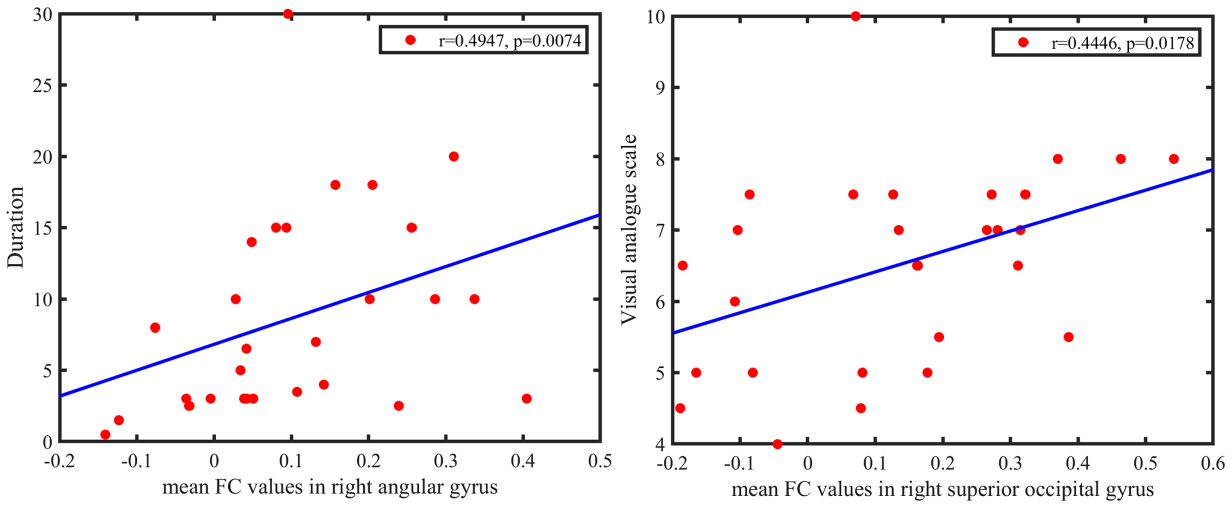

FIGURE 4
Top: Functional connectivity values between pgACG and right SOG are significantly positively correlated with visual analogue scale. Bottom: FC values between pgACG and right AG are weakly positively correlated with disease duration. pgACG, pregenual ACG; SOG, superior occipital gyrus; AG, angular gyrus.

HCs, the differential brain regions in MwoA patients are mainly located in the DMN and visual cortex. Our study extends our understanding of the brain network patterns in the ACG subregions of MwoA patients and helps us to further understand the underlying neural mechanisms in MwoA patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Second Affiliated Hospital, Hebei Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JC: Data curation, Formal analysis, Funding acquisition, Resources, Writing – original draft, Writing – review & editing. YL: Data curation, Formal analysis, Methodology, Resources, Validation, Visualization, Writing – review & editing. KC: Data curation, Formal analysis, Resources, Validation, Writing – review & editing. YC: Data curation, Formal analysis, Investigation, Writing – review & editing. KL: Methodology, Resources, Validation, Visualization, Writing – review & editing. XZ: Data curation, Formal analysis, Resources, Writing – review & editing. XW: Data curation, Investigation, Resources, Writing – review & editing. ZW: Project administration, Validation, Visualization, Writing – review & editing. XL: Methodology, Project administration, Software, Supervision, Writing

– review & editing. LL: Conceptualization, Project administration, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Exercise as a promising alternative for sciatic nerve injury pain relief: a meta-analysis

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Objective: The efficacy of drug therapies in managing neuropathic pain is constrained by their limited effectiveness and potential for adverse effects. In contrast, exercise has emerged as a promising alternative for pain relief. In this study, we conducted a systematic evaluation of the therapeutic impact of exercise on neuropathic pain resulting from sciatic nerve injury in rodent models.

Methods: The PubMed, Embase, and Web of Science databases were retrieved before April 2024. A series of studies regarding the effect of treadmill, swimming, wheel and other exercises on neuropathic pain induced by sciatic nerve injury in rats and mice were collected. Using predefined inclusion criteria, two researchers independently performed literature screening, data extraction, and methodological quality assessment utilizing SYRCLE's risk of bias tool for animal studies. Statistical analysis was conducted using RevMan 5.3 and STATA 12.0 analysis software.

Results: A total of 12 relevant academic sources were included in the analysis of controlled animal studies, with 133 rodents in the exercise group and 135 rodents in the sedentary group. The meta-analysis revealed that exercise was associated with a significant increase in paw withdrawal mechanical threshold [Standard Mean Difference[1] (*SMD*) = 0.84, 95% confidence interval (*CI*): 0.28–1.40, $p = 0.003$] and paw withdrawal thermal latency (*SMD* = 1.54, 95%*CI*: 0.93–2.15, $p < 0.0001$) in rats and mice with sciatic nerve injury. Subgroup analyses were conducted to evaluate the impact of exercise duration on heterogeneity. The results showed that postoperative exercise duration ≤3 weeks could significantly elevate paw withdrawal mechanical threshold (SMD = 1.04, 95% *CI*: 0.62–1.46, $p < 0.00001$). Postoperative exercise duration ≤4 weeks could significantly improve paw withdrawal thermal latency (SMD = 1.93, 95% *CI*:1.19–2.67, $p < 0.00001$).

Conclusion: Exercise represents an effective method for improving mechanical and thermal hypersensitivity resulting from sciatic nerve injury in rodents. Factors such as pain models, the initiation of exercise, the type of exercise, and the species of rodent do not significantly impact the development of exercise-

1 Standardized mean difference (SMD): It is used to measure the difference between the means of two independent samples, taking into account the sample standard deviation, and is suitable for comparisons of different measurement units or standard deviations. A positive SMD means that the mean of the experimental group is higher than that of the control group, while a negative SMD means the opposite.

induced hypoalgesia. However, the duration of postoperative exercise plays a crucial role in the onset of exercise-induced hypoalgesia.

KEYWORDS

pain model, exercise, sciatic nerve injury, neuropathic pain, meta-analysis

1 Introduction

Chronic pain is a pervasive global issue that incurs substantial treatment expenses and imposes significant burdens on both society and families (1). Additionally, individuals suffering from chronic pain frequently experience comorbid anxiety and depression (2).

Symptoms of chronic pain, particularly insomnia, can result in considerable physical and psychological suffering (3, 4). Chronic pain frequently manifests with a neuropathic component, affecting an estimated 10% of cases (5) and is characterized by intricate pathophysiological mechanisms involving a complex interplay of neurotransmitters, receptors, ion channels, and cellular processes. The intricate nature of these pain factors presents a significant challenge in developing effective treatment strategies (6).

Pharmacological interventions represent a mainstay of managing pathological pain, despite the potential side effects of nausea, drowsiness, weight gain, and pruritus (7). However, the efficacy of medication alone is often limited, necessitating the incorporation of non-pharmacological treatments such as surgery, electrical stimulation, stem cell therapy, acupuncture, and exercise to achieve optimal therapeutic outcomes (8). These complementary approaches have demonstrated positive therapeutic effects in the management of pathological pain (9, 10).

Exercise, as a non-pharmacological intervention, has shown significant effects in pain management. It mainly reduces pain through several mechanisms. First, exercise promotes blood circulation, accelerates tissue repair and inflammation resolution, which is the key to relieving acute and chronic pain. At the same time, it enhances muscle strength and flexibility, improves body posture, and reduces pain caused by poor posture or muscle tension. Secondly, exercise's positive regulation of the nervous system is also an important way to relieve pain. It can stimulate the endogenous analgesic system, release natural analgesic substances such as endorphins, regulate the transmission of pain signals, and reduce pain perception. In addition, exercise promotes neuroplasticity, including neuron regeneration and synaptic reconstruction, which helps restore damaged nerve function and relieve neuropathic pain. Exercise-induced pain relief has become a research hotspot in recent years due to its intricate link to the physiological responses of the human body. As a pain management modality, exercise offers a unique advantage in its ability to exert its influence on multiple organs and systems simultaneously, thereby benefiting the treatment of diverse medical conditions (11). Several studies have indicated that inadequate physical activity may contribute to the exacerbation of pain. Research conducted on both human subjects and rats has demonstrated that limitations in physical activity can result in heightened sensitivity to pain (12, 13).

Understanding the impact and underlying mechanisms of pain significantly influences clinical decision-making, providing a theoretical basis for the development of effective exercise intervention programs (14, 15). Meta-analyses on the effectiveness of exercise for pain relief are inconclusive due to substantial variations in pain models and measurement methods. These variations may also explain inconsistencies in research findings related to exercise methods, styles, intensity, duration, and specific pain conditions (16–18).

While numerous studies support the effectiveness of exercise for pain relief, others suggest it may not always be beneficial (19). Consequently, it is imperative to investigate the impact of various exercise regimens on distinct types of pain to prescribe exercise interventions that yield optimal results.

This study employs meta-analysis techniques to comprehensively evaluate the efficacy of diverse exercise interventions for alleviating pain in animal models of sciatic nerve injury. The primary objective is to elucidate the impact of exercise on the functional restoration of sciatic nerve tissue. Ultimately, this investigation aims to inform the development of future research on exercise prescription for pain management strategies. By exploring the potential of exercise-based interventions, this research contributes to the growing body of knowledge on multimodal treatment approaches for neuropathic pain, potentially complementing pharmacological interventions and stem cell therapies for a more comprehensive therapeutic approach.

2 Data and methods

The article adhered rigorously to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (20).

2.1 Literature search strategy

A comprehensive literature search strategy was employed to identify relevant studies for this systematic review. The search was conducted by the author across four electronic databases: Cochrane Library, PubMed, Embase, and Web of Science. To ensure thoroughness, a broad range of search terms were used, encompassing various exercise modalities (exercise, locomotion, running, swimming, environmental enrichment, treadmill, vibration, aerobic, strength, isometric, isotonic, isokinetic, endurance, weight, physiotherapy, resistance, training), alongside terms related to sciatic nerve injury (sciatic nerve crush, nerve ligation, chronic constriction injury) and pain (pain, neuropathic pain, nociceptive, hyperalgesia, alodynia, sensory recovery, sciatica). Notably, the search encompassed studies published from December 2023 onwards. The specific search strategy employed within each database is detailed elsewhere (potentially in Figure 1). In addition to the electronic search, manual inspection of retrieved articles and reference lists was conducted to ensure the capture of potentially relevant studies not identified by the initial database search. This comprehensive approach aimed to

#1 Exercise[Mesh] OR "Exercise therapy"[Mesh] OR Locomotion[Mesh] OR running[Title/Abstract] OR swim*[Title/Abstract] OR "environmental enrichment"[Title/Abstract] OR treadmill[Title/Abstract] OR vibration[Title/Abstract] OR aerobic*[Title/Abstract] OR strength*[Title/Abstract] OR isometric*[Title/Abstract] OR isotonic*[Title/Abstract] OR isokinetic*[Title/Abstract] OR endurance[Title/Abstract] OR weight*[Title/Abstract] OR physiotherapy[Title/Abstract] OR resistance[Title/Abstract] OR train*[Title/Abstract]
#2 "sciatic nerve crush"[Title/Abstract] OR " sciatic nerve cut"[Title/Abstract] OR "peripheral neuropathy"[Title/Abstract] OR " sciatic nerve constriction"[Title/Abstract] OR " sciatic nerve inflammation"[Title/Abstract] OR " sciatic nerve injury"[Title/Abstract] OR " sciatic nerve ligation"[Title/Abstract] OR "chronic constriction injury"[Title/Abstract]
#3 "pain"[Title/Abstract] OR "neuropathic pain"[Title/Abstract] OR "nociceptive"[Title/Abstract] OR "hyperalgesia"[Title/Abstract] OR "alodynia"[Title/Abstract] OR "sensory recovery"[Title/Abstract])) OR (sciatica[Title/Abstract]
#4 Other animals
#5 #1 AND #2 AND #3 AND #4

FIGURE 1
Retrieval strategies for PubMed database.

maximize the identification of relevant studies for inclusion in the systematic review.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

1. Research object: Basic experimental research on the construction of a sciatic nerve injury pain model in rats and mice.
2. Exercise Intervention: All animals in the study underwent a postoperative exercise intervention.
3. Control Group: A control group was established that included animals with the sciatic nerve injury pain model but without exercise intervention.
4. Outcome Measures: Studies had to report at least one of the following pain outcome measures: (1) Mechanical pain threshold measured by von Frey filaments; (2) Thermal pain threshold measured by thermal radiation.
5. Study Design: Controlled animal experiments were included.

2.2.2 Exclusion criteria

1. Absence of a Control Group.
2. Duplicate Studies: Studies with redundant data were excluded, such as those from the same author using the same experimental subjects and procedures.
3. Insufficient Data.
4. Animals with Altered Pain Perception.
5. Review Articles.

2.2.3 Literature screening and data extraction

The author independently conducted literature screening, data extraction, and cross-checking to ensure accuracy and minimize bias. In cases of disagreement, a third party was consulted to reach a consensus. If essential information was missing from the studies, attempts were made to contact the original authors for clarification. Additionally, Engage Digitizer software was utilized to extract data from measurement charts where necessary. The extracted data encompassed the following categories:

1. Basic Study Information: This included the first author, country/region of publication, and publication year.
2. Subject Characteristics: This included animal species, age, body mass, sex, and the specific pain model used.
3. Intervention Details: This included the duration, mode, intensity, and start time of exercise interventions for the experimental group, as well as any interventions administered to the control group.
4. Risk of Bias Assessment: Key elements were evaluated to assess the potential risk of bias within the included studies.
5. Outcome Measures: This included the specific pain outcome indicators employed in the studies, along with the corresponding data.

2.2.4 Literature quality assessment

The risk of bias in the original animal experiments included in this study was assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) animal experiment risk of bias assessment tool recommended by SYRF (21). The evaluation was conducted independently by the author, who reviewed the included articles for research bias across various aspects:

1. Sequence generation.
2. Baseline characteristics.
3. Allocation concealment.
4. Animal placement: This refers to whether the randomization process included assigning animals to different cages or housing conditions to minimize bias.
5. Blinding of Researchers.
6. Randomized outcome evaluation.
7. Blinding of testers.
8. Incomplete data reporting.
9. Selective Outcome Reporting.
10. Other sources of bias.
11. For each criterion, “Y” indicated a low risk of bias, “N” indicated a high risk of bias, and “U” indicated unclear risk.

2.3 Outcome

The specific outcomes assessed in this study were mechanical pain threshold and changes in thermal pain threshold.

2.4 Statistical analysis

Data analysis was conducted using RevMan 5.3 and STATA 12.0, provided by the Cochrane Library Collaboration Network, with software from StataCorp in College Station, Texas, United States. The heterogeneity of the included studies was assessed using the I^2 statistic. A value of $I^2 < 50\%$ and a Q-test p-value > 0.1 indicated low heterogeneity, allowing for the use of a fixed-effects model for analysis. Conversely, $I^2 \geq 50\%$ or a Q-test p-value ≤ 0.1 indicated significant heterogeneity, necessitating the use of a random-effects model. Since the outcome indicators (mechanical and thermal pain thresholds) were continuous data, the standardized mean difference (SMD) with its corresponding 95% confidence interval (*CI*) was used for analysis. Based on the analysis results, subgroup and sensitivity analyses were conducted to explore potential sources of heterogeneity. Additionally, Egger's test was employed for quantitative assessment of publication bias. A p-value < 0.05 from Egger's test indicated potential publication bias. In such cases, the trim and fill method was utilized to potentially adjust for this bias.

3 Results

3.1 Literature retrieval

Following the outlined literature retrieval strategy and systematic search of library databases for relevant scholarly articles, a total of 1,801 articles were identified (Figure 2). The breakdown by database was as follows: PubMed ($n = 286$), EMBASE ($n = 611$), Web of Science ($n = 745$), CNKI ($n = 38$), and Wanfang ($n = 120$). Utilizing Endnote software, duplicate articles ($n = 400$) were removed. Title and abstract screening excluded an additional 1,373 articles. Finally, full-text review of the remaining articles resulted in the exclusion of 16, yielding a final selection of 12 studies for inclusion in this analysis.

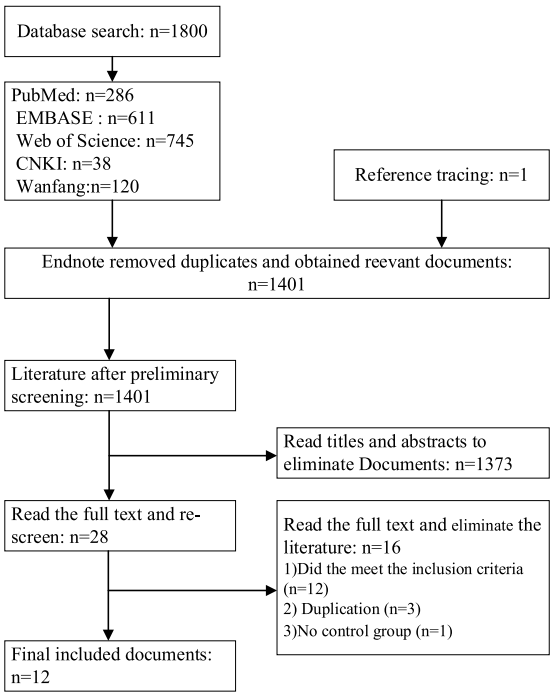


FIGURE 2
Flowchart of the literature retrieval process.

3.2 Basic characteristics of studies included in this research

This meta-analysis analyzed twelve controlled animal experiment articles published prior to April 2024 that explored the impact of exercise on pain management (16–18, 22–30). Three of these articles included two separate exercise regimens (16, 22, 29), resulting in a total of fifteen exercise protocols evaluated. The study population consisted of both rats (68.9%) and mice (31.1%). Within the rat population, 133 animals were assigned to the exercise intervention group, with an equal number assigned to the control group, for a total of 266 animals (133 rats and 133 mice).

The studies employed various sciatic nerve injury models, including partial ligation, chronic compression, and resection-repair. Within the exercise programs, treadmill exercise was most frequent (9 studies) (16, 18, 22, 23, 25–27). Swimming exercise programs were used in four studies (17, 22, 24, 29), and one study utilized a voluntary wheel running (28). Five studies initiated exercise interventions before surgery (18, 22, 27–29), while seven began exercise post-surgery (16, 17, 23–26, 30). Postoperative exercise duration ranged from 1 to 8 weeks with no reported adverse events (18, 23). Both control and exercise groups received the same pain model induction, with the control group not receiving any exercise intervention. This study focused on the therapeutic effects of exercise on mechanical and thermal hyperalgesia due to limited research on cold allodynia and exercise-induced spontaneous pain.

To ensure good homogeneity among studies, the included outcome indicators were the mechanical pain threshold measured by Von Fery filaments and the thermal pain threshold measured by thermal radiation. The comparisons based on different models are shown in Tables 1A–C.

3.3 The results of the risk of bias assessment

The risk of bias within the included studies was assessed using established criteria, and the evaluation results are presented in Table 2. This assessment focused on key areas such as random sequence generation, allocation concealment, blinding of outcome assessors, and selective outcome reporting. All studies adhered to complete data reporting standards. Baseline characteristics of the animals, including body weight, pre-surgery mechanical and thermal pain thresholds, were reported in all included articles. Three studies employed blinding for researchers (investigators conducting the experiment) (18, 22, 26), while six studies utilized blinding for pain testers who evaluated the animals' responses (22, 23, 25–28).

3.4 Meta-analysis results

3.4.1 The impact of exercise on mechanical pain threshold

Eight articles were included in this meta-analysis (16, 18, 22–26, 30). Two of these articles investigated two distinct exercise programs,

TABLE 1 Characteristics of the included studies with (A) PSNL model, (B) CCI model, and (C) SNTR model.

Author/year of publication	Animal species/sex/ body weight	Pain model	Sample size (exercise group/control group, *n*)	Movement begin time	Exercise interventions	Outcome measures
(A) PSNL model						
Almeida et al. (17), 2015	BALB/c mouse, male (23.5 + 0.24) g	PSNL	10/12	7 days postoperatively	Swimming, 1 min/d, preoperative acclimatization for 5 d. Start with 10 min/d and increase every 3 days of training 10 min, to 50 min, then stop increasing, 5/week, for a total of 5 weeks	Hot pain threshold
Kami et al. (27), 2016	C57BL/6 mouse, male, Weight was not provided	PSNL	6/6	12 days preoperatively	Treadmill, 10 min/d 2 weeks before surgery, 20–60 min 1 week before surgery, 2 days after surgery, 60 min/d for 5 consecutive days, 7 m/min	Hot pain threshold
Kami et al. (28), 2018	C57BL/6 J mouse, Weight was not provided	PSNL	8/6	14 days preoperatively	Runner, 14 days preoperatively to 14 days postoperatively	Hot pain threshold
Kuphal et al. (29), 2007	Sprague–Dawley rat, male, 250–300 g	PSNL	6/8	14 days preoperatively	Swimming, 14 days before surgery to 25 days after surgery, 90 min/d	Hot pain threshold
Kuphal et al. (29), 2007	CD1 mouse, male, 30–35 g	PSNL	10/10	5 days preoperatively	Swimming, continuous exercise for 5 days before surgery, and continuous exercise for 6 days after 1 day after surgery, 30 min/d	Hot pain threshold
(B) CCI model						
Chen et al. (22), 2012	Sprague–Dawley rat, male, 250–300 g	CCI	10/10	2 days preoperatively	Treadmill, no slope, from 20 m/min to 30 m/min, 15–60 min/d, 5 d/week, 6 weeks in total	Mechanical pain threshold, Hot pain threshold
Chen et al. (22), 2012	Sprague–Dawley rat, male, 250–300 g	CCI	10/10	2 days preoperatively	Swimming, start with 10 min/repetition and gradually increase to 90 min/repetition 1 training session per day for 90 min for 39 days	Mechanical pain threshold, Hot pain threshold
Cobianchi et al. (18), 2010	CD1 mouse, male, 40–45 g	CCI	8/11	14 days preoperatively	Treadmill, 12 m/min start, 1.2–31.2 m/min increments every 5 min, 1 h/d, 5 days/week, 2 weeks preoperatively plus 3–56 days postoperatively	Mechanical pain threshold
Huang et al. (25), 2017	Sprague–Dawley rat, male, 220–270 g	CCI	10/10	8 days postoperatively	Treadmill, 8% uphill, 14–16 m/min, 30 min/d, 3 weeks	Mechanical pain threshold, Hot pain threshold
Hung et al. (26), 2016	Sprague–Dawley rat, male, 220–270 g	CCI	10/10	3 days postoperatively	Treadmill, 8% uphill, 14–16 m/min, 30 min/d, 5 d/week for 4 weeks	Mechanical pain threshold, Hot pain threshold
Tsai et al. (16), 2017	Sprague–Dawley rat, male, 285–335 g	CCI	12/12	3 days postoperatively	Treadmill, 14–16 m/min, 30 min/d, 8% uphill, 3 weeks of continuous movement	Mechanical pain threshold, Hot pain threshold

(Continued)

TABLE 1 (Continued)

Author/year of publication	Animal species/sex/ body weight	Pain model	Sample size (exercise group/control group, *n*)	Movement begin time	Exercise interventions	Outcome measures
Tsai et al. (16), 2017	Sprague–Dawley rat, male, 285–335 g	CCI	12/12	2 days postoperatively	Treadmill, 14–16 m/min, 30 min/d, no slope, 3 weeks of continuous movement	Mechanical pain threshold, Hot pain threshold
Farzad et al. (24), 2018	Wistar rat, male, 180–220 g	CCI	7/7	3 days postoperatively	Swimming, 3 days of acclimatization training, the exercise time gradually increased to 60 min/d in the first week, and the total movement was carried out Move for 4 weeks	Mechanical pain threshold, Hot pain threshold
Safakhah et al. (30), 2017	Wistar rat, male, (200 ± 20) g	CCI	6/8	3 days postoperatively	Treadmill, 5 days acclimatization, 16 m/min, 30 min/d, 5 d/week for 3 weeks of exercise	Mechanical pain threshold, Hot pain threshold
(C) SNTR model						
Cobianchi et al. (23), 2013	Sprague–Dawley rat, female, (240 + 30) g	SNTR	8/15	3 days postoperatively	Treadmill, no slope, starting speed 6 m/min, increasing by 1.2–19.2 m/min every 5 min. No further increase in velocity, 1 h/d, total of 5 d	Mechanical pain threshold, Hot pain threshold

resulting in a total of ten exercise protocols evaluated (16, 22). The meta-analysis revealed a significant combined effect size (*SMD* = 0.84, 95%*CI*: 0.28–1.40, $p = 0.003$) for exercise compared to control in reducing mechanical pain sensitivity following sciatic nerve injury, as depicted in Figure 3.

3.4.2 Subgroup analysis results of exercise's impact on mechanical pain threshold

To explore potential sources of heterogeneity in the effect of exercise on mechanical pain, subgroup analyses were conducted based on exercise duration and mode (Figure 4). The analysis focused on the duration of postoperative exercise intervention. When the intervention lasted for three weeks or less (≤3 weeks), a significant increase in the mechanical pain threshold was observed in the exercise group compared to the control group (*SMD* = −1.04, 95% CI: −1.46 to −0.62, $p < 0.00001$). This finding suggests a substantial improvement in pain sensitivity with shorter exercise interventions. Importantly, the heterogeneity within this subgroup was low ($I^2 = 0\%$), indicating consistency across studies. However, for exercise interventions lasting four weeks or longer (≥4 weeks), the increase in mechanical pain threshold was not statistically significant (*SMD* = 0.62, 95% *CI*: −0.45 to 1.69, $p = 0.25$). Additionally, the heterogeneity within this subgroup was high ($I^2 = 82\%$), suggesting high risk of heterogeneity across studies. These results imply that exercise interventions exceeding four weeks may not be effective in improving mechanical pain sensitivity.

The subgroup analysis investigated the effect of different exercise modes on mechanical pain threshold, as depicted in Figure 5. Treadmill exercise showed a significant increase in mechanical pain threshold compared to the control group. The heterogeneity within the treadmill exercise group was moderate ($I^2 = 66\%$). In contrast, swimming exercise did not yield a statistically significant improvement in mechanical pain threshold. Additionally, the heterogeneity within the swimming exercise group was high ($I^2 = 88\%$). These findings suggest that treadmill exercise may be more effective than swimming exercise in improving mechanical pain sensitivity following sciatic nerve injury. While swimming showed a trend toward improvement, it did not reach statistical significance in this analysis.

3.4.3 Effect of exercise on thermal pain threshold

11 articles (16, 17, 22–30) investigated the effect of exercise on thermal pain threshold. Three of these articles included two distinct exercise programs, resulting in a total of fourteen exercise protocols evaluated (16, 20, 22). The meta-analysis revealed significant heterogeneity among the studies, necessitating the use of a random effects model. The pooled analysis indicated a significant effect size (*SMD* = 1.54, 95% CI: 0.93–2.15, $p < 0.0001$) favoring exercise compared to control in reducing thermal pain sensitivity following sciatic nerve injury (Figure 6). These findings suggest that exercise interventions may be beneficial for improving thermal allodynia in this population.

Given the limited research on exercise interventions for thermal pain and the substantial heterogeneity observed among studies, we hypothesized that variations in factors such as animal species, pain model, exercise type, timing of exercise initiation, and intervention duration might contribute to this heterogeneity. To explore these potential sources, a meta-regression analysis was conducted on the aforementioned variables (Table 3). The analysis revealed that species and pain models were not significant contributors to heterogeneity. However, the timing of postoperative exercise intervention emerged

TABLE 2 SYRCLE's risk of bias tool for animal studies.

First author, year of publication	1	2	3	4	5	6	7	8	9	10
Huang et al. (25), 2017	U	Y	U	U	N	U	Y	N	U	Y
Tsai et al. (16), 2017	U	Y	U	U	N	U	U	N	U	Y
Kami et al. (27), 2016	U	Y	U	U	N	U	Y	N	U	Y
Almeida et al. (17), 2015	U	Y	U	U	N	U	U	N	U	Y
Chen et al. (22), 2012	U	Y	U	U	Y	U	Y	N	U	Y
Hung et al. (26), 2016	U	Y	U	U	Y	U	Y	N	U	Y
Cobianchi et al. (23), 2013	U	Y	U	U	N	U	Y	N	U	Y
Kami et al. (28), 2018	U	Y	U	U	N	U	Y	N	U	Y
Cobianchi et al. (18), 2010	U	Y	U	U	Y	U	U	N	U	Y
Kuphal et al. (29), 2007	U	Y	U	U	N	U	U	N	U	Y
Farzad et al. (24), 2018	U	Y	U	U	N	U	U	N	U	Y
Safakhah et al. (30), 2017	U	Y	U	U	N	U	U	N	U	Y

"Y" indicates a low risk of bias, "N" indicates a high risk of bias, and "U" indicates unclear risk of bias. The table evaluates ten key areas: (1) sequence generation (randomization of allocation to groups), (2) baseline characteristics (similarity of groups at the study start), (3) allocation concealment (blinding those assigning animals to groups), (4) animal placement randomization (avoiding bias in housing), (5) blinding of researchers, (6) blinding of outcome assessors, (7) blinding of testers conducting pain assessments, (8) completeness of data reporting, (9) selective outcome reporting (reporting all relevant results), and (10) other potential sources of bias.

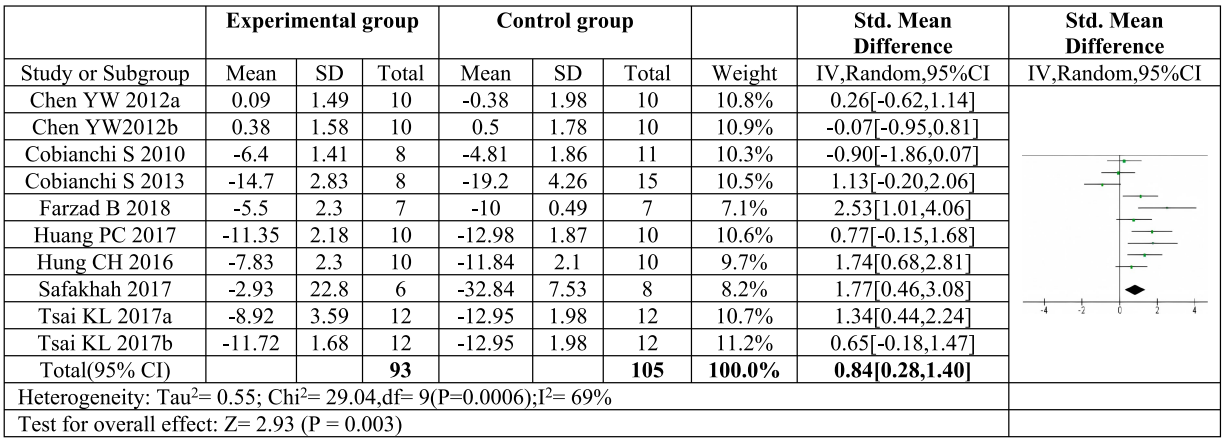


FIGURE 3
Forest plot of meta-analysis results for exercise on mechanical paw withdrawal threshold. The mechanical pain threshold of the exercise group was significantly higher than that of the control group ($p = 0.003$). [a,b]Represent different exercise programs in the same study.

as a significant source (p-value = 0.037), suggesting that the time point at which exercise begins after surgery may influence treatment effects.

3.4.4 Subgroup analysis of the effect of exercise on thermal pain threshold

To further explore the sources of heterogeneity, a subgroup analysis was conducted based on the duration of postoperative exercise intervention. For interventions lasting four weeks or less (≤4 weeks), a significant increase in thermal pain threshold was observed in the exercise group compared to the control group (*SMD* = 1.93, 95%*CI*: 1.19–2.87, $p < 0.00001$). However, the heterogeneity within this subgroup remained high ($I^2 = 75\%$).

In contrast, exercise interventions lasting at least five weeks (≥5 weeks) showed an increase in thermal pain threshold, but this increase was not statistically significant (SMD = 0.42, 95% *CI*: 0.08–0.83, $p = 0.10$). Moreover, the heterogeneity within this subgroup was low ($I^2 = 0\%$), indicating consistency in treatment effects across studies. These findings suggest that exercise interventions exceeding four weeks may not be as effective in improving thermal pain sensitivity following sciatic nerve injury, as depicted in Figure 7.

3.4.5 Sensitivity analysis results

To assess the robustness of the meta-analysis findings, a sensitivity analysis was conducted. This analysis evaluated the impact of excluding individual studies on the overall effect sizes for both mechanical and thermal pain thresholds. Each study was systematically removed from the analysis one at a time, and the remaining studies were reanalyzed. The results of the sensitivity analysis revealed that the exclusion of any single study did not significantly alter the combined effect sizes for exercise on either mechanical or thermal pain thresholds. This finding suggests a high level of consistency and reliability in the overall research findings.

	Experimental group			Control group				Std. Mean Difference	Std. Mean Difference
2.3.1 The postoperative exercise time ≤ 3 weeks									
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random,95%CI	IV, Random, 95%***CI***
Cobianchi S 2013	-14.7	2.83	8	-19.2	4.26	15	10.5%	1.13[-0.20,2.06]	
Huang PC 2017	-11.35	2.18	10	-12.98	1.87	10	10.6%	0.77[-0.15,1.68]	
Safakhah 2017	-2.93	22.8	6	-32.84	7.53	8	8.2%	1.77[0.46,3.08]	
Tsai KL 2017a	-8.92	3.59	12	-12.95	1.98	12	10.7%	1.34[0.44,2.24]	
Tsai KL 2017b	-11.72	1.68	12	-12.95	1.98	12	11.2%	0.65[-0.18,1.47]	
Subtotal (95% CI)			**48**			**57**	**51.3%**	**1.04[0.62,1.46]**	
Heterogeneity: Tau^2= 0.00; Chi^2= 2.87, df= 4(P=0.58); I^2= 0%									
Test for overall effect: Z= 4.84 (P < 0.00001)									
2.3.2 The postoperative exercise time ≥ 4 weeks									
Chen YW 2012a	0.09	1.49	10	-0.38	1.98	10	10.8%	0.26[-0.62,1.14]	
Chen YW2012b	0.38	1.58	10	0.5	1.78	10	10.9%	-0.07[-0.95,0.81]	
Cobianchi S 2010	-6.4	1.41	8	-4.81	1.86	11	10.3%	-0.90[-1.86,0.07]	
Farzad B 2018	-5.5	2.3	7	-10	0.49	7	7.1%	2.53[1.01,4.06]	
Hung CH 2016	-7.83	2.3	10	-11.84	2.1	10	9.7%	1.74[0.68,2.81]	
Subtotal (95% CI)			**45**			**48**	**48.7%**	**0.62[-0.45,1.69]**	
Heterogeneity: Tau^2=1.20; Chi^2= 21.80, df= 4(P=0.0002); I^2= 82%									
Test for overall effect: Z= 1.14 (P=0.25)									
Total (95% CI)			**93**			**105**	**100.0 %**	**0.84[0.28,1.40]**	
Heterogeneity: Tau^2= 0.55; Chi^2= 29.04, df= 9(P=0.0006); I^2= 69%									
Test for overall effect: Z= 2.93 (P = 0.003)									
Test for subaroun differences: Chi^2= 0.51.df=1(P=0.48) I^2=0%									

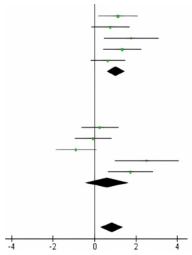


FIGURE 4
Forest plot of subgroup analysis: postoperative exercise duration on mechanical paw withdrawal threshold. Subgroup analysis based on postoperative exercise intervention time showed that postoperative exercise time ÿ 3 weeks could significantly improve the mechanical pain threshold, while postoperative exercise time ÿ 4 weeks had no significant improvement in mechanical pain threshold. [a,b]Represent different exercise programs in the same study.

3.5 Publication bias analysis

STATA 12.0 software was employed to assess publication bias. Funnel plots were generated to visualize potential bias for both mechanical and thermal pain thresholds following exercise intervention (Figure 8). Additionally, Egger's regression test was utilized for quantitative analysis of publication bias.

Egger's test yielded a *p*-value of 0.073, suggesting an absence of publication bias for the analysis of mechanical pain threshold. Conversely, the funnel plot for thermal pain threshold (Figure 9) exhibited asymmetry, and Egger's test confirmed this with a highly significant p-value of less than 0.001, indicating the presence of publication bias. To address this bias, a trim and fill method was implemented (Figure 10). This method statistically imputes missing studies to achieve a symmetrical funnel plot, suggesting the addition of four hypothetical studies. Despite a slight change in the effect size after adjusting for publication bias (*SMD* = 2.81, 95%*CI*: 0.31–1.74, $p = 0.005$), a significant difference between the exercise and control groups remained.

Thermal pain perception involves not only TRPV1 channels, but may also be affected by other temperature-sensitive ion channels, neurotransmitters, and receptors. In addition, thermal stimulation may trigger a wider range of neuroinflammatory responses, which may show greater variability under different experimental conditions. Mechanical pain perception is relatively more direct, and its neural pathways may be relatively simple. Therefore, under experimental conditions, changes in mechanical pain thresholds may be more consistent and predictable. The reasons why thermal responses may show deviations in meta-analysis involve many factors, such as the complexity of pain mechanisms, differences in experimental methods,

	Experimental group			Control group				Std. Mean Difference	Std. Mean Difference
2.5.1 Treadmill sports									
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random,95%CI	IV, Random, 95%*CI*
Chen YW 2012a	0.09	1.49	10	-0.38	1.98	10	10.8%	0.26[-0.62,1.14]	
Cobianchi S 2010	-6.4	1.41	8	-4.81	1.86	11	10.3%	-0.90[-1.86,0.07]	
Cobianchi S 2013	-14.7	2.83	8	-19.2	4.26	15	10.5%	1.13[-0.20,2.06]	
Huang PC 2017	-11.35	2.18	10	-12.98	1.87	10	10.6%	0.77[-0.15,1.68]	
Hung CH 2016	-7.83	2.3	10	-11.84	2.1	10	9.7%	1.74[0.68,2.81]	
Safakhah 2017	-2.93	22.8	6	-32.84	7.53	8	8.2%	1.77[0.46,3.08]	
Tsai KL 2017a	-8.92	3.59	12	-12.95	1.98	12	10.7%	1.34[0.44,2.24]	
Tsai KL 2017b	-11.72	1.68	12	-12.95	1.98	12	11.2%	0.65[-0.18,1.47]	
Subtotal (95% CI)			**76**			**88**	**82.1%**	**0.81[0.23,1.39]**	
Heterogeneity: Tau^2= 0.45; Chi^2= 20.44, df= 7(P=0.005); I^2= 66%									
Test for overall effect: Z= 2.73 (P = 0.006)									
2.5.2 Swimming									
Chen YW2012b	0.38	1.58	10	0.5	1.78	10	10.9%	-0.07[-0.95,0.81]	
Farzad B 2018	-5.5	2.3	7	-10	0.49	7	7.1%	2.53[1.01,4.06]	
Subtotal l(95% CI)			**17**			**17**	**17.9%**	**1.15[-1.39,3.70]**	
Heterogeneity: Tau^2=2.98; Chi^2= 8.41, df= 1(P=0.004); I^2= 88%									
Test for overall effect: Z= 0.89 (P=0.37)									
Total (95% CI)			**93**			**105**	**100.0 %**	**0.84[0.28,1.40]**	
Heterogeneity: Tau^2= 0.55; Chi^2= 29.04, df= 9(P=0.0006); I^2= 69%									
Test for overall effect: Z= 2.93 (P = 0.003)									
Test for subaroun differences: Chi^2= 0.07.df=1(P=0.79) I^2=0%									

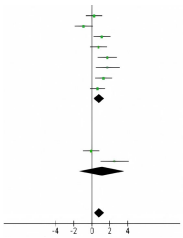


FIGURE 5
Forest plot regarding subgroup analysis of exercise forms of mechanical paw withdrawal threshold. Subgroup analysis was conducted based on different exercise methods. Treadmill exercise significantly increased the mechanical pain threshold, while swimming exercise did not significantly increase the mechanical pain threshold. [a,b]Represent different exercise programs in the same study.

uncertainties in data collection and analysis, and physiological adaptation and fatigue effects. These factors work together to lead to inconsistencies in the results of thermal pain thresholds in different studies. However, by adopting appropriate statistical methods and interpretation strategies, we can reduce this bias to a certain extent and improve the reliability and validity of meta-analysis results.

4 Discussion

4.1 The effect of postoperative exercise intervention duration on mechanical pain threshold

Subgroup analysis revealed that exercise interventions lasting four weeks or less (≤4 weeks) significantly improved mechanical pain sensitivity compared to control, while interventions exceeding four weeks (≥ 4 weeks) did not. This finding aligns with a previous meta-analysis by Guo et al. (14) on exercise for peripheral neuropathy in rats, which showed no significant improvement in mechanical pain sensitivity with interventions lasting five weeks or longer. Similarly, Chen et al. (22) investigated the effect of exercise on mechanical pain threshold using a chronic compression sciatic nerve injury model in rats. Their findings showed a significant difference in pain threshold between exercise and control groups early after surgery, but no difference by day 39 post-surgery. This suggests minimal improvement after six weeks of exercise. Grace et al. (31) also used a chronic compression model and found that mechanical pain sensitivity persisted in the control group for 15 weeks. Variations in pain duration across similar models might be due to differences in the severity of nerve damage caused by the specific pain model, potentially contributing to the observed heterogeneity in our findings. Overall, the duration of the

TABLE 3 Meta-regression analysis results of heterogeneity factors affecting paw withdrawal thermal latency.

Item	Regression coefficient	Standard error	*t*-value	*P*-value	95% *CI*
Species	−2.424	1.069	−2.270	0.053	[−4.889, 0.040]
Pain mode	−0.785	0.610	−1.290	0.234	[−2.191, 1.263]
Exercise mode	−0.519	0.773	−0.670	0.520	[−2.302, 1.263]
Start time	−0.531	0.836	−0.630	0.544	[−2.460, 1.398]
Intervention time	−2.136	0.854	−2.500	0.037	[−4.104, −0.168]

A significance level of $p < 0.05$ suggests that this factor influences the heterogeneity observed between studies.

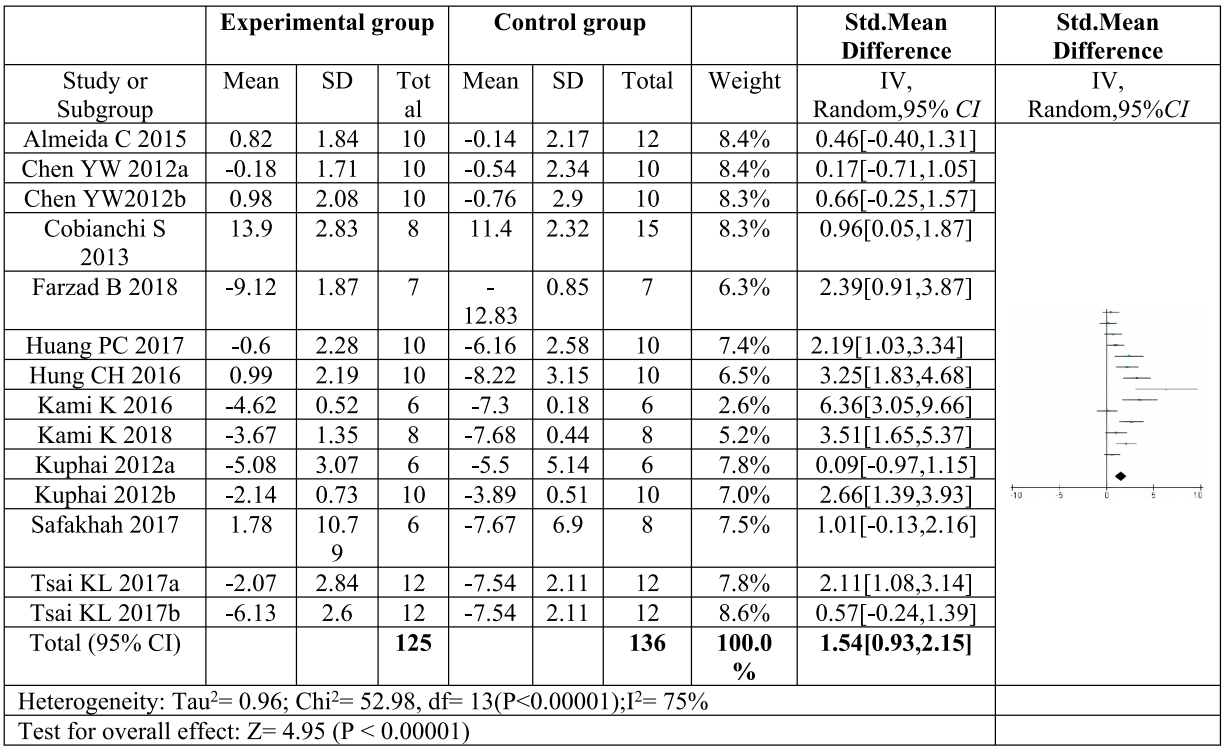


FIGURE 6
Forest plot regarding meta-analysis estimate for exercise on paw withdrawal thermal latency. The thermal pain threshold of the exercise group was significantly higher than that of the control group ($P < 0.00001$). [a,b]Represent different exercise programs in the same study.

exercise intervention significantly impacted the collective results. Most studies demonstrated a positive effect on reducing mechanical pain sensitivity before the end of the exercise program. These findings suggest that the duration of postoperative exercise plays a critical role in improving mechanical pain sensitivity through physical activity. Notably, exercise interventions within three weeks of surgery appear to have the most pronounced impact on improving mechanical pain sensitivity following sciatic nerve injury.

4.2 The effect of postoperative exercise intervention duration on thermal pain threshold

Sciatic nerve injury is known to significantly reduce thermal pain threshold and lead to thermal sensitivity symptoms. Assessing thermal pain threshold involves measuring the latency in response to thermal radiation. However, inconsistencies in the literature regarding the intensity of thermal radiation used during experiments can lead to varying outcomes. This variation in methodology for thermal pain threshold testing may be a significant contributor to the observed heterogeneity in results across studies.

A comprehensive review by Pitcher et al. (19) examined the impact of exercise on pain models in mice. Their analysis included 22 studies investigating thermal pain sensitivity in exercise-treated pain models for both rats and mice. Notably, the majority of these studies reported significant improvement in thermal pain sensitivity following exercise intervention. Pitcher et al. considered several factors that might influence the effectiveness of exercise, including animal characteristics (gender and species), timing and type of exercise initiation, the specific pain model used, and the duration of the exercise program (19). Importantly, their review did not identify a

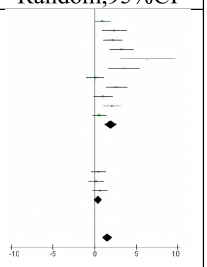
	Experimental group			Control group				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random,95%CI	IV, Random,95%CI
2.4.1 The postoperative exercise time ≤ 4 weeks									
Cobianchi S 2013	13.9	2.83	8	11.4	2.32	15	8.3%	0.96[0.05,1.87]	
Farzad B 2018	-9.12	1.87	7	-12.83	0.85	7	6.3%	2.39[0.91,3.87]	
Huang PC 2017	-0.6	2.28	10	-6.16	2.58	10	7.4%	2.19[1.03,3.34]	
Hung CH 2016	0.99	2.19	10	-8.22	3.15	10	6.5%	3.25[1.83,4.68]	
Kami K 2016	-4.62	0.52	6	-7.3	0.18	6	2.6%	6.36[3.05,9.66]	
Kami K 2018	-3.67	1.35	8	-7.68	0.44	8	5.2%	3.51[1.65,5.37]	
Kuphai 2012a	-5.08	3.07	6	-5.5	5.14	6	7.8%	0.09[-0.97,1.15]	
Kuphai 2012b	-2.14	0.73	10	-3.89	0.51	10	7.0%	2.66[1.39,3.93]	
Safakhah 2017	1.78	10.79	6	-7.67	6.9	8	7.5%	1.01[-0.13,2.16]	
Tsai KL 2017a	-2.07	2.84	12	-7.54	2.11	12	7.8%	2.11[1.08,3.14]	
Tsai KL 2017b	-6.13	2.6	12	-7.54	2.11	12	8.6%	0.57[-0.24,1.39]	
Subtotal (95% CI)			**95**			**104**	**74.9%**	**1.93[1.19,2.67]**	
Heterogeneity: Tau^2= 1.09; Chi^2= 39.51, df= 10(P<0.0001);I^2= 75%									
Test for overall effect: Z= 5.13 (P < 0.00001)									
2.4.2 The postoperative exercise time ≥ 5 weeks									
Almeida C 2015	0.82	1.84	10	-0.14	2.17	12	8.4%	0.46[-0.40,1.31]	
Chen YW 2012a	-0.18	1.71	10	-0.54	2.34	10	8.4%	0.17[-0.71,1.05]	
Chen YW2012b	0.98	2.08	10	-0.76	2.9	10	8.3%	0.66[-0.25,1.57]	
Subtotal (95% CI)			**30**			**32**	**25.1%**	**0.42[-0.08,0.93]**	
Heterogeneity: Tau^2= 0.00; Chi^2= 0.59, df= 2(P = 0.74); I^2= 0%									
Test for overall effect: Z=1.64 (P = 0.10)									
Total (95% CI)			**125**			**136**	**100.0 %**	**0.84[0.28,1.40]**	
Heterogeneity: Tau^2= 0.96; Chi^2= 52.98, df= 13(P<0.00001); I^2= 75%									
Test for overall effect: Z= 4.95 (P < 0.00001)									
Test for subaroun differences: Chi^2= 10.91.df=1(P=0.0010) I^2=90.8%									

FIGURE 7
Forest plot regarding subgroup analysis of postoperative exercise duration of paw withdrawal thermal latency. In subgroup analysis with postoperative exercise time, the postoperative exercise time ≤ 4 weeks significantly increased the thermal pain threshold, and the postoperative exercise ≥ 5 weeks. There was no significant increase in the heat pain threshold. [a,b]Represent different exercise regimens for the same study.

single factor that definitively influenced the success of exercise in enhancing thermal sensitivity. However, their findings echo the results of the current study. Exercise interventions lasting four weeks or less (≤4 weeks) were associated with a significant improvement in thermal pain sensitivity following sciatic nerve injury. In contrast, exercise programs exceeding five weeks (≥5 weeks) did not yield a significant improvement in thermal pain sensitivity, but may still play a role in promoting recovery processes.

4.3 Analysis of the reasons for the differences in the results of postoperative exercise intervention on mechanical pain threshold and thermal pain threshold

Mechanical and thermal pain are mediated by distinct receptors and neural pathways. At the primary level of sensory input, these pathways differentiate between various physical sensations, including nociceptive heat/cold, mechanical stimulation, and itching (32). Studies have shown that Mas-related G protein-coupled receptors (MRGPRs) are prominently expressed in primary sensory neurons (33). Specifically, nociceptors expressing transient receptor potential vanillic acid receptor 1 (TRPV1) are responsible for thermal pain, while mechanical pain is mediated solely by nociceptors (34). Importantly, there is no observed interaction between these two receptor systems in pain production (35). Furthermore, nerve growth factor (NGF) plays a crucial role in neuropathic pain development (36). Its high-affinity receptor, tyrosine kinase receptor A (TrkA), mediates mechanical pain sensitivity resulting from cutting injury and inflammatory pain, but does not affect basal mechanical and thermal pain thresholds (37). These findings, along with the influence of higher neural centers on pain processing, highlight the distinct characteristics of mechanical and thermal pain generation. Consequently, the variations in underlying mechanisms contribute to the observed inconsistencies in the effects of exercise interventions on these two types of pain (38).

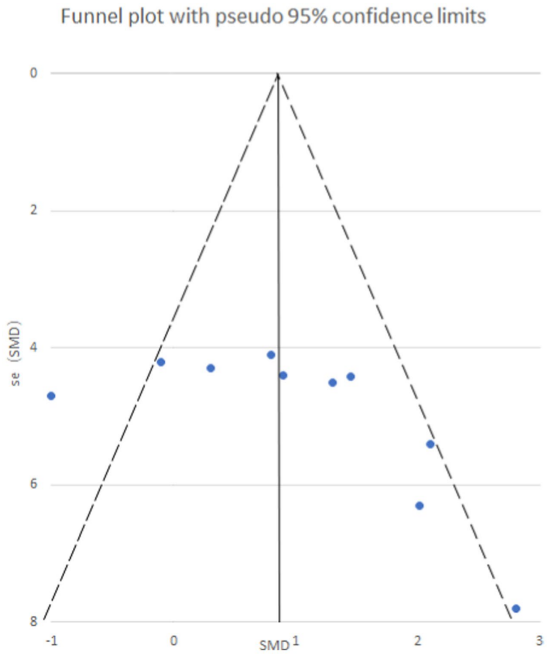


FIGURE 8
Mechanical pain threshold funnel plot. The funnel plot is symmetrical and has no publication bias.

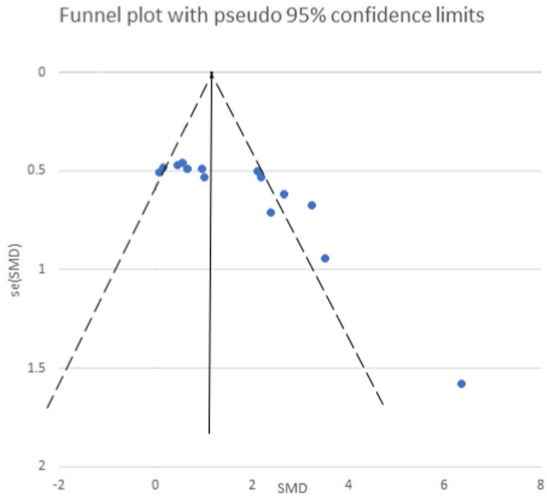


FIGURE 9
Thermal pain threshold funnel plot. The funnel plot is asymmetrical and there is publication bias.

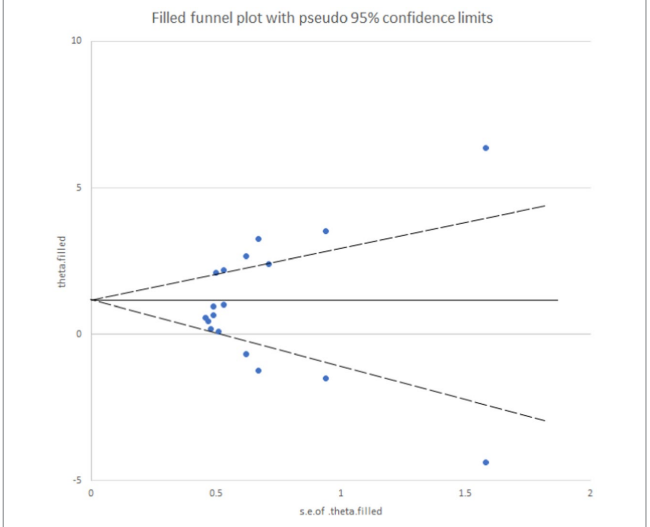


FIGURE 10
Analysis chart of trim and fill method for thermal pain threshold index. After adding four studies using the trimming and patching method, publication bias was eliminated.

4.4 Analysis under different pain models

When exploring exercise as an effective means of relieving pain from sciatic nerve injury, we must not only focus on the overall conclusion of the impact of exercise duration on pain behavior, but also need to conduct an in-depth analysis of the development, duration, and spontaneous recovery of hypersensitivity reactions under different pain models. Characteristic. These subtle differences are critical to fully understanding the effects of exercise interventions and developing targeted pain management strategies. The following is a detailed analysis and discussion of this issue.

This meta-analysis shows that in animal models of sciatic nerve injury, short-term postoperative (≤3 weeks) exercise intervention significantly improves mechanical pain thresholds, while mid-term postoperative (≤4 weeks) exercise intervention significantly improves mechanical pain thresholds. Thermal pain threshold. However, when the duration of exercise was extended to more than 4 weeks, its relief effect on mechanical pain and thermal pain was no longer significant. This finding suggests that exercise can effectively reduce pain hypersensitivity caused by nerve damage within a specific period of time, but beyond this time window, its effect may gradually weaken or disappear.

4.4.1 Differences in specificity among different pain models

Although the overall trends are consistent, different pain models exhibit significant differences in the development and duration of hypersensitivity reactions and spontaneous recovery. These differences may arise from a variety of factors, including the severity of the nerve injury, the anatomy of the injury site, and the physiological responses of the individual animals (39).

4.4.2 Development and duration of hypersensitivity reactions

The rate of development and duration of hypersensitivity reactions vary in different pain models. For example, in some models, significant mechanical and thermal pain hypersensitivity occurs immediately after nerve injury and lasts from weeks to months; in other models, the hypersensitivity may be more gradual and persistent. The time is relatively short. This difference directly affects the optimal time point and duration of exercise intervention (40).

4.4.3 Spontaneous recovery phenomenon

Of note, animals in some models experience spontaneous recovery of hypersensitivity reactions within weeks of injury (41).

This phenomenon shows that the nervous system has a certain self-healing ability and can reduce pain hypersensitivity to a certain extent. Therefore, long-term exercise intervention may not provide additional pain relief in these models because the animals are already in the process of spontaneous recovery. However, this does not mean that exercise intervention has no value in alleviating initial hypersensitivity reactions; on the contrary, short-term exercise intervention can still significantly reduce pain levels and provide positive support for the animal's recovery process (42).

4.4.4 Deep explanation and recognition of exercise effectiveness

4.4.4.1 Discussion on physiological mechanisms

The reason why exercise can alleviate the pain hypersensitivity caused by sciatic nerve injury to a certain extent may be related to its impact on multiple physiological mechanisms. Exercise can promote blood circulation, increase the release of neurotrophic factors, and promote nerve regeneration and repair (43). At the same time, exercise can also regulate the function of the immune system, reduce inflammatory reactions and neuroimmune reactions, thereby indirectly relieving pain (44). However, the effects of these physiological mechanisms may be affected by factors such as pain model specificity and exercise duration.

4.4.4.2 Recognize the importance of model specificity

When drawing conclusions about the effectiveness of exercise, we must acknowledge differences in specificity between pain models. This difference is not only reflected in the development and duration of hypersensitivity reactions, but may also affect the specific effects and application strategies of exercise intervention. Therefore, when formulating an exercise-based pain management program, we need to fully consider factors such as individual pain model characteristics (45, 46), injury severity, and physiological responses to achieve personalized and precise treatment (47).

4.4.5 Suggestions for future research directions

In order to further verify and expand the conclusions of this article, future research can start from the following aspects:

Refining the classification of pain models: Carry out a more detailed classification and comparison of different sciatic nerve injury models to clarify their specific differences in the development, duration and spontaneous recovery of hypersensitivity reactions.

Explore the optimal time window for exercise intervention: Through more experimental studies, determine the optimal starting time and duration of exercise intervention under different pain models to maximize its pain relief effect.

In-depth study of the impact of exercise on physiological mechanisms: using advanced molecular biology and neuroimaging techniques, in-depth exploration of the specific impact of exercise intervention on physiological mechanisms such as blood circulation, neurotrophic factor release, immune system function, and its relationship with pain relief internal connections.

Formulation of personalized treatment plans: Develop personalized exercise treatment plans based on individual pain model characteristics, physiological responses and other factors to improve the pertinence and effectiveness of pain management.

4.5 Reasons for the few effects of long-term exercise

4.5.1 Spontaneous recovery phenomenon

It is pointed out that in some models, untreated animals will spontaneously recover over time, and their pain thresholds gradually approach or reach the level of trained animals (48). Therefore, although prolonged exercise may help with initial relief, the later effects are no longer significant.

4.5.2 Exercise fatigue or adaptation

Prolonged exercise may cause fatigue or adaptation in animals, thereby reducing the pain-relieving effect of exercise (49).

4.5.3 Complexity of pain mechanisms

Emphasizes the complexity of pain mechanisms, which may involve changes in multiple neurotransmitters, receptors, and ion channels (50). Prolonged exercise may not be sufficient to sustainably affect these complex pathophysiological processes.

5 Limitations of this research

This study has several limitations that should be acknowledged. Incomplete data and the inability to contact original authors for clarification resulted in the exclusion of potentially relevant studies. Additionally, variations in exercise interventions and pain measurement methods across studies may have contributed to the observed inconsistencies in results. Despite employing sensitivity and subgroup analyses, the issue of heterogeneity remains unresolved. Furthermore, the limited literature available on exercise interventions for chronic pain primarily involves male subjects. This restricts our ability to draw definitive conclusions regarding potential gender-based differences in the analgesic efficacy of exercise. Inconsistencies in the types of exercise employed further complicate efforts to compare exercise intensity and elucidate the relationship between intensity and pain reduction (24, 25). While exercise remains a cornerstone of pain management, tailored to individual presentations, further research is necessary to address these limitations. Given established sex differences in pain mechanisms (51), future studies should explore whether exercise has differential effects on pain improvement based on gender.

6 Conclusion

Exercise has emerged as an effective intervention for improving both mechanical and thermal allodynia resulting from sciatic nerve injury in rodents. Notably, the species, method, and timing of exercise initiation appear to have minimal influence on the overall effectiveness of the intervention. However, the duration of pain sensitization in the specific pain model significantly impacts the success of exercise-induced analgesia. Studies have shown that exercise demonstrably improves sciatic nerve damage in animals. Postoperative exercise interventions lasting less than three weeks resulted in a significant improvement in mechanical allodynia, while those lasting less than four weeks yielded a significant improvement in thermal hyperalgesia. These findings highlight the importance of considering the duration

of pain sensitivity within the chosen pain model for future research on exercise-induced analgesia.

Future research should prioritize investigating the specific exercise movements or modalities that induce positive changes in pain-related molecules. While exercise demonstrates promise as a pain management strategy, it is important to acknowledge that it may not be a universally effective treatment for all types of pain. Therefore, further studies are needed to explore the potential benefits of combining exercise with existing therapies such as medication, acupuncture, and even novel approaches like stem cell tissue engineering. This multi-faceted approach has the potential to address pain relief from various perspectives and improve patient outcomes.

In summary, the different responses of mechanical pain threshold and thermal pain threshold to exercise intervention may originate from their respective unique molecular mechanisms. Further studies should delve into the interplay between these mechanisms and how they jointly regulate the process of neuropathic pain. By deeply understanding these molecular features, we can provide a theoretical basis for developing more precise and effective pain treatment strategies.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

SL: Formal analysis, Writing – original draft. QL: Data curation, Writing – review & editing. HW: Visualization, Writing – review & editing. HZ: Data curation, Project administration, Writing – review & editing. QZ: Project administration, Writing – review & editing. JS: Methodology, Writing – review & editing. JZ: Supervision, Writing – review & editing. PF: Funding acquisition, Supervision, Writing – review & editing. AZ: Supervision, Funding acquisition, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Comparison of the efficacy of pulsed radiofrequency in treating acute herpetic neuralgia and postherpetic neuralgia in the thoracic segment

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Objectives: This study aimed to compare the efficacy of pulsed radiofrequency (PRF) to dorsal root ganglia (DRG) in treating acute herpetic neuralgia (AHN) and postherpetic neuralgia (PHN) in the thoracic segment.

Methods: A total of 243 patients with thoracic herpes zoster-related pain (AHN or PHN) from January 2020 to September 2022 were retrospectively analyzed. They were divided into two groups based on the timing of PRF after herpes zoster onset: an acute herpetic neuralgia group (within 90 days) and a postherpetic neuralgia group (more than 90 days). All patients were treated with PRF at the thoracic DRG. The Visual Analog Scale (VAS), the Athens Insomnia Scale (AIS), the Generalized Anxiety Disorder-7 items (GAD-7), and the Patient Health Questionnaire-9 items (PHQ-9) scores were assessed before and at 1 week, 1 month, 3 months, 6 months, and 12 months after surgery, and the results were then compared between the two groups.

Results: Postoperative scores of VAS, AIS, GAD-7, and PHQ-9 in both groups were significantly lower than preoperative scores ($P < 0.001$). From 1 month to 12 months after surgery, the AHN group showed significantly lower VAS, AIS, GAD-7, and PHQ-9 scores compared to the PHN group ($P < 0.001$). In the AHN group, there was a gradual improvement in these scores from 1 week to 12 months post-surgery. Conversely, the PHN group's scores began to worsen slowly from 1 week to 12 months post-surgery. Over time, the difference in scores between the two groups also increased gradually.

Conclusion: PRF to the DRG is an effective treatment for patients with AHN or PHN who do not respond well to conventional treatments. For AHN patients, PRF to the DRG significantly enhances early pain control, improves sleep and psychological status, and may even prevent the development of PHN.

KEYWORDS

pulsed radiofrequency, herpes zoster, postherpetic neuralgia, dorsal root ganglia, neuropathic pain, sleep quality

Introduction

Herpes zoster (HZ) is an acute skin disease caused by the reactivation and replication of the varicella-zoster virus (VZV) in the dorsal root ganglion (DRG) (1). It mainly manifests as clustered blisters distributed along nerve segments on one side of the body, accompanied by pain and paresthesia during the acute/subacute phase, which is the first 3 months after the onset of shingles (2). The pain during this period is called acute herpetic neuralgia (AHN).

Postherpetic neuralgia (PHN) is the final stage (more than 3 months) of VZV infection and is characterized by severe refractory neuropathic pain (3). Preventing the transition from AHN to PHN is a fundamental therapeutic principle, especially for older patients at an early stage (<3 months) (2, 4, 5). Both pulsed radiofrequency (PRF) and short-term spinal cord stimulation (stSCS) have proven to be effective in relieving AHN (6). The DRG contains many receptor channels and is an important hub for many nociceptive signal transduction. The proximal end of the DRG nerve cell body extends to the dorsal horn of the spinal cord (7, 8). Persistent abnormal electrical activity in the spinal cord through the DRG can lead to neuropathic processes, such as central sensitization, and increase the risk of PHN development (9). Therefore, the DRG is a crucial target for treating herpes zoster-related pain.

PRF applied to the DRG has been shown to be an effective treatment in studies on herpes zoster-associated pain (AHN or PHN), especially for intractable pain in the thoracic segment. The application of PRF to the DRG is recommended for pain control and prevention of PHN (9). The effect of PRF on the DRG in PHN patients has been reported (10). PRF to the DRG is more effective in the treatment of acute herpetic pain than PHN. Early intervention of PRF in the treatment of AHN may be more helpful in controlling pain and preventing PHN. Although studies have explored PRF therapy for acute herpes zoster pain, large sample sizes and long-term follow-up studies are lacking. This study retrospectively analyzed the clinical effect of PRF on the DRG in treating AHN and PHN.

Materials and methods

Patients

Medical records were obtained from all patients who received pulsed radiofrequency therapy for herpes-related pain (AHN or PHN) from January 2020 to September 2022. We included the medical records of 243 patients with herpes zoster-related pain (AHN or PHN) in a thoracic segment (Figure 1). A total of 281 patients were included before follow-up, of which 38 were lost to follow-up (three deceased and 35 lost contact). Data such as sex, age, height, weight, BMI, preoperative VAS, smoking status, drinking status, hypertension, diabetes, insomnia, and postoperative oral medication of patients were recorded.

Pain intensity (measured using the Visual Analog Scale, VAS), sleep quality (measured using the Athens Insomnia Scale, AIS), and psychological burden (measured using the Generalized Anxiety Disorder-7 items, GAD-7, and the Patient Health Questionnaire-9 items, PHQ-9) of patients were followed up at 1 week, 1 month, 3 months, 6 months, and 12 months after the operation. The therapeutic effects between the two groups were compared.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (KYLLSL-2022-205).

Patients were included if they met the following inclusion criteria: (1) Met the diagnostic criteria of HZ and PHN; (2) the lesion occurred in the thoracic spinal nerves; (3) persistent intense pain, with/without local skin hyperalgesia, sensory abnormalities; (4) pain levels not well controlled by standard pharmacotherapy (antiepileptic drugs, antidepressants, lidocaine patches, opioids, etc.); and (5) 24-h VAS ≥5. After the preliminary selection, patients were excluded if they had the following exclusion criteria: (1) unwillingness or inability to complete the follow-up; (2) severe coagulation disorder; (3) severe liver or kidney dysfunction; (4) history of drug abuse; (5) severe cardiopulmonary disease; or (6) intellectual inability to complete self-evaluation using VAS or AIS.

Surgical procedure

The application of PRF to the DRG in treating all patients with either AHN or PHN in the thoracic segment was performed by the same team of doctors. Continuous ECG monitoring was carried out throughout the procedure, and the diseased spinal nerve was preoperatively determined, based on the patient's pain site. The patient was in the prone position for the surgical procedure. The surgical area was disinfected routinely. Under local infiltration anesthesia, a needle with a 5 mm exposed tip was inserted layer by layer into the DRG of the spinal nerve under C-arm guidance (Figure 2). Upon reaching the expected position, a high-frequency (50 Hz, 500 μs width, <0.2 volts) sensory stimulation test and a low-frequency (2 Hz, 1,000 μs width, <0.5 volts) motor stimulation test were conducted. These tests confirmed the accurate placement of the needle tip. Subsequently, the treatment was carried out with PRF parameters set at 42°C, 2 Hz, with a field intensity of 90 V, for a duration of 900 s.

During follow-up, it was found that some patients continued to take oral medications, such as pregabalin and opioids, due to poor response to PRF. These cases were recorded and analyzed. However, due to the extended follow-up period, accurate information on the oral doses and treatment courses of the drugs for many patients could not be obtained. Therefore, the number of patients who continued to take medications was used as one of the indicators for comparing the efficacy between the groups. Even though this method introduces some systematic bias, it still provides valuable insights into the difference in treatment effect between the two groups.

Efficacy evaluation and follow-up

The Visual Analog Scale (VAS) was used to evaluate the level of pain, with 0 indicating no pain and 10 indicating maximum pain. The patient selected a number between 0 and 10 on a caliper to indicate the intensity of their pain.

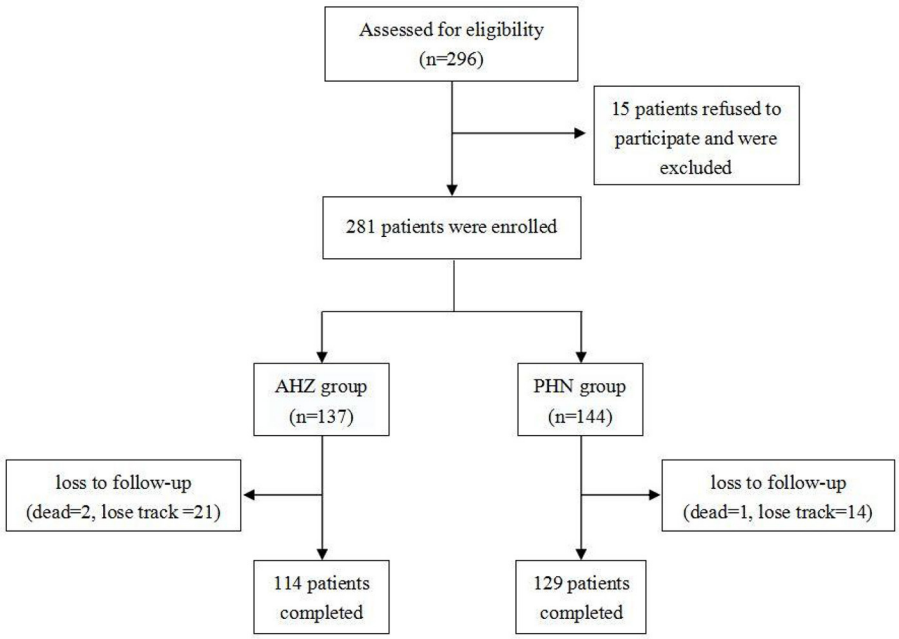

FIGURE 1
Flow chart of case enrollment and follow-up.

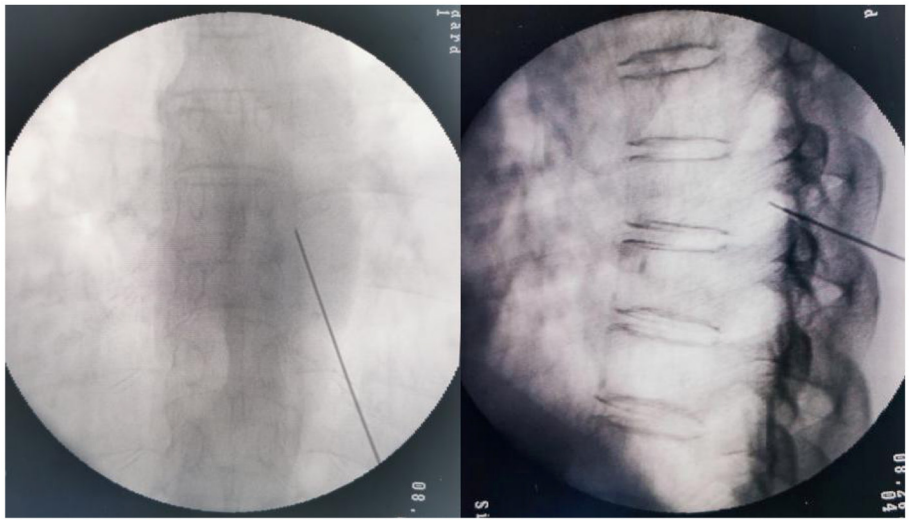

FIGURE 2
Puncture of the thoracic DRG under the guidance of an X-ray. The left is the anteroposterior view, and the right is the lateral view.

The Athens Insomnia Scale (AIS) (11) was used to assess sleep quality. An AIS score of 6 was considered insomnia, scores between 4 and 6 suggested suspected insomnia, and scores below 4 indicated no sleep disturbance.

The Generalized Anxiety Disorder-7 item (GAD-7) (12) scale and the Patient Health Questionnaire-9 items (PHQ-9) (13) were used to evaluate anxiety and depression, respectively. The scores ranging from 0 to 4 indicated normal levels, while the scores ranging from 5 to 9 indicated symptomatic levels, with higher scores indicating more severe symptoms, up to a maximum score of 27.

Follow-up mainly consisted of outpatient visits, supplemented by telephone and online follow-ups. Patients were asked to fill out the evaluation forms honestly. Follow-up sessions were scheduled before operation, 1 week, 1 month, 3 months, 6 months, and 12 months post-operation.

TABLE 1 General information of the AHN group and the PHN group.

	AHN group ($n = 114$)	PHN group ($n = 129$)	*P*-value
Sex (M/F)	46/68	59/70	0.398
Age (year)	70.4 ± 7.6	71.4 ± 7.5	0.313
Height (cm)			
Male	170 ± 6	169 ± 7	0.591
Female	158 ± 5	158 ± 7	0.895
Weight (kg)			
Male	70 ± 6	70 ± 7	0.326
Female	62 ± 5	61 ± 5	0.216
BMI	23.0 ± 3.0	23.1 ± 3.3	0.883
VAS	6.8 ± 0.8	6.8 ± 0.7	0.924
Smoking (*n*, %)	31 (27.2)	38 (29.5)	0.696
Drinking (*n*, %)	24 (21.1)	28 (21.7)	0.901
Diabetes (*n*, %)	15 (13.1)	21 (16.3)	0.494
Hypertensive (*n*, %)	23 (20.1)	32 (24.8)	0.389
Insomnia (*n*, %)	35 (30.7)	47 (36.4)	0.098
Oral medications (*n*, %)	10 (8.8)	33 (25.6)	0.001
Pregabalin	6	21	
Opioids	4	12	

Statistical analysis

SPSS 23.0 statistical software was used for analysis. Data were expressed as mean ± standard deviation. A *t*-test was performed to measure the data such as age, height, etc. Scores from the VAS, AIS, GAD-7, and PHQ-9 were compared between the two groups using repeated-measures analysis of variance. The chi-squared test was performed to compare categorical data such as sex, hypertension, diabetes, and oral medications. A *P*-value of < 0.05 was considered statistically significant.

Results

General information of the AHN group and the PHN group

Twelve months after surgery, the number of patients requiring oral medication (pregabalin or opioids) in the PHN group was 3.3 times greater than in the AHN group, indicating a statistical difference ($P = 0.001$). There were no statistically significant differences in terms of patients' basic information, including sex, age, height, weight, BMI, VAS, smoking, drinking, hypertension, diabetes, and insomnia, between AHN group and PHN group (see Table 1).

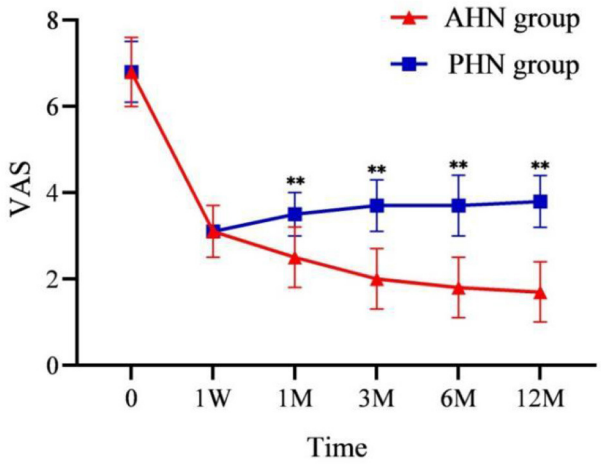

FIGURE 3
Changes of VAS in the AHN group and the PHN group. $^{**}P < 0.001$. AHN group, $n = 114$; PHN group, $n = 129$. VAS, Visual Analog Scale. Time: postoperative follow-up time. W, week; M, month. 0 = preoperative.

Postoperative VAS changes in the AHN group and the PHN group

The VAS scores of both the AHN and PHN groups were significantly lower than those before the procedure ($P < 0.001$). In addition, the VAS score of the AHN group gradually decreased over time, while the PHN group's VAS score gradually increased from 1 week to 12 months after surgery ($P < 0.001$). The difference between the two groups gradually increased after 1 month (Figure 3). The results of repeated-measures analysis of variance showed a statistically significant time effect between the two groups ($F = 1{,}872.990$, $P < 0.001$), indicating that VAS scores in both groups significantly reduced over time compared with those before surgery. Time*group effect was also statistically significant ($F = 164.289$, $P < 0.001$), indicating that the decrease in VAS scores in the AHN group was significantly greater than that in the PHN group.

Postoperative changes in AIS, GAD-7, and PHQ-9 scores in the AHN and PHN groups

AIS, GAD-7, and PHQ-9 scores significantly decreased after surgery compared to preoperative scores ($P < 0.001$). In the AHN group, AIS, GAD-7, and PHQ-9 scores decreased over time following the procedure. In contrast, the PHN group's AIS, GAD-7, and PHQ-9 scores gradually increased at all time points post-procedure. From 1 to 12 months after surgery, the differences between the two groups became significant ($P < 0.001$) and increased over time (Figures 4, 5A, B).

Repeated-measures analysis of variance of AIS, GAD-7, and PHQ-9 scores yielded similar results to those of VAS. The time effect has a statistical difference ($F = 3{,}413.527$, $P < 0.001$; $F = 2{,}366.545$, $P < 0.001$; $F = 2{,}384.951$, $P < 0.001$), and the time*group

interaction effect was also significant ($F = 228.316$, $P < 0.001$; $F = 266.207$, $P < 0.001$; $F = 392.077$, $P < 0.001$). This indicates that there were significant differences in AIS, GAD-7, and PHQ-9 scores between the two groups before and after surgery. Moreover, there were significant differences between the groups ($P < 0.001$), with the AHN group showing a more substantial decrease in AIS, GAD-7, and PHQ-9 scores compared to the PHN group.

Discussion

PHN is a chronic neuropathic pain that is an unpredictable sequela of herpes zoster, which is induced by the varicella-zoster virus. It is usually seen in the elderly and the immunocompromised individuals (2, 14). PHN is defined as pain that lasts for more than 3 months after the recovery of herpes zoster, which is characterized by local skin allodynia or hyperalgesia (15). The pain is typically described as burning and tingling sensation and can be accompanied by numbness, leading to psychosocial dysfunction and a negative impact on the quality of life (5). Prevention of PHN can be achieved by vaccinating high-risk groups against herpes zoster, the early and regular use of antiviral drugs, and the aggressive and effective treatment of pain in the early stages of acute herpes zoster (16–19).

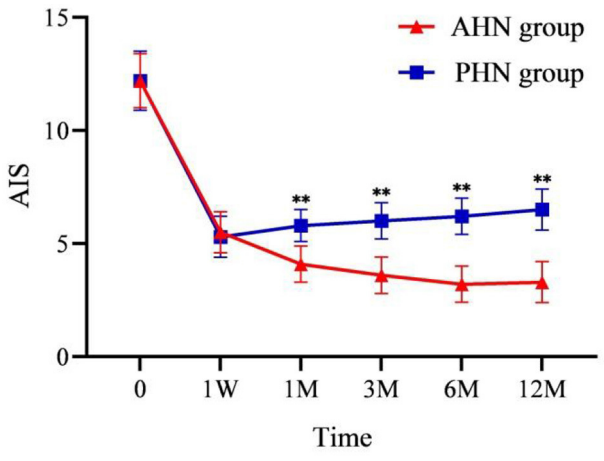

FIGURE 4
Changes of AIS in the AHN group and the PHN group. $^{**}P < 0.001$. AHN group, $n = 114$; PHN group, $n = 129$. AIS, Athens Insomnia Scale. Time: postoperative follow-up time. W, week; M, month. 0 = preoperative.

Studies have reported that early and effective pain intervention treatment may reduce pain and complications associated with herpes zoster and PHN (20, 21). Once PHN occurs, the pain usually persists for months to years, with the longest observed case being 20 years. Although the current first-line drugs for the treatment of PHN (4, 22–25), such as pregabalin, gabapentin, and a 5% lidocaine patch, can relieve pain, some patients do not experience adequate relief. Opioids have also long been prescribed to patients with PHN to reduce pain (26). Therefore, in this study, patients with severe pain after PRF surgery still required oral pregabalin or opioids, and the number of PHN patients requiring oral drugs was higher than that of AHN patients.

It should be noted that due to the long follow-up period, many patients could not accurately recall the dosage and duration of pregabalin and opioids. However, they could remember whether they took these drugs. This affects the integrity of the data, but valuable insights can still be obtained by comparing the number of patients taking oral medications in the two groups. Future studies should record oral medication dosages more meticulously.

PRF therapy is an effective complementary method for pain relief, being a grade B recommended therapy for the DRG (10, 27). Clinically, PRF can relieve AHN and PHN to a certain extent. Studies have suggested that early pain management of herpes zoster can reduce pain and prevent PHN (9, 28, 29). Further analysis of the therapeutic effects of PRF to the DRG in patients with AHN or PHN is beneficial in assisting clinicians to select a more suitable timing for pain treatment.

Histopathological studies have found that patients with severe PHN experience the loss of cells, axons, and myelin in the sensory ganglia, accompanied by fibrosis (30). This suggests that pain perception in patients with PHN may be caused by the ectopic firing of nociceptors and low-threshold afferents in the dorsal root

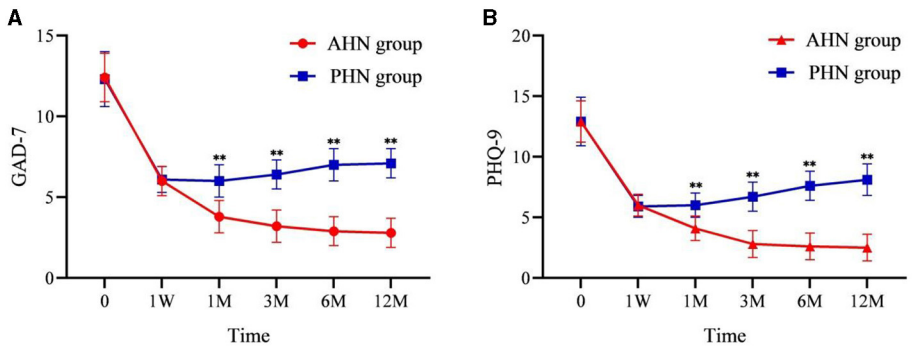

FIGURE 5
Changes of GAD-7 **(A)** and PHQ-9 **(B)** in the AHN group and the PHN group. $^{**}P < 0.001$. AHN group, $n = 114$; PHN group, $n = 129$. GAD-7, Generalized Anxiety Disorder-7 items; PHQ-9, Patient Health Questionnaire-9 items. Time: postoperative follow-up time. W, week; M, month. 0 = preoperative.

ganglion (31). PRF targeting the DRG can more effectively relieve pain caused by varicella-zoster virus invading the skin.

In our study, we followed up with 114 patients with AHN and 129 patients with PHN. To control pain and prevent PHN as much as possible, the researchers focused on treating pain in the acute phase of HZ (within 3 months after the onset of herpes zoster). The results showed that PRF to the DRG resulted in significantly more effective pain relief for AHN compared to PHN.

In the study of PRF in treating PHN, Han et al. (32) suggested that high-voltage PRF could offer better analgesic effects. PRF can be effectively used for treating PHN in the upper limbs because it operates at a safe temperature of 42°C, providing a protective effect on the nerve root. In addition, high-voltage, long-duration PRF to the DRG is effective and safe for treating HZ neuralgia in the subacute stage (33).

Aggarwal et al. (28) showed that early pain control can significantly improve sleep quality in patients with HZ. This finding is similar to our results. In our study, postoperative pain relief was more significant in the AHN group than in the PHN group, resulting in a considerable improvement in sleep quality for AHN patients. Conversely, the sleep quality of PHN patients did not improve as significantly as that of AHN patients. This disparity may be due to the long-term pain experienced by PHN patients, which severely affects sleep quality (34). Yamada et al. (35) pointed out that insufficient sleep may be a new risk factor for PHN.

Chronic pain imposes a severe psychological burden on patients (36–39). In our study, anxiety (measured using the GAD-7 scale) and depression (measured using the PHQ-9) in patients within the AHN group improved with pain relief and were significantly better than those in the PHN group. This indicates that the effective control of pain in acute herpes zoster can better reduce the psychological burden on patients. The study emphasizes the importance of early diagnosis and treatment of zoster-related pain (40).

Although rare, complications of PRF therapy to the DRG can be potentially severe. The risk of paraplegia due to injury to the Adamkiewicz artery during PRF therapy to the DRG cannot be ruled out (41). Similarly, ultrasound is of great value in detecting blood vessels and monitoring motor-evoked potentials during PRF-DRG. It can detect early signs of spinal cord ischemia, allowing the procedure to be stopped in time (42).

Limitations of the study

Our study has some limitations. As a retrospective study, it may introduce some bias in the data and lack the rigor of multicenter randomized controlled studies. Currently, there is no international standard for setting the parameters of pulsed radiofrequency therapy. Conducting a multicenter, prospective, double-blind controlled study is the next step worth pursuing.

Conclusion

PRF to the DRG is an effective treatment for patients with AHN or PHN who do not respond well to conventional treatments. For AHN patients, PRF to the DRG significantly enhances early pain control, improves sleep and psychological status, and may even prevent the development of PHN.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Department of Geriatric Cardiology, the First Affiliated Hospital of Xi'an Jiaotong University (KYLLSL-2022-205). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

HuaW: Conceptualization, Writing – original draft. DZ: Investigation, Resources, Supervision, Writing – original draft. SW: Formal analysis, Methodology, Project administration, Software, Writing – review & editing. HuiW: Data curation, Project administration, Supervision, Writing – review & editing. HN: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of meridian sinew tuina after identifying the treatment area under ultrasound localization combined with greater and third occipital nerve injections in cervicogenic headache: a randomized controlled trial protocol

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Introduction: Cervicogenic headache (CEH) is a secondary headache characterized by chronic, unilateral headache. Ultrasound-guided injections of the greater occipital nerve (GON) and the third occipital nerve (TON) are effective in the treatment of CEH, as is meridian sinew tuina for the treatment of CEH, but the evidence of clinical efficacy of combining these two therapies is valid. Therefore, we have designed a randomized controlled trial with the aim of investigating the efficacy and safety of ultrasound localization meridian sinew tuina combined with GON and TON injections for the treatment of CEH.

Methods and analysis: In this study, we enroll 60 patients experiencing CEH. The control group receives ultrasound-guided injections of GON and TON. The intervention group is treated with ultrasound localization meridian sinew tuina combined with the injection of GON and TON. Meridian sinew tuina is performed once a day for 30 min for 3 days. The primary observational index includes the Short-Form of McGill Pain Questionnaire (SF-MPQ). The Secondary outcomes include Cervical Range of Motion (ROM) and Medical Infrared Thermography (MIT). MIT is used to measure the change in skin temperature in the area of the patient's meridian sinew tuina treatment of GON and TON before and after the intervention. There are 5 time points assessed as baseline, day 3, day 15, day 30, and day 60.

Discussion: This study proposes to combine ultrasound-guided injections of GON and TON for the treatment of CEH after identifying the treatment area of meridian sinew tuina under ultrasound localization. Meanwhile, MIT is utilized to provide objective evidence of the efficacy of CEH.

Clinical trial registration: ChiCTR2300076128.

KEYWORDS

cervicogenic headache, meridian sinew tuina, ultrasound localization, greater occipital nerve, third occipital nerve, medical infrared thermography

Introduction

Cervicogenic headache (CEH) is a syndrome manifesting as chronic, unilateral headaches originating from organic or functional abnormalities in the cervical spine or its associated soft tissues (1). Epidemiological evidence suggests the prevalence of CEH ranges from 2.2 to 4.1%, with figures potentially rising to 15–20% in individuals experiencing chronic headaches (2–4). The pathogenesis of CEH is primarily linked to lesions or inflammatory irritations of the cervical structures innervated by the higher cervical nerves, leading to pain that may extend to the occipital, cervical, parietal, frontal, and periorbital areas (5, 6). The greater and third occipital nerves (GON and TON) are notably implicated in the onset of CEH, with involvement of the cervical nerve being a prevalent cause (7).

Current physical therapies for CEH include cold packs, spinal manipulation, and posture enhancement (8, 9). Nonetheless, pharmacological treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids offer only temporary relief and are associated with significant adverse effects (10, 11). Although radiofrequency ablation has effectively reduced CEH pain symptoms, it carries potential adverse effects, including sensory dullness and numbness, reported in 12–13% of cases (12, 13). This underscores the urgent need for new, safer, and more productive therapeutic options to improve the management of CEH.

Meridian sinew tuina, deriving from the Meridian Sinew theory and tuina therapy elucidated in the Emperor's Internal Canon, is deeply rooted in traditional Chinese medical practices. Meridian Sinews (Jingjin), considered extensions of the twelve regular meridians, predominantly connect tendons, muscles, and joints. The foundational concepts of Meridian Sinew theory are detailed in the "Meridian Sinew" chapter of the Spiritual Pivot (Ling Shu) and its subsequent commentaries. This theory's therapeutic potential for cervicogenic headache (CEH) has been explored, revealing a notable correlation between CEH and disturbances in the foot-sun meridian sinew, particularly given its extensive distribution in the head and neck area (14, 15). This distribution aligns with the regions innervated by the greater and third occipital nerves, correlating with the primary pain sites in CEH (16).

The anatomical structures associated with the foot-sun meridian sinew, ranging from superficial to deep, include the trapezius, splenius capitis, semispinalis capitis, rectus capitis posterior major, and Obliquus capitis inferior (17). Through the application of meridian sinew tuina, a manipulative therapy grounded in traditional Chinese medicine, there is potential to alleviate the compression on high cervical nerves, improve local blood circulation, reduce aseptic inflammation, and thus mitigate pain while relaxing stiff soft tissues in CEH patients (18). Clinical evidence suggests that meridian sinew tuina is a safe and effective treatment modality for CEH (19). Leveraging meridian sinew theory as a framework, Legge et al. reported favorable outcomes in managing chronic pain conditions (20).

However, the physiological mechanisms underpinning the Efficacy of meridian sinew tuina for CEH remain under-researched. Previous animal studies have shown that massage simulation can improve pain behavior in mice, an effect attributed to reduced peripheral inflammation. This reduction was mediated by the mechanosensitive channel protein Piezo and senescence-related pathways (21, 22). More recently, tuina manipulation in a neuropathic pain model was found to have an analgesic effect, potentially linked to the modulation of inflammation by noncoding RNA (23).

In 2019, the Chinese Society of Pain of the Chinese Medical Association published the clinical practice consensus titled "Clinical Diagnosis and Treatment of Cervicogenic Headache: A Consensus of Chinese Pain Specialists." This consensus endorses the use of ultrasound-guided blocks of the greater and/or third occipital nerve (GON and/or TON) as a principal diagnostic and therapeutic approach for cervicogenic headache (CEH) (6). Traditionally, the technique for administering GON injections relied on superficial bony anatomical landmarks to infiltrate local anesthetics and corticosteroids around the nerves at the superior cervical line level. However, this approach risks inadvertently anesthetizing adjacent structures or intravascular injections into structures such as the occipital arteries due to imprecision in needle placement (24).

Ultrasound-guided techniques have revolutionized this procedure by allowing real-time visualization of the needle's trajectory, thereby ensuring the precise delivery of an optimal dose of compounded betamethasone directly to the affected area. This method significantly reduces the localized inflammatory response, promptly relieving or eliminating pain. Additionally, ultrasound guidance provides clear visualization of the dispersion of the injected solution, reducing the likelihood of adverse effects (7, 25). Clinical evidence supports that ultrasound-guided interventions for GON and TON injections effectively alleviate CEH symptoms and improve patient quality of life (26). Given the critical nature of neck structures, this study will eschew the use of anesthetic agents to avoid the risk of severe complications.

This study introduces an innovative ultrasound localization technique for guiding meridian sinew tuina therapy in treating cervicogenic headache (CEH), followed by targeted injections into the greater and third occipital nerves. This method, devoid of radiation, offers a precision advantage over traditional body palpation and C-arm guided localization, allowing for the accurate release of the entrapped occipital nerves and adjacent soft tissues. Preliminary clinical trials have demonstrated that this integrative approach significantly alleviates pain symptoms in CEH patients.

Building on this foundation, our randomized controlled trial aims to investigate novel therapeutic strategies for CEH. We aim to assess the impact of combining ultrasound-localized meridian massage with

Abbreviations: CEH, Cervicogenic headache; GON, Greater occipital nerve; TON, Third occipital nerve; SF-MPQ, Short-form of McGill pain questionnaire; ROM, Range of motion; MIT, Medical infrared thermography.

injections into the greater and third occipital nerves. This approach will be evaluated based on its effectiveness in improving pain score indices, headache visual analog scores, pain intensity, and cervical spine mobility in CEH patients. This research seeks to contribute to developing more effective, precision-based treatments for those suffering from CEH.

Methods and design

Trial design

This study is designed as a single-center, randomized, parallel-controlled trial. Participants will be randomly allocated to one of two groups: the control group, which will receive ultrasound-guided injections into the greater and third occipital nerves (GON and TON), or the intervention group, which will undergo ultrasound-localized meridian sinew tuina in conjunction with GON and TON injections, maintaining a 1:1 ratio. The effectiveness of these treatments will be assessed at five distinct time points: at baseline, 3 days post-treatment commencement, 15 days post-treatment conclusion, and 30 and 60 days following the end of treatment.

This trial has been registered with the China Clinical Trial Center, bearing the identifier ChiCTR2300076128. It is committed to following the guidelines as set forth by the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (27) and adheres to the ethical standards outlined in the Declaration of Helsinki (28) (Figure 1) (see trial flow in Figure 2).

Participants

Inclusion criteria

- Individuals diagnosed with cervicogenic headache (CEH) (1) as per established criteria.
- Participants aged between 18 and 65 years.
- Those willing to participate in the study and who have provided signed informed consent are also included.
- Individuals not currently participating in other clinical trials.
- Only patients with cervicogenic headache who also met a score of ≥5 on the Visual Analogue Scale for Pain (VAS) and had a duration of illness of more than 3 months will be included in the intervention and control groups.

Exclusion criteria

- History of head, neck, or shoulder trauma or presence of infectious skin diseases.
- Patients with traumatic headaches, medication-overuse headaches, hypertension-related headaches, or other headache disorders.
- Imaging findings indicating intracranial or extracranial organic lesions, neck fractures, or dislocations.
- Presence of severe cardiac, cerebral, pulmonary, renal, or rheumatoid immune diseases.
- Long-term use of analgesics or sedative-hypnotics that cannot be discontinued for the study duration.
- Pregnant or breastfeeding women.

Suspension criteria

- Occurrence or suspicion of a serious adverse event during the trial.
- Confirmation or suspicion of pregnancy during the treatment phase.
- Development of a drug allergy during treatment.

Recruitment

Recruitment will target patients with CEH at the Tuina Department of Guilin Municipal Hospital of Traditional Chinese Medicine, Guangxi, China. Recruitment strategies include hospital-based poster displays and social media outreach, particularly through platforms like WeChat.

Patient safety

- The tuina massage will be administered with moderate force to avoid harm, strictly observing contraindications.
- Injections will be performed gently, ensuring slow administration of the medication to avoid entry into the vertebral artery.
- Aseptic techniques will be meticulously observed throughout the injection to maintain patient safety and prevent infection.

Intervention

Before trial commencement, all participants will be thoroughly informed about the study's potential risks and benefits. A written informed consent form will be obtained from each participant before randomization.

Control group: ultrasound-guided GON and TON injections

The control group will receive injections consisting of a compound betamethasone solution (1 mL of a 7 mg/1 mL concentration, produced by Hangzhou Merck Sharp & Dohme Pharmaceutical Co., Ltd.) diluted with 0.9% sodium chloride solution (4 mL of a 0.9 g/100 mL concentration). The procedural methodology for ultrasound-guided GON and TON injections adheres to the guidelines established by the Chinese Association for the Study of Pain in their "Experts Consensus on Ultrasound-guided Injections for the Treatment of Spinal Pain in China (2020 edition)." Before injection, hair in the occipital region will be trimmed.

Ultrasound-guided GON injection procedure

Patients are prone, with the procedure initiated on the right side for demonstration. The treatment area is first sterilized. A transverse short-axis image of the posterior occipital region is obtained using a high-frequency linear array probe (L14-6Ns, manufactured by Myeri, B-mode, operating frequency 8–12 MHz). The probe is then moved sacro-laterally until an echogenic arc shadow (the spinous process of C1 is not visible in the ultrasound image at this time) is visualized. Moving toward the sacral end reveals the first bifurcated ultrasound image (C2 spinous process). Rotating the probe counterclockwise around the C2 spinous process axis while moving laterally allows for the visualization of the C1 transverse process, resulting in a long-axis scanning image that includes

Study point					
Phases	**Baseline**	**Treatment period**	**Follow-up period**		
Number of visits	1	2	3	4	5
Time（day）	0 day	3 days	15 days	30 days	60days
Inclusion/exclusion criteria	O				
Informed consent	O				
Random assignment	O				
Demographic information	O				
Medical and past history	O				
Interventions					
Intervention group		O			
Control group		O			
Assessments					
ROM	O	O			
SF-MPQ	O	O	O	O	O
MIT	O	O			
Safety evaluation	O				
Adverse events	O				
Serious adverse event record	O				
Compliance assessment	O				

FIGURE 1
SPIRIT schedule. This figure outlines the phases, timing, interventions, and assessments planned throughout the trial. Key abbreviations include ROM (range of motion), SF-MPQ (Short-Form McGill Pain Questionnaire), and MIT (medical infrared thermography), with O denoting key assessment points.

the obliquus capitis inferior muscle (from the C1 transverse process to the C2 spinous process obliquely axial position). The GON is superficially identified in the obliquus capitis inferior muscle in Figure 3. A 5 mL syringe (0.53 mm × 50 mm, 25 G), inserted from the medial edge of the probe and aligned with the ultrasound plane, is used to approach the GON slowly. Upon confirming needle placement via negative aspiration, 2.5 mL of the medication is administered. Following injection, the puncture site is covered with a sterile dressing and localized pressure is applied for 3 min.

Ultrasound-guided third occipital nerve (TON) injection procedure

Participants are positioned prone to this procedure. The procedure begins by placing the cephalad side of the probe over the

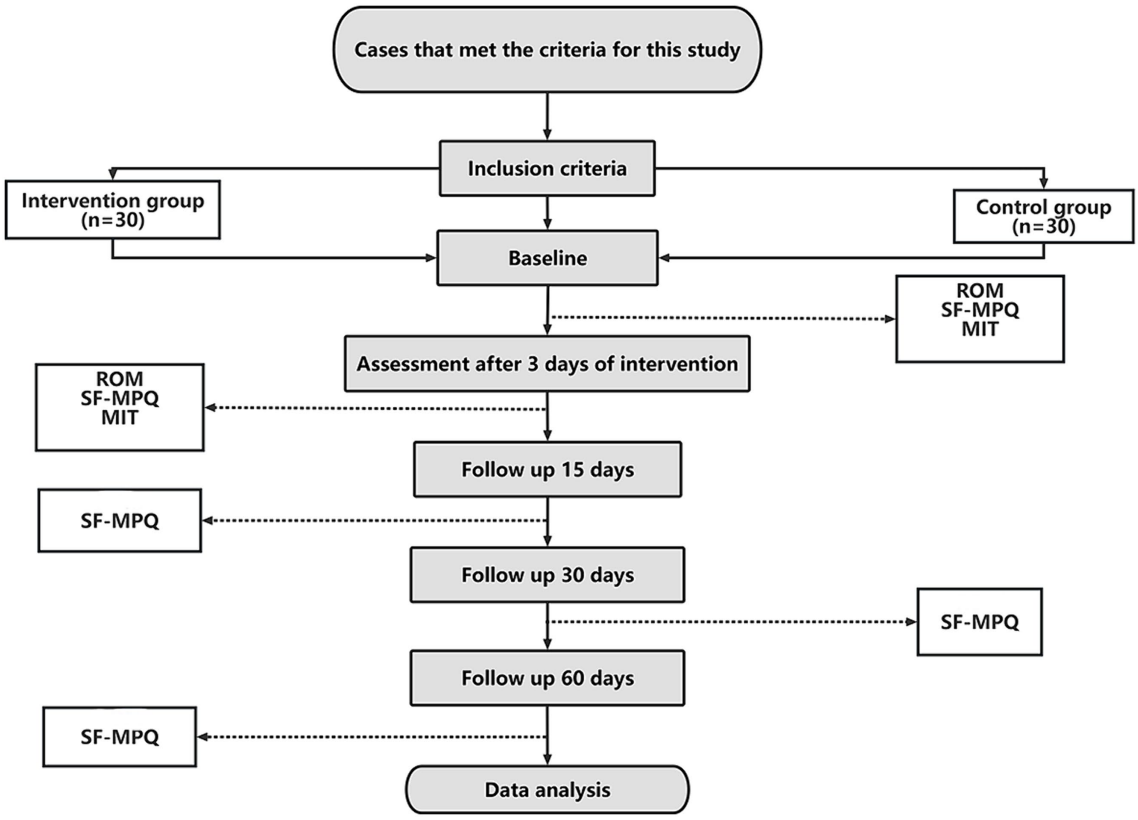

FIGURE 2
Trial flow chart. This chart provides a visual representation of the trial's flow, from participant enrollment to the completion of follow-up assessments.

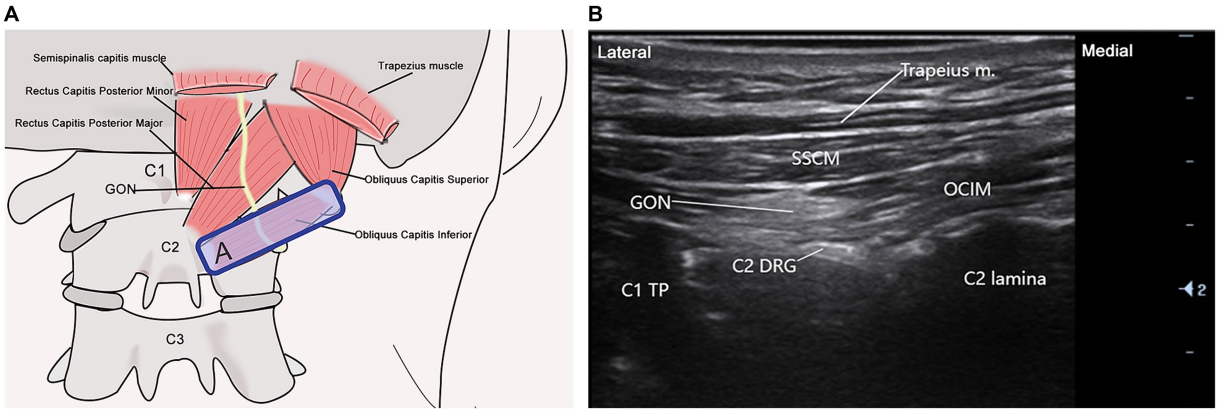

FIGURE 3
Ultrasound-guided GON scan. **(A)** This illustration illustrates the probe positioning for greater occipital nerve (GON) scanning along the C1 transverse process to the C2 spinous process oblique axis. **(B)** The ultrasonographic image depicts the anatomical relationship between the greater occipital nerve and surrounding structures. Abbreviations include C1 (atlas C1), C2 (axis C2), GON, C1 transverse process (C1 TP), semispinalis capitis muscle (SSCM), obliquus capitis inferior muscle (OCIM), C2 dorsal root ganglion (C2 DRG), and the trapezius muscle. The blue rectangle (A) indicates the probe position.

mastoid process, aligning it parallel to the cervical spine's long axis. As the ultrasound probe glides sacralward, the transverse processes of C1 and C2 become visible on the ultrasound display. Continuing the movement sacralward and slightly towards the spinous process, a wave-like acoustic shadow emerges, depicting the articulations between C2-C3 and C3-C4, as illustrated in Figure 4. At this juncture, the TON, traversing over the C2-C3 joint surface, is identified. A 5 mL syringe (0.53 mm × 50 mm, 25 G) is inserted from the probe's lateral sacral edge with the probe stabilized. The needle is guided in-plane towards the TON, and upon confirming the position via

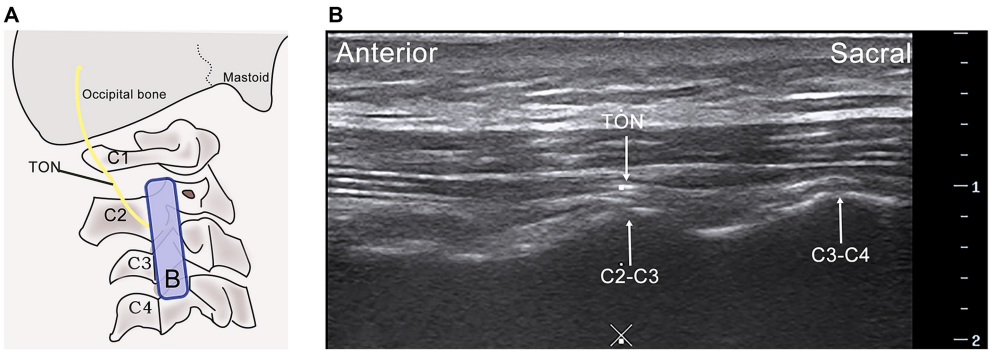

FIGURE 4
Ultrasound-guided Third Occipital Nerve (TON) scan. **(A)** The probe is placed for the long-axis scan of the C2-C3 articular pillar, illustrating the path of the third occipital nerve. **(B)** Ultrasonographic visualization of the third occipital nerve, highlighting its anatomical relationship with surrounding structures. C2-C3 facet joint (C2-C3), C3-C4 facet joint (C3-C4), C4 vertebra (C4), Midline (x), Probe indication (Blue rectangle B).

negative aspiration, 2.5 mL of the therapeutic solution is administered. Following injection, the site is covered with a sterile dressing and compressed locally for 3 min to ensure hemostasis.

Intervention group: ultrasound localized meridian sinew tuina combined with GON and TON injections

Treatment protocol

The intervention entails a regimen of daily meridian sinew tuina therapy for three consecutive days, with each session spanning 30 min, starting from the baseline. On the third day, participants receive a single session of ultrasound-guided injections into the greater and third occipital nerves (GON and TON), marking the completion of the treatment course. Each participant undergoes one full course of this combined treatment.

Meridian sinew tuina

Certified tuina therapists with at least three years of clinical experience in traditional Chinese medicine perform all treatments. These practitioners have undergone rigorous training and assessments in tuina techniques, particularly for this study. Initially, therapists utilize ultrasound to precisely locate the GON and TON on the right side. They then outline the treatment areas "A" and "B" adjacent to the ultrasound probe with a marker, as shown in Figures 3A, 4A. The participant, positioned prone, undergoes specific tuina techniques, including Dhyana-thumb-pushing (Yi Zhi Chan pushing), plucking, kneading with the Thumb, and Thumb pressing in areas "A" and "B" for 20 min, as demonstrated in Figure 5.

Subsequently, the therapist employs palpation to assess the head and neck regions, mapping the superficial to deep layers along the foot's solar meridian tendons. The examination progresses from gentle to firm pressure, utilizing techniques such as following, pressing, and touching to identify subcutaneous areas of tenderness or nodules. Targeted tuina maneuvers like thumb kneading, Thumb pressing, and lateral plucking are applied to these points, especially along the foot's solar meridian tendons in the head and neck region. This process also aims to relax muscles such as the trapezius, splenius capitis, semispinalis capitis, rectus capitis posterior major, and Obliquus capitis inferior. The total treatment time for this phase is 10 min.

Observational indicators

Primary observational indicators

Short-Form McGill Pain Questionnaire (SF-MPQ)

Pain evaluation is performed using the SF-MPQ, a globally recognized instrument for describing and quantifying pain experiences (29). The SF-MPQ consists of three main components: the Pain Rating Index, which assesses the quality of pain; the Visual Analogue Scale for headache, offering a subjective measure of pain intensity; and the Present Pain Intensity section, which provides a snapshot of the current pain level.

Secondary observational indicators

Cervical Range of Motion (ROM)

As the American Academy of Orthopedic Surgeons recommended, ROM evaluation is an essential method for quantifying mobility within the cervical joint (30). This measurement involves assessing the extent of movement in various directions from a standardized neutral position, noted as 0°. The established normal ranges of motion are as follows: for flexion and extension, from 0° to 45°; for lateral flexion (both left and right), from 0° to 40°; and for rotation (left and right), from 0° to 70°.

Medical infrared thermography

- *Instrumentation*: The study employs the X640D digital infrared thermography system by Ge Wu You Xin Company. Image analysis is conducted using IRToolPRo software, which provides a comprehensive temperature detection range from 0°C to 300°C with a precision of ±0.3°C. The system boasts a pixel size of 17UM, a frame rate 30 Hz, and operates within the 8 ~ 14UM band. For enhanced visual contrast, the color scale mode is selected.
- *Testing conditions*: The testing environment is precisely controlled to ensure optimal data accuracy. The laboratory temperature is

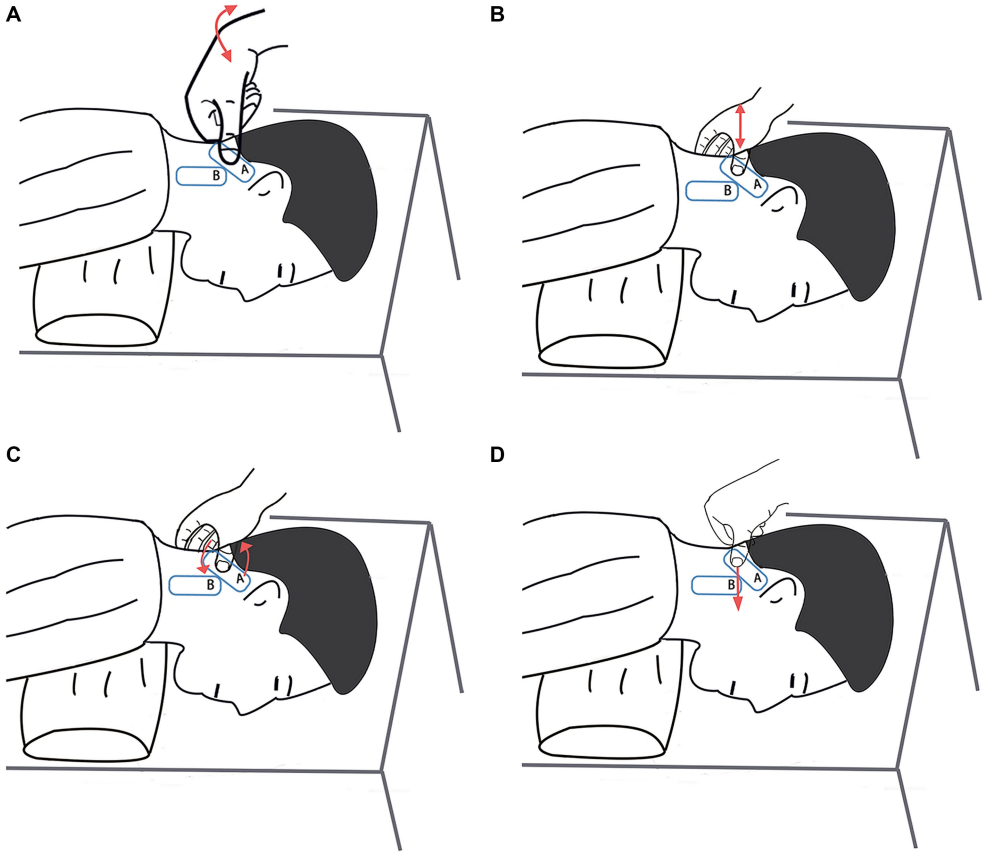

FIGURE 5
Meridian sinew tuina techniques. **(A)** Dhyana-thumb-pushing (Yi Zhi Chan pushing). **(B)** Plucking. **(C)** Kneading with the Thumb. **(D)** Thumb pressing.

maintained between 20°C and 23°C, with strict avoidance of any direct sunlight or artificial light exposure and minimal indoor air movement (31). Relative humidity is regulated within the 20 to 30% range, creating ideal conditions for thermographic analysis.

- *Operational method*: Participants first acclimate to the laboratory environment by resting quietly for five minutes, allowing skin temperature stabilization. They then stand upright, exposing the head and neck area, and position themselves one meter from the infrared thermography camera. The attending physician adjusts the camera focus to ensure the capture of clear thermal images. Infrared thermal data collection encompasses the highest, lowest, and average temperatures at the skin surface areas corresponding to the bilateral greater occipital nerve and the third occipital nerve, as illustrated in Figure 6.

Sample size calculation

Derived from preliminary trial results, this study divides patients into two groups via a randomized approach. The primary efficacy endpoint is assessed using the Visual Analog Scale (VAS) scores within the Short-Form McGill Pain Questionnaire (SF-MPQ), with observed mean VAS scores of 2.40 and 3.60, alongside standard deviations of 1.10 and 1.50, for the two groups, respectively. Utilizing G*Power 3.1.9.2 for statistical calculations, with a test significance level (α) set at 0.05 and a power (1-β) of 0.9 for a two-sided test, the sample size requirement for eachup is determined to be 27 participants (32). Factoring in a 10% potential dropout rate, this necessitates 30 participants per group for both the observation and control cohorts.

$$N = 2 \times \left[\left(Z_{\alpha/2} + Z_{\beta/2} \right) \times \sigma / \delta \right]^2$$

Randomization and blinding

The study employs a simple randomization technique, utilizing SPSS 20.0 software for sequence generation, random seeding, and group allocation. Produced and stored in sealed opaque envelopes, randomization cards facilitate assignment anonymity. Eligibility confirmation leads to an envelope opening by researchers external to the treatment, assessment, and statistical analysis processes, ensuring that participant assignment is devoid of bias. Blinding extends to statisticians and data handlers, who remain uninformed of group allocations until post-treatment, enhancing study integrity. Participant treatment is conducted in separate rooms to prevent inter-subject communication.

Data collection and management

The data collection managers for this study are full-time staff who are clinically trained but not involved in the clinical intervention

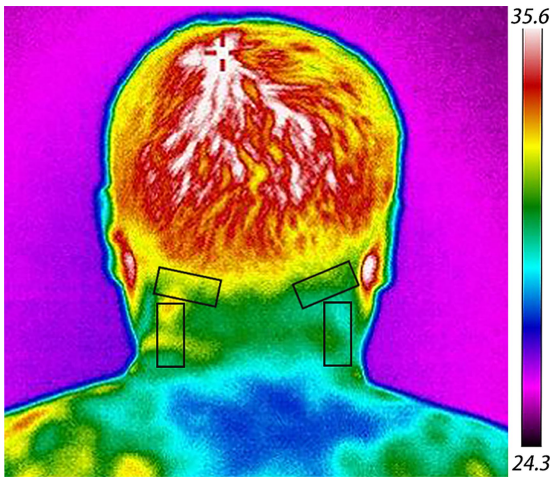

FIGURE 6
Medical infrared thermography image. The black rectangle delineates the area where data collection occurs.

process, ensuring rigorous verification and accuracy. All findings are strictly derived from original data, with error corrections on case report forms (CRFs) marked without obfuscation. Researchers meticulously document and electronically record patient information, with post-study CRFs securely stored and electronic data fixed against unauthorized modifications. Patient confidentiality is paramount, with participant follow-ups conducted telephonically upon consent.

Data analysis

The principle of Intention-To-Treat (ITT) analysis and Per-Protocol (PP) analysis will be followed in the process of statistical analysis. Descriptive analysis will be used for the baseline characteristics of the patients in each group, data will be presented as mean or median with standard deviation or interquartile range for continuous variables and as frequency distributions for categorical variables. Two-sample t-test for quantitative data or Chi-square test for qualitative data will be performed as homogeneity test, and analysis of covariance will also be performed if an adjustment is needed for a baseline characteristic. For quantitative data that do not conform to a normal distribution, data are expressed as median (IQR). In all analyses, statistical significance will be accepted as a 2-tailed $p < 0.05$. For the primary outcome, SF-MPQ scores will be assessed by using the linear mixed-effects model with the interaction effects of time and group. Participants who do not complete the study will be treated as having no change from baseline at all times. A Bonferroni correction will be used to account for multiple comparisons. Correlation analysis will be conducted between the difference of medical infrared thermography (MIT) and the other outcome measures by the Pearson correlation analysis. All statistical analyses will be conducted with SPSS software, version 25.0 (SPSS Inc).

Discussion

Cervicogenic headache (CEH) represents a prevalent headache disorder, posing significant treatment challenges for clinicians. Given its commonality, identifying effective treatment strategies is paramount. Meridian sinew tuina, with its roots stretching back thousands of years within traditional Chinese medicine, has significantly enhanced health and well-being (33). Research suggests that the pain-relieving effects of meridian sinew tuina may stem from a synergy of psychological factors, such as the placebo effect influenced by patient expectations, and physiological mechanisms, including improved local blood circulation, relaxation of tense connective tissues, enhanced local nociception, and the reabsorption of inflammatory mediators (34). These factors collectively contribute to the modulation of central nociception. Hence, it is critical to substantiate the therapeutic Efficacy of meridian sinew tuina in managing CEH through robust evidence (35–37).

In the modern medical landscape, infrared thermography has emerged as a non-invasive, safe, and objective tool for assessing treatment efficacy, diagnosing pain disorders, and investigating traditional Chinese meridians (31). This technology captures the infrared heat radiation emitted by the body, allowing for an intuitive evaluation of temperature variations. Advanced computer-aided color mapping visually represents these temperature differences across the body's surface, utilizing various colors to highlight temperature anomalies indicative of underlying pathologies (38, 39). In the context of soft tissue inflammation or nerve compression around the head and neck, these disturbances can manifest as either increases or decreases in surface temperature, reflecting alterations in local tissue metabolism and blood circulation. Medical infrared thermography's capacity to visualize pain sources and objectively measure treatment outcomes offers a novel and objective basis for evaluating CEH treatments (40).

This study heralds several innovative approaches and advantages, primarily in clinical treatment met grohodology. Utilizing ultrasound technology, we precisely identify the anatomical locations of the greater and third occipital nerves (GON and TON), enabling targeted meridian sinew tuina. The integration of meridian sinew tuina with GON and TON injections represents a novel approach that may accelerate recovery in cervicogenic headache (CEH) patients, fostering a synergistic effect between sympathetic nervous system and traditional Chinese therapeutic massage (41). The trial's design is meticulous, ensuring clarity, transparency, and reproducibility, thereby facilitating the possibility of replication by other researchers.

However, this protocol trial is not without its limitations. Being conducted at a single center, the study's ability to generalize findings across different populations is restricted. Additionally, the intrinsic characteristics of meridian massage preclude the possibility of blinding practitioners and participants, challenging the implementation of a double-blind randomized controlled trial (RCT). Despite these constraints, the study adheres strictly to separation principles among operators, allocators, and statisticians to mitigate potential biases. The rigorous adherence to treatment protocols aims to yield reliable clinical evidence for CEH management.

In conclusion, our randomized controlled clinical trial is meticulously designed to investigate a safe and effective manual therapy protocol, offering a reference point for the clinical management of CEH. Our aspiration is that the findings from this study will furnish theoretical and practical insights, paving the way for future research in this domain.

Ethics statement

The studies involving humans were approved by Ethics Committee of Guilin Municipal Hospital of Traditional Chinese Medicine, Guangxi, China. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

QH: Writing – original draft. YL: Writing – review & editing. LO: Data curation, Formal analysis, Writing – original draft. LG: Data curation, Formal analysis, Writing – original draft. JQ: Methodology, Supervision, Writing – review & editing. JK: Writing – review & editing. ST: Methodology, Supervision, Writing – review & editing. SZ: Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1439922/full#supplementary-material

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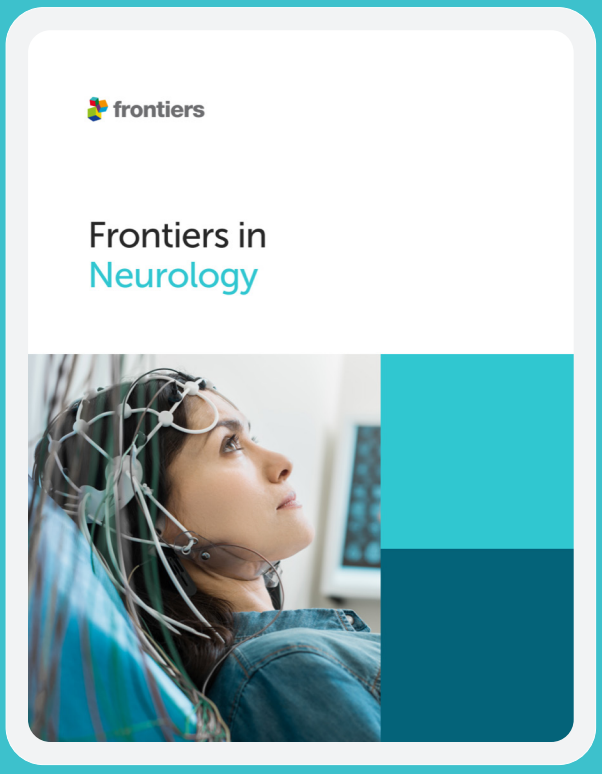

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