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New advances in the field of nerve regeneration

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Published in
Frontiers in Neurology

ISSN 1664-8714
ISBN 978-2-8325-6015-0
DOI 10.3389/978-2-8325-6015-0

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New advances in the field of nerve regeneration

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Citation

Lu, H., Zhang, W., Ling, S., Shao, B.-Z., Aleinikova, O., Yang, X., eds. (2025). *New advances in the field of nerve regeneration*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-6015-0

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frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 05 February 2025
DOI 10.3389/fneur.2025.1541159

OPEN ACCESS

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RECEIVED 07 December 2024
ACCEPTED 02 January 2025
PUBLISHED 05 February 2025

CITATION
Qiu O and Zhang W (2025) Editorial: New advances in the field of nerve regeneration. *Front. Neurol.* 16:1541159. doi: 10.3389/fneur.2025.1541159

Editorial: New advances in the field of nerve regeneration

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KEYWORDS

nerve regeneration, peripheral nerve injury, diagnostic innovation, molecular mechanism, cellular mechanism

Editorial on the Research Topic
New advances in the field of nerve regeneration

Nerve regeneration remains a significant challenge in neurology and regenerative medicine, given the complexities of restoring both structural and functional recovery in injured nerve tissues. Recent advancements, spanning novel diagnostic tools, therapeutic strategies, and cellular-level insights, highlight a collective effort to address these challenges. This editorial synthesizes key findings from groundbreaking research published in the Research Topic, *New Advances in the Field of Nerve Regeneration*, *Frontiers in Neurology* (2023–2024), emphasizing their impact on advancing the understanding and treatment of peripheral nerve disorders.

Diagnostic innovations: from imaging to screening

Accurate diagnosis is foundational to effective treatment. Chen, Zou, et al. highlight the utility of B-mode ultrasound imaging in diagnosing carpal tunnel syndrome, with its ability to visualize structural changes such as nerve swelling and flattening, providing hand surgeons with a non-invasive auxiliary tool to enhance accuracy. Complementing this, Dong et al. explore advanced imaging modalities for peripheral nerve injury, emphasizing their potential to refine injury characterization. Meanwhile, Zhou et al. provide a large-scale analysis of spinal muscular atrophy carrier screening, emphasizing the significance of early identification in preventing genetic disorders.

Therapies for peripheral nerve injuries

Therapeutic interventions have seen notable progress, particularly in nerve regeneration. Liu Z. et al. investigate repetitive transcranial magnetic stimulation (rTMS) for peripheral facial paralysis, demonstrating efficacy differences based on stimulation sites. Xu et al. review advancements in autologous peripheral nerve transplantation, underscoring strategies to optimize recovery, and also discusses emerging technologies, such as bioengineered grafts and nerve conduits, that enhance functional outcomes. Furthermore, Zou, Dong, et al. discuss techniques and graft materials for repairing peripheral nerve defects, and highlight the importance of combining advanced biomaterials with precise surgical approaches to improve functional recovery in patients with severe nerve injuries, offering insights into overcoming surgical challenges.

Cellular and molecular mechanisms in nerve regeneration

Understanding cellular interactions and molecular pathways is crucial for advancing nerve repair. Jiang et al. delve into the interplay between Schwann cells and the extracellular matrix, shedding light on their pivotal roles in regeneration. Zhang et al. explore kinase signaling in peripheral nerve repair, revealing therapeutic targets that may revolutionize regenerative strategies. Aisaiti et al. extend this perspective with a bibliometric analysis on mesenchymal stem cells, identifying trends and gaps in stem cell-based therapies for nerve repair.

Emerging concerns: nitrous oxide and cosmetic surgery

Unique challenges in peripheral neuropathy are also receiving attention. Zou, Yi, et al. review nitrous oxide-induced neuropathy, elucidating mechanisms and advocating for heightened awareness in clinical practice. Similarly, Chen, Li, et al. investigate nerve injuries post-cosmetic surgery, offering recommendations to minimize risks and improve outcomes.

Mapping the research landscape

Visualization studies provide a macroscopic view of research trends. Wang et al. analyze sciatic nerve injury treatment, identifying key research frontiers and facilitating targeted innovation. This aligns with efforts by Liu G. et al., who propose a modified approach for lumbar interbody fusion, enhancing surgical outcomes for spinal conditions linked to nerve injuries.

Conclusion

The collective efforts highlighted in these studies underscore a vibrant era of progress in peripheral nerve research. From novel diagnostic tools and therapeutic approaches to deepening insights into molecular mechanisms, the field is advancing toward improved patient outcomes. As this body of work continues to grow, interdisciplinary collaboration will remain crucial to overcoming remaining challenges and translating these findings into clinical practice.

Author contributions

OQ: Supervision, Writing – review & editing. WZ: Writing – original draft.

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

frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 14 September 2023
DOI 10.3389/fneur.2023.1250808

OPEN ACCESS

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RECEIVED 30 June 2023
ACCEPTED 04 September 2023
PUBLISHED 14 September 2023

CITATION
Dong Y, Alhaskawi A, Zhou H, Zou X, Liu Z, Ezzi SHA, Kota VG, Abdulla MHAH, Olga A, Abdalbary SA, Chi Y and Lu H (2023) Imaging diagnosis in peripheral nerve injury. *Front. Neurol.* 14:1250808. doi: 10.3389/fneur.2023.1250808

Imaging diagnosis in peripheral nerve injury

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Peripheral nerve injuries (PNIs) can be caused by various factors, ranging from penetrating injury to compression, stretch and ischemia, and can result in a range of clinical manifestations. Therapeutic interventions can vary depending on the severity, site, and cause of the injury. Imaging plays a crucial role in the precise orientation and planning of surgical interventions, as well as in monitoring the progression of the injury and evaluating treatment outcomes. PNIs can be categorized based on severity into neurapraxia, axonotmesis, and neurotmesis. While PNIs are more common in upper limbs, the localization of the injured site can be challenging. Currently, a variety of imaging modalities including ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) and positron emission tomography (PET) have been applied in detection and diagnosis of PNIs, and the imaging efficiency and accuracy many vary based on the nature of injuries and severity. This article provides an overview of the causes, severity, and clinical manifestations of PNIs and highlights the role of imaging in their management.

KEYWORDS

peripheral nerve injury, imaging, ultrasound, magnetic resonance imaging, positron emission tomography

Introduction

Peripheral nerve injury (PNI) refers to any damage or trauma to the nerves located outside the central nervous system, such as those in the limbs or face. This can be caused by a variety of factors, including physical trauma, compression, inflammation, or disease. PNI can result in a range of symptoms, including pain, weakness, numbness, and loss of function (1). Peripheral nerves are complex structures that serve as conduits for relaying information between the brain and other body parts. They consist of axons, which are long, thin fibers that carry electrical impulses and supporting cells known as Schwann cells. These cells wrap around the axons to

form a myelin sheath in myelinated nereves, which acts as an insulator and helps to speed up signal transmission (2). When a peripheral nerve is injured, the axons can be damaged or severed, disrupting the flow of signals between the brain and the affected area of the body. In addition, the Schwann cells can also be damaged, which can further impede nerve function and delay the healing process. There are several types of PNI, each with its own specific symptoms and treatment options. The types of PNI include compression injuries; these occur when a nerve is compressed or pinched, often as a result of repetitive motions or sustained pressure (Figure 1). Examples of compression injuries include carpal tunnel syndrome, which affects the median nerve in the wrist, and ulnar nerve entrapment, which affects the nerve that passes across on the interior of the elbow of the elbow. Stretch injuries occur when a nerve is stretched beyond its normal range of motion, often as a result of a sudden impact or overextension. Stretch injuries can cause damage to the nerve fibers and the myelin sheath, leading to symptoms such as pain, weakness, and numbness. Also, crush injuries are where the nerve is compressed or squeezed, often as a result of a direct blow or trauma. Crush injuries can cause severe damage to the nerve fibers and the surrounding tissue, leading to symptoms such as loss of sensation and motor function. Moreover, transection injuries occur when a nerve is completely severed, often as a result of a sharp object or traumatic injury. Transection injuries require immediate medical attention and always require surgical intervention to repair the damaged nerve (3–5). The symptoms of PNI can differ depending on the severity and type of the injury. Common symptoms include pain, numbness, tingling, weakness, and loss of motor function. In some cases, PNI can also cause changes in skin color or temperature, as well as muscle wasting or atrophy. Treatment options for PNI depend on the type and severity of the injury. Mild cases of PNI may be treated with rest, physical therapy, and over-the-counter pain medication. More severe cases may require surgical intervention, such as nerve grafting or nerve repair. In some cases, medication such as steroids or painkillers may also be prescribed to help manage symptoms (1). Recovery from PNI can be a slow and gradual process and may take several weeks or months. During this time, physical therapy and rehabilitation can be an important part of the recovery process, helping to restore function and improve overall mobility (6). In some cases, however, PNI can lead to permanent damage and long-term disability.

PNI are categorized into five groups by Sidney Sunderland as follows: Axon damage in grade 1 is indicated by denervation alterations on electromyography. Endoneurial tube injury, grade 2, is characterized by acute denervation alterations on the EMG. On an EMG, grade 3 is marked by a total destruction of the axon and endoneurial tubes. Grade 4 nerve disruption is characterized by an intact epineurial tube and persistent denervation alterations on the electromyogram (EMG). Complete nerve transection in grade 5 is indicated by no EMG contraction potentials (7).

In conclusion, peripheral nerve injury is a complex and potentially debilitating condition that can result from a variety of causes. Understanding the different types of PNI and their symptoms can help individuals recognize when they may be at risk for injury, and seek appropriate treatment as soon as possible. While recovery from PNI can be a slow and challenging process, with the right care and support, many individuals are able to regain function and mobility and return to their normal activities.

Radiological imaging is a crucial tool in the diagnosis of peripheral nerve injuries. MRI, ultrasound, and CT scans are all commonly used modalities in this process. Each of these imaging techniques provides

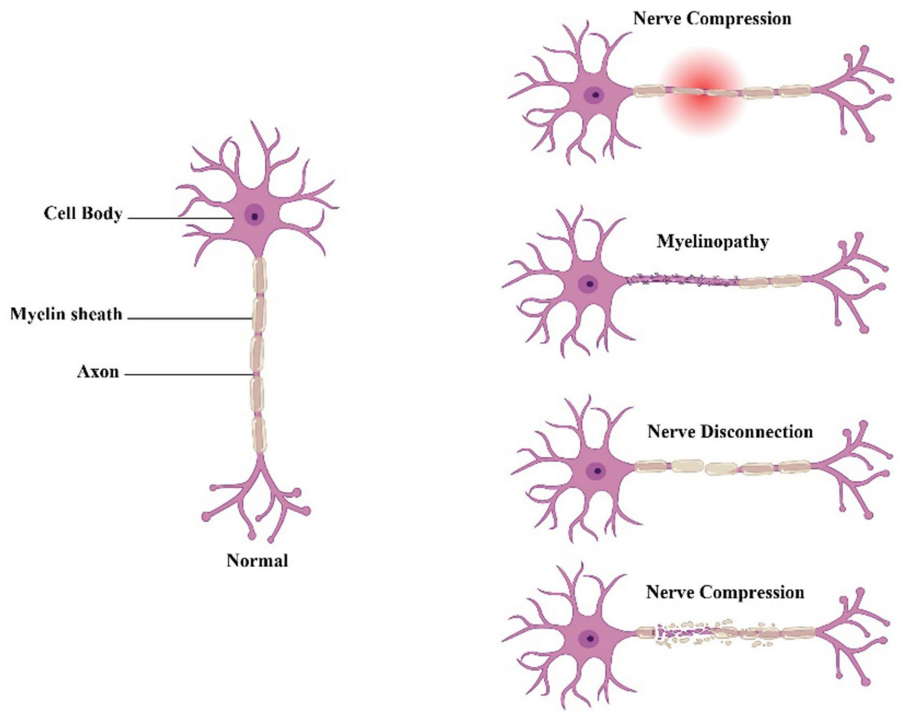

FIGURE 1
Neuropathic pain caused by different types of peripheral nerve damage.

unique benefits and can help identify the location and severity of nerve damage. In the following sections, we will provide a more detailed description of each imaging modality and how it is used in the diagnosis of peripheral nerve injuries.

Ultrasound

Peripheral nerve injuries (PNIs) can vary greatly in causes, severity and clinical manifestations. Depending on the site, severity and cause, therapeutic intervention could range from conservative medication treatment to various surgeries, which would require precise orientation and planning to avoid further iatrogenic damage (8). Common causes of PNIs include penetrating injury, compression, stretch and ischemia (9), while causes including electric shock, thermal damage, infections and toxic/chemical damage are relatively rare (10, 11). Based on severity, PNIs can also be categorized into neurapraxia, axonotmesis, and neurotmesis, according to H. J. Seddon (12). If untreated, PNIs sometimes result from compression from surround tissues or abnormal nerve healing, as in carpal tunnel syndrome and traumatic neuromas, respectively. On the other hand, while studies have suggested that PNIs occur more often in upper limbs, especially in the median nerve, radial nerve and ulnar nerve (13, 14), localization of the injured site is challenging as physical examination is less accurate inpatients with less prominent symptoms.

Ultrasound (US) is a safe and time-effective non-invasive imaging modality often applied in the diagnosis and management of peripheral nerve injuries. Compared with magnetic resonance imaging (MRI), US is not only capable of depicting nerve images in real-time, but more affordable as well. One of the reasons for applying US in peripheral nerve injuries is that peripheral nerve injuries majorly occur at relatively superficial sites (Figure 2), which could be captured in high-resolution by ultrasonography with high-frequency probes (15). In two clinical studies, C. Cokluk and K. Aydin investigated the efficacy of US in evaluating PNIs in 36 patients with upper extremity PNIs and 22 patients with lower extremity PNIs (16, 17). Their findings suggest that US can be used to assess the extent of the injury, determine if the nerve is completely or incompletely severed, detect the presence of hematoma or foreign bodies, evaluate nerve stumps and perilesional scar tissue, and identify the presence of neuromas. Additionally, Cokluk et al. conducted another study in 14 patients with penetrating PNIs ranging from glass cut to civilian gunshot, where US was applied intraoperatively adjacent to the injured site (8). Particularly in pediatrics, when patients and peripheral nerves are smaller, ultrasound is particularly suited for the examination of peripheral nerves. An advantage over MRI is that no anesthesia or intravenous contrast is necessary. Orthopedic implants and bullet fragments, which pose problems for MRI, may not always be a problem for ultrasonography. For a comprehensive assessment of several nerves, muscle denervation, and deeper tissues, MRI is better suited. Decision-making is aided by both ultrasound and MRI, which play complementary roles in the evaluation of nerve damage (18). In comparison with electro-diagnostics, US not only identified nerve injuries but also accurately localized the injuries, determined their severity, identified the presence of neuromas or stumps, and detected the formation of perineural scar tissue pre- and intraoperatively. Additionally, High-frequency probes used in contemporary ultrasound devices In order to obtain (semi)-quantitative assessments of the many histological components of the peripheral nerve, probes and equipment enable a "real-time dissection" of the nerve. Using highly sensitive color/power Doppler imaging, ultrasound can also enable the observation of tiny vascular structures with sluggish blood flow. As a result, ultrasonography can offer a precise visual representation of the structure of superficial nerves including nerve fascicles, interfascicular epineurium and epifascicular epineurium (19). Depending on the stage of injury and the particular kind of neuropathy, the perfusion pattern of the peripheral nerve varies greatly. High-sensitive color/power Doppler imaging, on the other hand, can be used to visualize tiny vascular structures with sluggish blood flow and can precisely measure the peripheral nerve's microcirculation in both normal and pathological circumstances. As a result, the peripheral nerve's perfusion pattern might be thought of as a fascinating diagnostic component, particularly when healing from damage with axonotmesis, and sonographic follow-up can be helpful in this regard (19). By combining steady-state/fast imaging with steady-state (CISS/FIESTA) MRI, Shaye et al. discovered that preoperative high-resolution neurovascular imaging was associated with higher rates of surgical success in cases of medically intractable TN (20).

In addition to penetrating injuries and foreign objects, chronic compression from surrounding tissues is a frequent cause of PNIs, with CTS being the most prominent disorder. The carpal bones and transverse carpal ligament (TCL) collectively constitute a restricted osteofibrous canal, allowing the median nerve and digital flexor tendons to traverse from the forearm into the hand. Congenital anomalies, extended manual labor, inflammation, and tissue edema may lead to nerve compression, initially causing sporadic nocturnal paresthesia and dysesthesias. These symptoms may then escalate in frequency and advance to anesthesia and thenar muscle atrophy due to extensive axonal degeneration (21, 22). Although the symptoms of CTS are distinctive, certain studies have indicated that ultrasound (US) can identify patients with unfavorable surgical outcomes resulting from anatomical predisposition (23–26). In these cases, US-guided acupotomy could be a potential alternative. A recent study conducted by Zhou et al. compared the effectiveness of ultrasound-guided acupuncture and conventional acupuncture in loosening the TCL in 100 cadaveric upper limb specimens (27). The study found that the use of ultrasound guidance in acupuncture significantly reduced the incidence of injury to blood vessels and tendons compared to the conventional method. However, the incidence of median nerve injury was found to be similar in both methods. These findings suggest that ultrasound guidance may be a safer alternative to conventional acupuncture for loosening TCL, particularly in cases where there is a higher risk of injury to nearby structures. Recent evidence suggests that neuromuscular ultrasound (NMUS) is emerging as an important tool for the diagnosis and management of peripheral nerve disorders. NMUS enables real-time visualization of neural structures and provides critical information about nerve structure and function to complement clinical examination and electrodiagnostic studies. Examples of dynamic NMUS techniques used to evaluate and monitor peripheral neuropathy include: (1) Identification of underlying etiology in tarsal tunnel syndrome using threshold values for tibial nerve cross-sectional area within the tarsal tunnel. (2) Elucidation of etiologic factors in proximal tibial neuropathies by ultrasound. (3) Application of the Bochum ultrasound score, which assesses ulnar nerve cross-sectional area at Guyon's canal

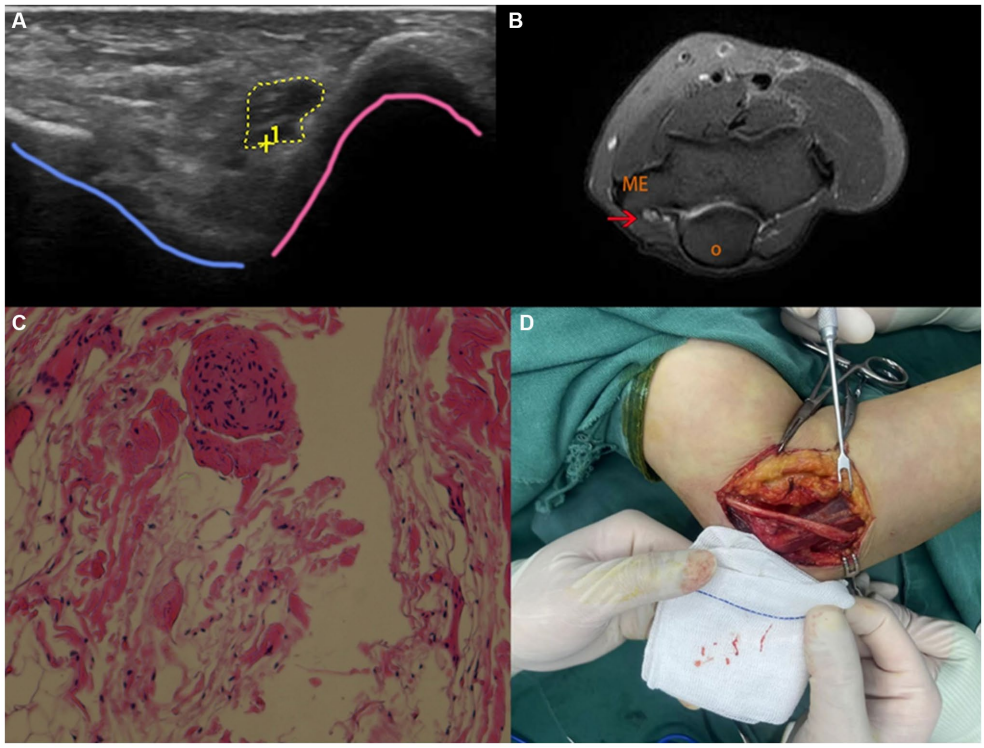

FIGURE 2
US, MRI, pathological examination and intraoperative images of a 54-year-old female patient suffering from numbness and tenderness on the ulnar side of left hand. **(A)** US imaging on the left elbow showed hypoechoic thickening of the nerve fascicles at the cubital tunnel; **(B)** MRI showed significant thickening of the left ulnar nerve at the cubital tunnel with increased T2-weighted signal intensity. Red arrow marks the ulnar nerve swelling. O (olecranon), ME (medial epicondyle). **(C)** Pathological examination indicated small piece of fibrofatty tissue; **(D)** intraoperative image showed adhesion and edema of the ulnar nerve and surrounding tissue.

and the arm, radial nerve area at the spiral groove, and sural nerve area in the calf. (4) Quantitative measures of intraneural blood flow, such as manual Doppler signal counts or Doppler waveform analysis to determine blood flow velocity. (5) Contrast-enhanced ultrasound and measurement of maximum perfusion intensity for accurate characterization of intraneural vascularity (28).

In conclusion, ultrasound is an increasingly valuable imaging tool for diagnosing and managing peripheral nerve injuries (PNIs). Its real-time capability and high resolution provide safe, cost-effective scans that help assess injury extent and nerve severance. In both the acute and chronic phases of peripheral neuropathy, (semi)-quantitative measures of the peripheral nerve can be combined with various sonographic patterns of its histological components. Therefore, acute and chronic compression of the peripheral nerve may be distinguished using high-resolution ultrasound imaging (19). Ultrasound has paved the way for innovative treatment options, improving patient outcomes and quality of life in cases of PNIs.

Computed tomography (CT)

CT scan is mainly useful for identifying bony abnormalities that may be contributing to nerve injuries, such as bone spurs, fractures, or joint dislocations. CT scans use X-rays to create detailed images of the bones and other radiopaque tissues in the body, making them an excellent tool for identifying these types of structural abnormalities (29, 30). In some cases, CT imaging may be used as an initial screening tool for peripheral nerve injuries, particularly if there is suspected involvement of nearby bones or joints (31) and CT scans can be used to locate locations where nerves are compressed due to conditions including tumors, herniated discs, or bone spurs. CT scans can be a useful tool for identifying the potential causes of PNI by making the structures close to the nerves visible (32). However, CT imaging is less useful for visualizing radiolucnettissues such as nerves, as they do not show up well on traditional CT scans. In order to visualize nerves more clearly, a specialized type of CT scan called CT myelography may be used. This involves injecting a contrast dye into the spinal fluid, which then fills the nerve sheaths and allows for better visualization of the nerves on the CT scan (33, 34).

While CT myelography can be helpful for identifying nerve injuries, it is not without risks. The injection of contrast dye carries a small risk of allergic reactions or other adverse effects, and the procedure can be uncomfortable for some patients. Additionally, CT myelography exposes patients to ionizing radiation, which can increase the risk of cancer over time (33).

Overall, CT imaging can be a valuable tool for diagnosing peripheral nerve injuries, particularly when used in conjunction with other imaging modalities such as MRI and ultrasound. While it may not be the first choice for visualizing nerves, it can provide important information about bony abnormalities that may be contributing to nerve injury. As with any medical imaging test, the decision to use CT imaging for diagnosing peripheral nerve injuries should be made on

a case-by-case basis, taking into account the patient's individual needs and medical history.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a non-invasive imaging based diagnostic tool that can be employed to detect peripheral nerve injury (35, 36). High magnetic field MRI imaging can be utilized to execute high contrast neurography with the help of fat suppression sequences and this kind of imaging modality enables us to observe structural connectivity through the use of diffusion tensor imaging and tractography (35). Peripheral nerve MRI can reveal pathological changes such as nerve compression, inflammation, or tumors in peripheral nerves and other associated components of the peripheral nervous system (Figure 3) (36).

MRI can help diagnose peripheral nerve injury by providing detailed images of the nerves and surrounding tissues. It can identify the location and extent of nerve damage, which can help guide treatment decisions. For example, if a patient has carpal tunnel syndrome, MRI can show whether there is compression of the median nerve in the wrist (35). In addition to diagnosis, MRI can also be used to monitor the progression of nerve injuries over time (36). some researches indicate The nerve lesion is clearly revealed by MR-neurography, which also aids in determining whether surgery is necessary and the best course of action (37, 38). In a cohort study, the paper also supports this view. It suggests that for roughly 4 weeks within the first 90 days following the trauma, MR-neurography has a considerable time-saving effect on decision-making. This could aid in overcoming the paradigm of "watch and wait" tactics used in the first three to six months following a peripheral nerve injury (39).

The benefits of using MRI for diagnosing peripheral nerve injury include its non-invasive nature and its ability to provide detailed images of soft tissues. Unlike other diagnostic tools such as electromyography (EMG), which involves inserting needles into muscles to measure electrical activity, MRI does not require any invasive procedures (35). Additionally, MRI can provide information about the entire length of a nerve, whereas EMG only measures activity at specific points along a nerve (36). This makes MRI a valuable tool for diagnosing complex cases where multiple nerves may be affected.

Magnetic resonance imaging (MRI) can reveal pathological changes in peripheral nerves (35, 36, 40–45). Affected nerves and

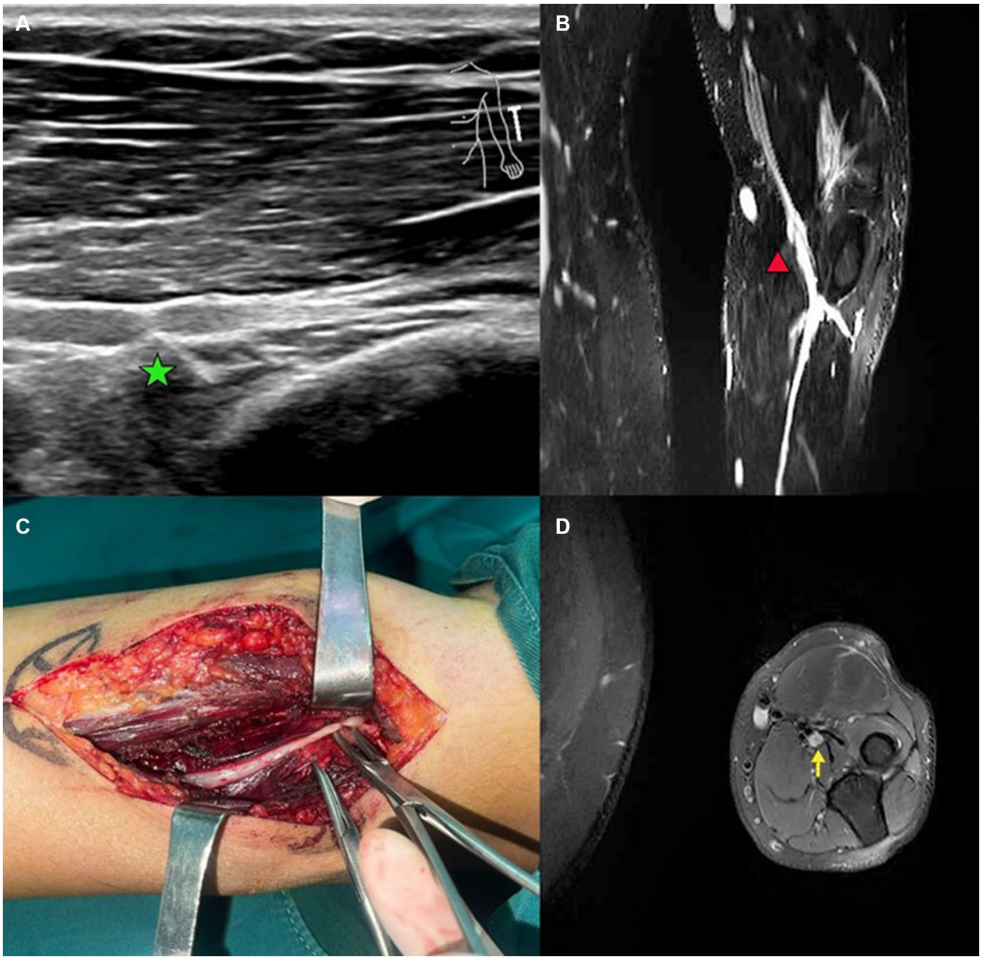

FIGURE 3
A case of patient with radial nerve entrapment. **(A)** US imaging of the radial nerve. Green star marks the proximal site of segmental entrapment. **(B)** Functional MRI of the radial nerve. Red triangle marks the site of radial nerve swelling. **(C)** Intraoperative image of deep branch of radial nerve. Segmental entrapment is observed. **(D)** MRI image of entrapped radial nerve. Yellow arrow makes the radial nerve swelling.

associated structures show changes in both morphology and signal intensity when observed with the assistance of magnetic resonance imaging (45). MRI can also help us visualize in great detail, nerve lesions in areas that are normally difficult to localize with the help of diagnostic modalities such as computed tomography or ultrasound imaging owing to superior contrast and resolution (45). Magnetic resonance neurography is a specialized magnetic resonance based technique that has already been proven to help evaluate, characterize and diagnose traumatic and compressive lesions which affect the peripheral nerves, their nerve roots, and the nerve plexii (46, 47).

Coming to focal neuropathies, irrespective of whether they are traumatic or have been caused as a result of nerve entrapment, Magnetic resonance neurography has helped improve the diagnostic accuracy in a significant manner by allowing us to directly visualize the underlying pathological changes that accompany such neuropathies. This technique has also enabled the first *in vivo* visualization of neuronal degeneration and nerve regeneration and associated changes (46). Next, when we consider, demyelinating neuropathies, an intraneural T2WI signal increase was seen upon conducting an MRI examination (46). However, the hyperintensity observed on the T2WI appeared to be restricted to the lesion side of the injury without any proximal or distal fascicles being seen (46).

Together with ultrasound, MRI has been instrumental in enabling the diagnosis and management of patients with peripheral neuropathies and associated ailments. Neurons are often compressed due to anatomical constrains as they generally travel through structures such as myofascial planes or confined spaces such as fibro-osseous or fibromuscular tunnels in the proximity of a joint. The enlargement of the contents of the such tunnels due to tumors, injuries, and associated oedemas and hematomas, or repetitive muscle contraction can lead to further compression of the nerve and related structures. The lesions associated with entrapment neuropathies usually present as non-enhancing fusiform lesions on MRI and there is also a flattening of the nerve at the site of entrapment (44).

According to a retrospective review of patients who underwent neuromuscular ultrasound, this imaging modality is more sensitive than magnetic resonance-based approaches. Additionally, ultrasound also shows equivalent specificity, and seems to better identify multifocal lesions than MRI based modalities (Table 1) (32). However, there is a caveat to this result in that, the study in question actually excluded conditions such as idiopathic carpal and cubital tunnel syndromes and when it comes to the comparison, the authors compared the accuracy of ultrasound and MRI for the detection of focal peripheral nerve pathologies in patients with mononeuropathies and brachial plexopathies alone (32). Ultrasound based imaging helped detect these lesions more frequently as compared to MRI based approaches and talking about specificity and exclusion, it was seen that ultrasound excluded nerve pathologies with equal accuracy as compared to MRI. Ultrasound imaging was also noted to be accurate in more patients (32).

Both MRI and ultrasound are accurate methods in visualizing peripheral nerves (32). However, ultrasound is preferred as it has been shown to be more sensitive in detecting peripheral nerve pathology (32). Together, ultrasound and MRI are instrumental in facilitating diagnosis and management of patients with peripheral neuropathies (32).

Both MRI and ultrasound imaging have benefits and limitations in the diagnosis of peripheral nerve injuries. Ultrasound is more sensitive than MRI in detecting peripheral nerve pathology, has equivalent specificity, and better identifies multifocal lesions than MRI

TABLE 1 Comparison between US and MRI in terms of affordability, clinical application, image quality and suitability for various clinical settings.

Criteria	Ultrasound	MRI
Cost	Less expensive	More expensive
Accessibility	Widely available	Limited availability
Safety	Non-invasive and no radiation exposure	Non-invasive but exposure to magnetic field and radio waves
Imaging speed	Real-time imaging	Longer acquisition time
Image quality	Good for superficial structures, bones, and joints	Better for soft tissue contrast
Sensitivity	Can detect small nerve injuries	High sensitivity
Specificity	Less specific in determining the type of injury	More specific in determining the type of injury
Patient comfort	Comfortable and well-tolerated	Claustrophobic and noisy environment
Operator dependency	Highly operator-dependent	Less operator-dependent
Suitability for different types of injuries	Suitable for evaluating peripheral nerve entrapment and focal neuropathies	Suitable for evaluating more complex injuries, such as nerve root avulsion or plexus injuries

(32). However, ultrasound has limitations such as operator dependence, limited field of view, and difficulty visualizing deep-seated nerves or those surrounded by bone or air-filled structures (32). One of the most significant technical constraints of this diagnostic method is the "incorrect" interpretation of the ultrasonic artifacts. When the ultrasound beams strike the target structure at an angle other than perpendicular (oblique insonation angle), anisotropy artifact results. Because of this, certain sound waves may reflect but not return to the probe, rendering what would ordinarily appear to be a hyperechoic structure to appear hypo- or anechoic (48).

On the other hand, MRI provides high contrast neurography by fat suppression sequences and shows structural connectivity through the use of diffusion tensor imaging (32). It can reveal pathological changes in the peripheral nervous system such as nerve compression, inflammation or tumors (32). Moreover, it can provide information about the central nervous system that may not be visible on ultrasound. However, MRI has limitations such as being expensive compared to ultrasound and requiring patients to lie still for an extended period during scanning. Additionally, some patients may experience claustrophobia during an MRI scan (32).

Positron emission tomography (Pet) imaging

As a primary symptom of PNIs, allodynia could occur without significant changes in nerve morphology, adding to difficulty for diagnosis by US or MRI. However, allodynia is generally associated with altered glucose metabolism, which can be accurately detected by PET imaging (Figure 4). In 2015, a study by Behera et al. observed increased 18F-FDG on PET/MRI in association with

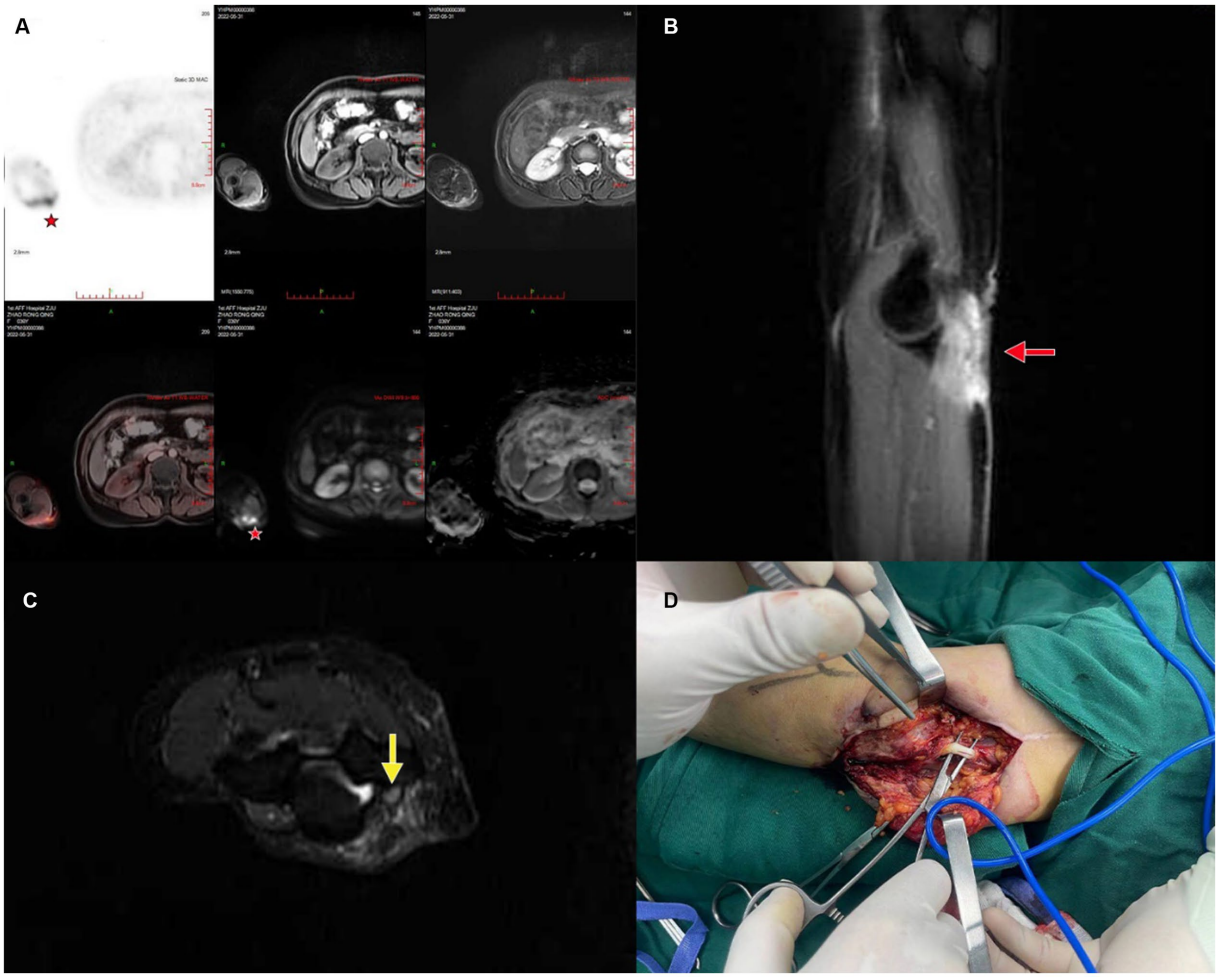

FIGURE 4
A case of patient suffering initially from allodynia and later a mass on the right elbow, which was pathologically confirmed as epithelioid sarcoma with ulnar nerve injury. **(A)** PET/CT showing the affected area; **(B)** coronal plane of the mass adjacent to ulnar nerve, red arrow marks the mass; **(C)** sagittal plane of the mass and the ulnar nerve, yellow arrow marks the swelling of the ulnar nerve; **(D)** intraoperative image of mass excision and nerve preservation.

allodynia caused by PNIs in a small animal model, and concluded that allodynia could lead to increased cellular metabolism by sensitizing the sensory neurons and inducing nerve regeneration (49). On the other hand, compared with US or MRI, PET imaging detects molecular changes and therefore makes it possible to target certain signaling pathways in PNI. Endoplasmic reticulum sigma-1 receptor (S1R) is widely distributed in the nervous system and could bind to various ligands to exert neuroprotective and regenerative functions (50–53). Given that S1R could bind to a range of different proteins, Bin et al. designed a S1R-specific radioligand, 18F FTC-146, and observed accurate binding to sites of PNIs on PET/MRI, which was further confirmed by autoradiography and immunostaining (54).

Furthermore, the electrophysiology of PNIs is distinctly different, thus the necessity of electromyography (55). Nerve conduction *via* voltage-gated ion channels, however, can be measured differently using radioligands. In terms of pain perception and transmission in peripheral sensory nerve, a study in 2022 pointed out that 18F-radiocaine, a radio-labeled derivative of lidocaine, could be used for PET/MRI imaging of sciatic nerve ligation in rats, as observed by Nicole et al. not only was the uptake of 18F-radiocaine greater in the acute and chronic phase, but the uptake in nerve tissue is significantly higher than in muscle as well (56).

While PET imaging in PNIs is accurate, available with various ligands, and can detect in absence of significant morphological changes, it is still limited by side-effects associated with radiopharmaceutical, and relatively low affordability compared with electromyography, US and MRI.

Conclusion

In summary, magnetic resonance imaging is an effective tool for diagnosing peripheral nerve injury. It provides detailed images of nerves and surrounding tissues without requiring any invasive procedures. The benefits of using MRI include its ability to identify the location and extent of nerve damage and its ability to monitor changes over time. Ultrasound has a lot of advantages in the diagnosis and

treatment of peripheral nerves, like non-invasiveness, real-time imaging, cost-effectiveness, et al. As compared to other imaging examination methods, ultrasound has the unique strength of being real-time. It can provide real-time dynamic imaging to monitor surgical procedures and treatment outcomes in real time. In the diagnosis of peripheral nerves, MRI and ultrasound exhibit significant complementarity and can be combined to provide more comprehensive and accurate diagnosis. MRI provides high-resolution static imaging of peripheral nerves, while ultrasound provides real-time dynamic functional information. The integration of the two modalities can maximize the diagnostic level. Peripheral nerve imaging using high-resolution ultrasound and MRI is now possible with greater precision thanks to the development of higher frequency probes and enhanced MR field strength.

Author contributions

HL and YC designed the study. YD and AA drafted the manuscript. HZ, XZ, and ZL performed literature selection and drew the figures. SE and VK collected patient data. SA, AO, and MA revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The study was funded by Zhejiang Provincial Natural Science Foundation Academic Exchange Program (grant number: LS21H0600010). The funding bodies had no role in the design of the study; in the collection, analysis, interpretation of data and in drafting the manuscript.

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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frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 20 October 2023
DOI 10.3389/fneur.2023.1258759

OPEN ACCESS

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RECEIVED 14 July 2023
ACCEPTED 06 October 2023
PUBLISHED 20 October 2023

CITATION
Chen Q, Li P, Zhao Q, Tu T, Lu H and Zhang W (2023) Occurrence and treatment of peripheral nerve injuries after cosmetic surgeries.
Front. Neurol. 14:1258759.
doi: 10.3389/fneur.2023.1258759

Occurrence and treatment of peripheral nerve injuries after cosmetic surgeries

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Although non-invasive and minimally invasive aesthetic procedures increasingly dominate the cosmetic market, traditional plastic surgery remains the most effective improvement method. One of the most common complications in plastic surgery, peripheral nerve injuries, though has a low incidence but intrigued plastic surgeons globally. In this article, a narrative review was conducted using several databases (PubMed, EMBASE, Scopus, and Web of Science) to identify peripheral nerve injuries following cosmetic surgeries such as blepharoplasty, rhinoplasty, rhytidectomy, breast surgeries, and abdominoplasty. Surgery-related nerve injuries were discussed, respectively. Despite the low incidence, cosmetic plastic surgeries can cause iatrogenic peripheral nerve injuries that require special attention. The postoperative algorithm approaches can be effective, but the waiting and treatment processes can be long and painful. Preventive measures are undoubtedly more effective than postoperative remedies. The best means of preventing disease is having a good understanding of anatomy and conducting a careful dissection.

KEYWORDS

nerve injuries, peripheral nerves, plastic surgeries, cosmetic surgeries, treatment algorithm, occurrence

Introduction

Plastic surgeons are cognizant that non-invasive and minimally invasive aesthetic procedures with limited complications and downtime are gradually capturing a significant share of the market (1). Traditional cosmetic plastic surgeries are still indispensable due to their high effectiveness (2). Despite the low occurrence, peripheral nerve injuries are one of the common complications that can be a complex problem with various causes (3, 4). Besides causing patients significant anxiety, they also frustrate practitioners. Chronic pain, hyperesthesia, hypoesthesia, and numbness are common symptoms of peripheral nerve injury that must be considered seriously to distinguish them from infectious, neoplastic, and wound-related causes that can be prevented with antibiotics and proper tissue handling (5, 6).

The purpose of this article was to comprehensively review the literature on peripheral nerve injuries associated with cosmetic surgery (as shown in Figure 1). The specific nerve injuries that

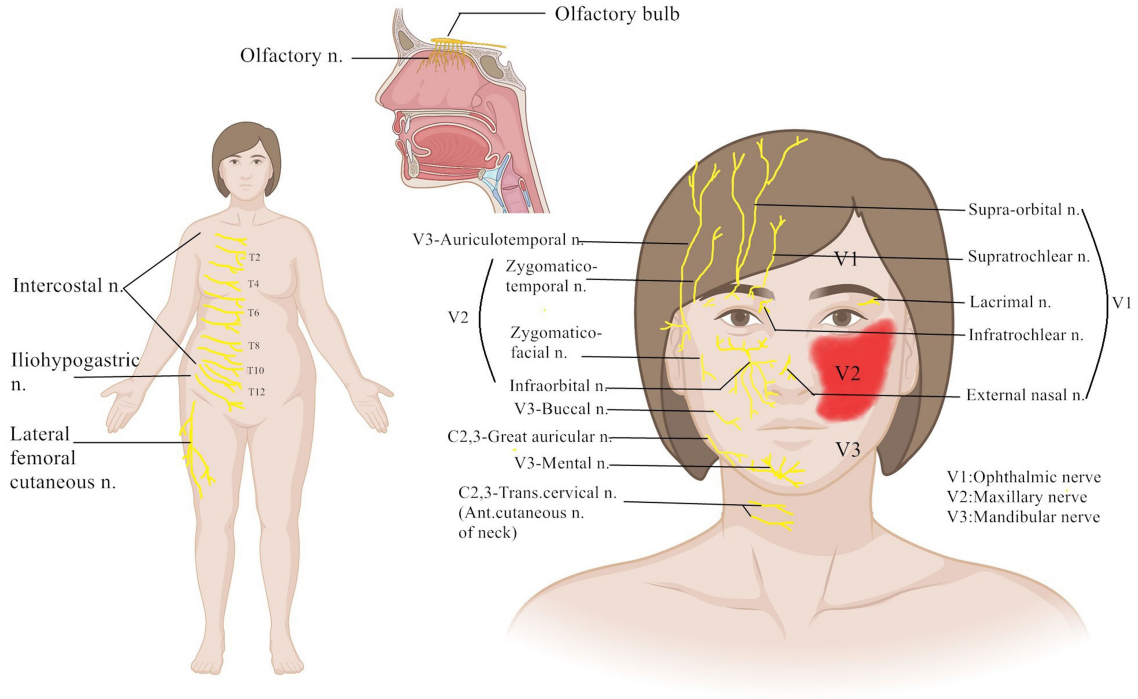

FIGURE 1
Distribution of peripheral nerves associated with common cosmetic surgery.

occur following cosmetic surgery, such as faciocervical, breast, and abdominal procedures, will be discussed, respectively. Injuries of this type are also subject to potential treatments.

Methods

Literature search strategy

A literature search was performed in October 2022 using the PubMed, EMBASE, Scopus and Web of Science databases. Search strategies included blepharoplasty, rhinoplasty, rhytidectomy, breast augmentation, breast reduction, mastopexy, abdominoplasty, and liposuction, combined with key subject terms: nerve injury, pain, neuroma, neuropathy, hyperalgesia, paresthesia, and allodynia. Literature was restricted to aesthetic surgeries, ranged from January 1950 to October 2022, and all articles except narrative reviews, editorials, commentaries, and letters were considered. Additional studies were included by reviewing the reference lists of included literature and referencing relevant articles based on search results. Inclusion and exclusion criteria were established before conducting the search, as shown in Table 1. A total of 277 citations were initially identified, 95 of which were eliminated as duplicates or non-English. After evaluating the titles and abstracts according to the inclusion and exclusion criteria (Table 1), 114 articles were excluded as irrelevant studies. Literature screening and evaluation were independently done. Discrepancies were resolved by the two authors through discussion. Hand searching added 5 articles that met our criteria. Furthermore, 12 studies were excluded because the full text was unavailable. Ultimately, a total of 60 studies published between January 1976 and October 2022 were finally included in this review (Figure 2). The quality of the included studies was screened through assessing using the American Society of Plastic Surgeons, Scales for Rating Levels of Evidence (7). The search and screening were done independently by QC, PL, and QZ, and the discrepancies were resolved by communication and discussion.

Abbreviations: SON, supraorbital nerve notch; SIT, smell identification test; SMAS, superficial musculoaponeurotic system; VAS, visual analog pain scale; DN4, Douleur Neuropathique 4.

Results

Blepharoplasty

Blepharoplasty is currently the most popular aesthetic procedure, which improves the appearance of one's upper eyelids, lower eyelids, or both (8, 9). However, upper blepharoplasty can cause injury to the supraorbital nerve or supratrochlear nerve, while lower blepharoplasty may damage the infraorbital nerve (3). It was reported in several papers that the combination of an infra-brow and a supra-brow resulted in 1.8% (8/432) (10), and 0.8% (5/564) (11) incidence of transient forehead numbness, which gradually subsides within six months with no documented facial nerve injuries. Booth et al. (12) demonstrated the incidence of altered forehead sensation was 74% (32/43 brows), while Lee et al. (13) encountered no such case (14, 15). Turin et al. (16) reported two cases of temporary nerve palsy of the frontal branch of the facial nerve, which resolved completely without permanent nerve damage (150 cases). It is noteworthy that multiple studies (13, 14, 17) have demonstrated the need for careful surgical

TABLE 1 Inclusion and exclusion criteria for the literature review.

Inclusion criteria	Exclusion criteria
• English language	• Non-English language
• Study type: randomized controlled trials; cohorts; case series; case reports; cross-sectional studies; meta-analyses; systematic reviews	• Study type: narrative reviews; editorials; commentaries; letters
• Procedure was blepharoplasty, rhinoplasty, rhytidectomy, breast augmentation, breast reduction, mastopexy, abdominoplasty, and liposuction	• Procedure was not blepharoplasty, rhinoplasty, rhytidectomy, breast augmentation, breast reduction, mastopexy, abdominoplasty, and liposuction
• Procedure was cosmetic	• Procedure was not cosmetic
• Procedure was surgical	• Procedure was not surgical
• Complications included nerve injury, pain, neuroma, neuropathy, hyperalgesia, paresthesia, and allodynia	• Complications did not include nerve injury, pain, neuroma, neuropathy, hyperalgesia, paresthesia, and allodynia

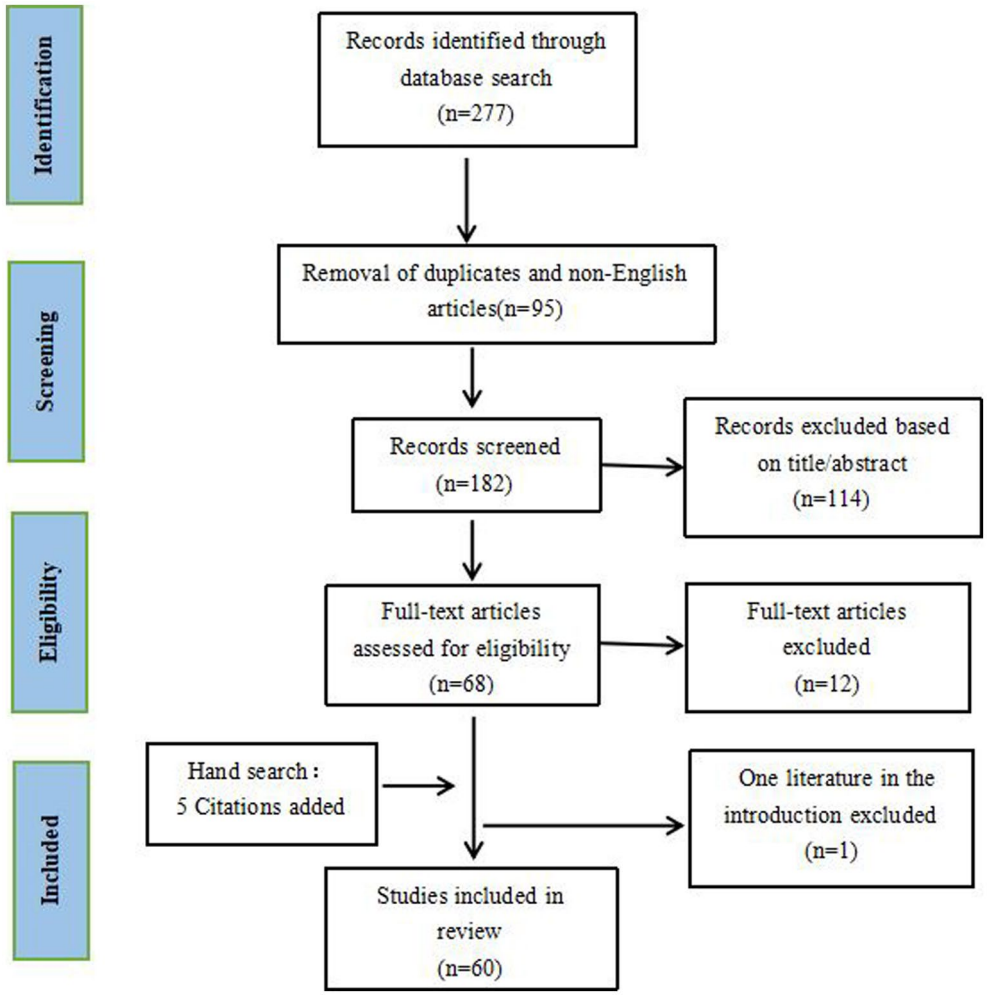

FIGURE 2
Flowchart demonstrating the schematic of searching and screening strategy.

skills at the supraorbital nerve notch(SON) and glabellar area to avoid damaging the supratrochlear and supraorbital nerves. According to one study (18), the deep branch of the supraorbital nerve traverses the periosteum. It passes between the periosteum and the pericranium towards the top of the head, providing sensation to the frontoparietal scalp. Researchers (11) demonstrated that damage to the supraorbital nerve's deep branch causes most distress, paresthesia, and numbness following brow lifts, while the superficial branch is more likely to be injured because it penetrates the frontalis muscle to provide sensation to the forehead and anterior region of the scalp. During dissection and fixation, care must be taken to prevent damage to the superficial branch.

Lower eyelid blepharoplasty has a complex anatomy that can lead to injury to the infraorbital nerve (19). In a previous study (20), six

patients developed numbness (injury to the infraorbital nerve) following 34 lower eyelid blepharoplasties (17.65%). Five of them recovered within three months; the other recovered within six months after surgery. In another retrospective study (21), 184 consecutive patients received transconjunctival orbital fat grafts without any numbness or nerve injury noted. The levator labii superioris muscle, which overlies the infraorbital nerve, remains intact during surgery as a floor of the premaxillary space (22), so there should be no damage to the nerve. Consequently, to reduce the incidence of injury to the infraorbital nerve (21, 23), the authors suggested that the surrounding soft tissues should be dissected along the sides above the anterior periosteum near the infraorbital anterior portal. To reveal the inferior margin of the orbit, the soft tissues should be pulled away with a cold light retractor.

In the literature cited above, it has been reported that the transient injury incidence of the supraorbital nerve or supratrochlear nerve injury was, on average, 4.0% (45/1119), whereas the frontal branch of the facial nerve was 1.3% (2/150), and the infraorbital nerve was 2.8% (6/218), and no permanent nerve injury has been reported. Therefore, in blepharoplasty, the most frequently injured nerve was the supraorbital nerve or supratrochlear nerve injury.

Rhinoplasty

Cosmetic rhinoplasty is a popular cosmetic procedure performed globally that encompasses several procedures (24), including alteration of the nasal dorsum, the radix, the nasal tip, and the nasal base, septoplasty, and premaxillary augmentation. Various grafts and allografts are available for cosmetic rhinoplasty, including cartilage, bone, expanded polytetrafluoroethylene, silicone, porous polyethylene, and calcium hydroxyapatite (25). Patients may experience some degree of postoperative olfactory dysfunction following nasal surgery (26). Therefore, any type of nasal surgery, including cosmetic rhinoplasty, may deteriorate olfactory function (27, 28), even without directly damaging the nasal mucosa or the olfactory nerve (29). It should be noted that patients who undertake rhinoplasty need to participate in the Smell Identification Test to evaluate their olfactory function (30–32). Anosmia is an olfactory deficiency diagnosed using the SIT score < 20. Normosmia was referred to as having a SIT score > 35. Hyposmia is termed a composite test score of 20–35.

Furthermore, Shemshadi et al. (33) demonstrated that some degrees of olfactory dysfunction could occur following rhinoplasty, 87.5% (57/65) at postoperative week one. As a result of several studies investigating the effect of open aesthetic rhinoplasty on olfaction, 10 patients (29.5%) (26), 8 patients (10.8%) (34), and 7 patients (10.2%) (35) developed olfaction dysfunction. In particular, Brinner et al. (36) reported that 24% of normal patients (a total of 184 subjects) believed they had impaired sense of smell due to surgery. Conversely, some patients already had an impaired sense of smell before surgery without being unaware of it (36).

The olfactory bulb is mostly vulnerable to damage in the cosmetic rhinoplasty (33, 35, 36). Studies above reported an average incidence of postoperative olfactory dysfunction of 31.8% (26, 27, 33, 34). The patients mostly recovered their baseline olfactory function within six weeks to six months despite initially reducing their function (33, 34, 36).

Rhytidectomy

A rhytidectomy or facelift consists of a forehead lift, a mid-face lift, and a lower facelift, and most patients undergo two or three procedures. Mitz and Peyronie's description of the superficial musculoaponeurotic system (SMAS) (37) led to a new epoch in rhytidectomy. Injuries to the facial nerve are among the most severe complications of rhytidectomy. A retrospective study conducted by Baker et al. (38) demonstrated that in a summary of 7,068 cases, the incidence of facial nerve injury was reported to be 0.7% (range 0.4% to 2.6%), and the incidence of permanent injury was 0.1%.

In a recent meta-analysis of the incidence of complications with different facial slimming techniques (39), the permanent injury rate of the facial nerve was reported from 0% to 0.08% for all types of SMAS manipulation techniques. Furthermore, they found that temporary facial nerve injury was reported in SMASectomy/imbrication (0.84%, $n = 3{,}454$), SMAS flap (0.79%, $n = 17{,}247$), SMAS plication (0.69%, $n = 5{,}081$), deep plane (0.69%, $n = 1{,}597$), and composite (1.52%, $n = 858$), and high lateral SMAS (1.85%, $n = 1{,}300$). Permanent facial nerve damage occurred in the high lateral SMAS (0.08%, $n = 1{,}300$) and the SMAS flap (0.04%, $n = 14{,}253$), and no perpetual facial nerve injuries were covered for the deep plane ($n = 1795$), SMAS plication ($n = 5{,}638$), SMAS imbrication ($n = 3{,}254$), and composite ($n = 727$).

Researchers (40) found a provisional facial nerve injury rate of 7.1% (primary surgery) and 2.2% (secondary surgery), with both primary and secondary facelifts using lamellar SMAS techniques (41).

Multiple studies (40–42) have explained the reasons for facial nerve injury, including suture placement, transection, electrocauterization, excessive traction and stretching, crushing injuries caused by surgical instruments, distorted anatomy, and adhesion from a previous procedure. In some studies (43, 44), researchers have suggested that facial nerve function generally recovers three to six months after an injury due to multiple interconnections and intermingling of the facial nerve branches (45).

Anatomical studies (41, 44, 46, 47) have further confirmed that the frontal branches are separate from the SMAS and contained within a distinct layer.

Therefore, according to the studies mentioned above, the incidence of facial nerve injury is nearly 1.0% (temporary) and 0.03% (permanent). The marginal mandibular branch and the cervical branch are most vulnerable to be injured. It is also beneficial to have a good understanding of the location of facial nerve branches, the retaining ligaments, and the soft-tissue plane of the face to decrease the incidence of facial nerve injury.

Breast surgeries

Aesthetic breast surgeries usually include augmentation, mastopexy, and reduction mammaplasties, with breast augmentation being the most frequently performed procedure (48). As part of a retrospective study by Broyles et al., all cases of augmentation, mastopexy, and reduction who complained of postoperative chronic pain failed to respond to physical or drug therapy (49). Surgical repair was then projected. Anesthesia blockade of suspected injured nerves was found to be effective prior to surgery. One or more intercostal nerves were found to be injured and resected and implanted into

adjacent muscles. Except for the patient who underwent augmentation, both mastopexy and reduction patients responded well to therapy (49).

Brown et al. conducted a prospective study to examine objective sensory changes using a Semmes Weinstein monofilament following subfascial breast augmentation (50). According to the study, the greater the initial breast volume, the greater the sensory loss at 12 weeks in the nipple-areolar complexes. The calculated ratio was 102% to 4%. Helmy et al.'s study examined nipple-areolar complex sensitivity changes, showing a low incidence, which rebounded one year later to 1.66% (51). A peri-areolar approach tends to have fewer sensation changes.

Another retrospective study conducted by Ducic et al. (5, 52) demonstrated that 74% of the patients that presented with pain in the surgical scar had concomitant injuries of intercostal nerves (2nd to 7th) due to mechanical trauma of sharp dissection or compressive scar entrapment. As a result of blunt tissue dissection, 7% suffered from traction-stretch neuropathy. Furthermore, the lateral zone could be the most damaged area (79%). Specifically, augmentations through peri-areolar incisions tended to injure intercostal nerves (3rd to 4th) in the central zone, whereas the inframammary approach mostly affected intercostal nerves (5th to 6th) in the inferior zone, and for transaxillary incisions, the second intercostal nerve in the lateral zone was the most injured. Intercostal nerves (3rd to 5th) in the central, inferior, and lateral zones were involved in breast reduction, and intercostal nerves (3rd to 4th), usually in the central zone, were affected by mastopexy. Their recommendations included physical therapy, avoiding compressive garments, and corresponding oral medications in the initial stages of injured nerve symptoms. If the symptoms persist beyond three to six months, surgical treatment with selective neuroma excision and proximal end implantation is advised. The effectiveness of the recommended treatment has not been systematically tested.

During cosmetic breast surgeries, the intercostal cutaneous nerves are most vulnerable to damage (8.86% to 10.01%). It is estimated that 13.57% of total injuries and 1.66% of permanent injuries occur on average during cosmetic breast surgeries (5, 51). It is interesting to note that the injury not only results from sharp or blunt dissection but is also determined by the volume of prosthesis implanted in augmentation mammaplasties.

Abdominoplasty

Aesthetic abdominoplasty is a cosmetic surgery that removes excess skin and fat, tightening the muscles and fascia to make the abdomen thinner and firmer (53, 54). A retrospective study by Chatel et al. evaluated persistent postsurgical pain in 67 patients who underwent abdominoplasty using a visual analog pain scale (VAS) with the Douleur Neuropathique 4 (DN4) questionnaire (55), of these patients, 19.4% (13) reported neuropathic pain accompanied by hypoesthesia or hyperesthesia. The identified risk factors were acute postoperative pain, history of bariatric surgery, prolonged hospitalization, depressive status, substantial stress, and significant postoperative complications. Though specific nerve injuries were not discussed, the authors emphasized the importance of preemptive approaches and early postoperative diagnosis.

Another retrospective study done by Uchelen et al. (56) reviewed 86 patients who had underwent abdominoplasty found that 9 patients (10.5%) were documented with nerve injuries. Among which, 8 patients (9.3%) experienced sensibility disorder of the thigh. Special attention to preserve the lateral cutaneous nerves of the thigh was emphasized by the authors.

Pechter et al. described a case of right femoral nerve damage that manifested as the patient being unable to extend her right knee immediately following the performance of abdominoplasty. Her right patellar reflex and sensibility in the anteromedial thigh and medial leg were diminished (57). Two days after surgery, the patient was subjectively better and fully recovered without any surgical complications or neurologic deficits. Considering her rapid recovery, it is likely that she suffered a mild neuropraxic injury or a possible side effect of local anesthetic. Another case reported by Ege et al. (58), who underwent abdominoplasty 3 weeks ago, sustained the anterior abdominal skin burnt resulted from sensory loss. The case reminded us the importance to inform our patients of possible skin injury due to the loss of sensation.

An anatomical study by Chowdhry et al. conducted a surgical recommendation to prevent lateral femoral cutaneous nerve injury in abdominoplasty (59). Based on their dissection of 23 fresh cadaver abdomens, careful dissection in about 4 cm anterior superior iliac spine and preservation of the scarpa fascia near the inguinal ligament can provide a safe strategy to avoid lateral femoral cutaneous nerve injury in abdominoplasty.

According to a review by Ducic et al., specific nerve injury rates were 1.94%, and permanent injury rates were 1.02% after abdominoplasty (6). Among all the patients, the rates of hypoesthesia, chronic pain, and temporary weakness or paralysis were 7.67%, 1.07%, and 0.44%, respectively. The nerves directly injured were the lateral femoral cutaneous nerves (1.36%) and iliohypogastric nerves (0.10%) (60–62). The authors recommended a timely, multidisciplinary treatment to optimize symptoms related to nerve injury, including a rigorous diagnostic examination followed by initial conservative treatment. Medication treatment with painkillers, nerve blocks, or steroid injections are also recommended in the short term. A peripheral nerve surgeon should be consulted if the symptoms persist for over three months.

Based on the studies, the most injured nerve in cosmetic abdominoplasty is the lateral femoral cutaneous nerve. A permanent nerve injury occurs in 1.02% of cases. In abdominoplasty, nerve injuries may be reduced by carefully handling the anterior superior iliac spine and area near the inguinal ligament.

Discussion

Although cosmetic surgery is on the rise, plastic procedures remain the most impregnable in comparison with burgeoning non-invasive or minimally invasive procedures due to their radical improvements. However, radical changes caused by these invasive operations are the source of iatrogenic complications (63). Although peripheral nerve injuries are rare, they continue to be a serious concern for affected patients and plastic surgeons. Thus, all plastic surgeons should be familiar with the vulnerable nerves for specific surgeries, respectively, to reduce the possible damage as much as possible. This review, though not complete, lists the vulnerable nerves and their symptoms following commonly performed plastic surgeries. The complication was discussed in relation to preventing, diagnosing,

TABLE 2 Weighted rates of nerve complications by cosmetic surgery.

Surgery type	Complication type	Complication rate %	Treatment	Prognosis
Blepharoplasty	Supraorbital nerve or supratrochlear nerve	4.0	Conservative	Fully recovery
	The frontal branch of the facial nerve	1.3	Conservative	Fully recovery
	Infraorbital nerve	2.8	Conservative	Fully recovery
	Permanant nerve injury	N/A	N/A	N/A
Rhinoplasty	Olfactory dysfunction	31.8	Conservative	Fully recovery
	Permanant nerve injury	N/A	N/A	N/A
Rhytidectomy	Facial nerve injury	1.0	Conservative	Fully recovery
	Permanant nerve injury	0.03	Conservative & surgery	Partially recovery
Breast surgeries	Intercostal cutaneous nerve	8.86 to 10.01	Conservative	Fully recovery
	Long thoracic nerve	0.01	Conservative	Fully recovery
	Permanant nerve injury	1.66	Conservative	Partially recovery
Abdominoplasty	The lateral femoral cutaneous	1.36	Conservative	Fully recovery
	Iliohypogastric	0.1	Conservative	Fully recovery
	Permanant nerve injury	1.02	Conservative & surgery	Partially recovery

Conservative treatment: pain medications, nerve blocks, or steroid injections.

and treating it to provide some information for plastic surgeons (Table 2). Raising concerns in a timely manner is essential.

Treatment algorithm

There are several challenges associated with nerve injuries, both in terms of diagnosis and therapy. Based on the opinions of the authors of included studies, we developed a recommended treatment algorithm to assist fellow surgeons with various problems (Figure 3).

Before surgeries, patients should be informed of the potential symptoms of nerve injuries, including chronic pain, hyperesthesia, hypoesthesia, and possible numbness. Mastering the related anatomy and careful dissection are necessary for a better outcome at surgery. Prevention is better than treating injuries after they have occurred.

Although some pain and paresthesia are expected to be normal in the early postoperative period, symptoms over three months can indicate nerve injuries. Early diagnosis and treatment are crucial (64) because postponed or improper treatment can result in irreversible consequences or even additional morbidities (65, 66). In addition to a comprehensive physical examination, common complications such as infection, seroma, hematoma, or fluid collection, together with other probable causes, for example, hernia, endometriosis, or abdominal visceral diseases, should be excluded. A Tinel's sign or relief of tenderness after the targeted injection of anesthetic nerve blocks proximal to the focal point is a strong indication of nerve injury (3). Providing the diagnosis to patients validates the cause of their symptoms and reduces their emotional stress (67).

Initially, conservative modalities, such as scar massage, desensitization, and sensory reeducation, are advised for symptoms associated with some nerve injuries that can self-resolve over time. Furthermore, medication treatment that includes pain relievers, tricyclic antidepressants, anticonvulsants, steroid injections, or nerve blocks may also be helpful (6). Besides, standardized diet, nutrition, and supplementation recommendations and protocols may be of great importance for better nerve regeneration and functional recovery (68). If no improvement is seen over the first three months, referring to a peripheral nerve surgeon for possible surgical treatment, which involves exploring the suspected injured nerves with corresponding management, such as neurolysis, neurectomy, and implantation, is necessary (69, 70). This algorithmic approach generally eliminates most symptoms, but prevention remains the best treatment.

Limitations and future

While this narrative review has provided insights into peripheral nerve injuries following cosmetic surgeries, there are several limitations to consider: 1. Limited Sample Size: the rarity of peripheral nerve injuries in the context of cosmetic surgeries makes it challenging to gather a large sample size for systematic analysis. 2. Potential Bias: the existing literature on peripheral nerve injuries may exhibit a bias towards highlighting severe or exceptional cases. Moreover, it appears that the majority of documented peripheral nerve injuries have a sensory component. This bias could be attributed to the influence of personal emotions, potentially impacting the objectivity of the reported results. 3. Heterogeneity of Data: the studies included in this review vary in terms of study design, patient demographics, surgical techniques, and follow-up periods. This heterogeneity can make it difficult to draw uniform conclusions and may introduce confounding variables. 4. Lack of Long-term Follow-up: many of the studies reviewed primarily focus on the immediate postoperative period and short-term outcomes. Long-term follow-up data on the persistence of nerve injuries and their impact on patients' quality of life are often lacking. 5. Variable Reporting Standards: the reporting of peripheral nerve injuries across different studies may lack uniformity, making it challenging to compare and compile data accurately.

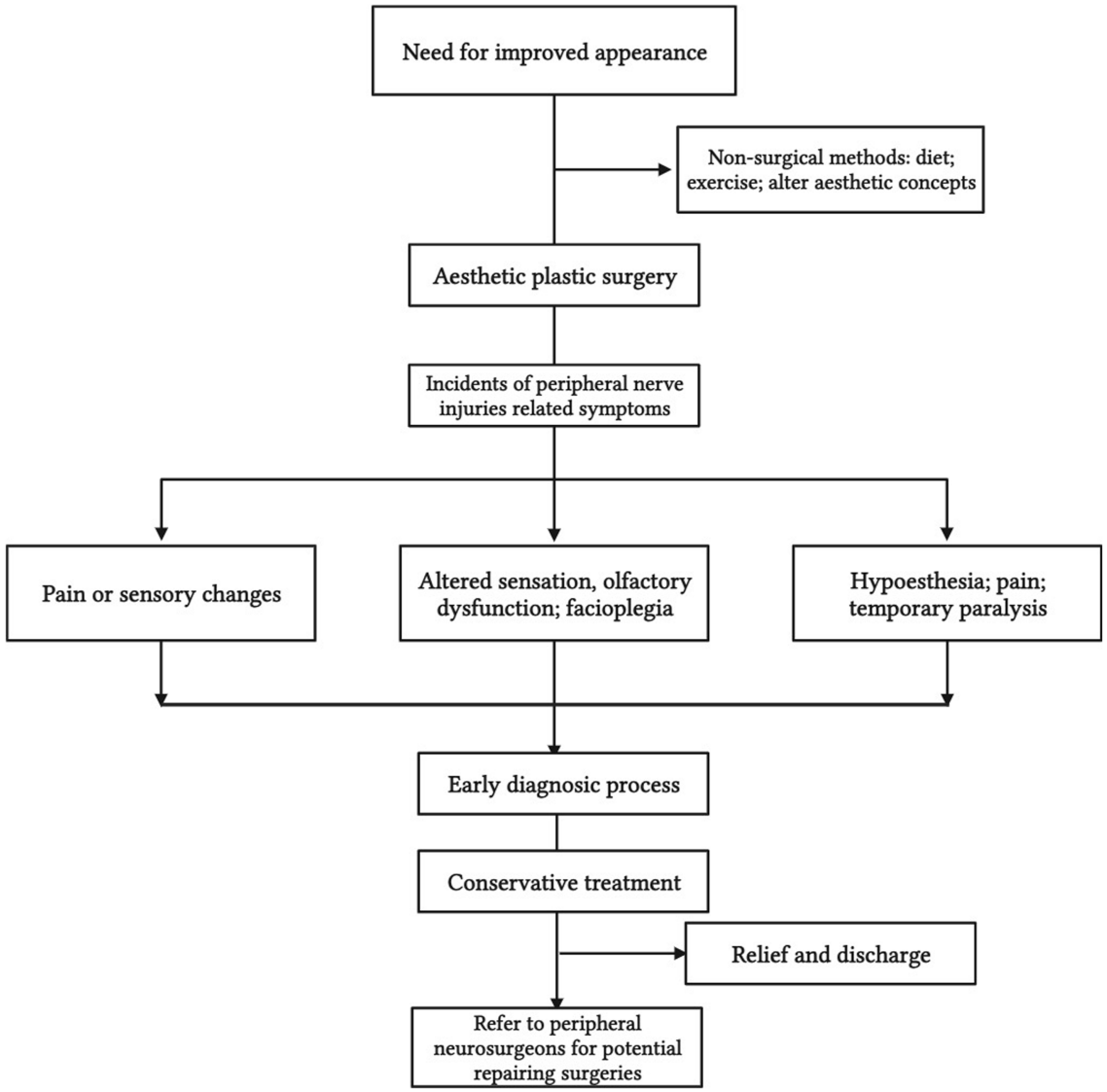

FIGURE 3
A detailed treatment algorithm relating complications of nerve injuries.

To address these limitations and further advance our understanding of peripheral nerve injuries following cosmetic surgeries, future research should consider the following aspects: 1. Prospective Studies: conducting large-scale, multicenter prospective studies specifically focused on peripheral nerve injuries in cosmetic surgeries would provide more robust data and reduce selection bias. 2. Standardized Reporting: the development of standardized criteria for reporting peripheral nerve injuries and their outcomes is essential. This would facilitate better comparisons between studies and enhance the accuracy of meta-analyses. 3. Long-term Follow-up: longitudinal studies with extended follow-up periods are necessary to assess the long-term consequences of peripheral nerve injuries and the effectiveness of various treatment modalities on patients' quality of life. 4. Advancements in Preventative Techniques: research should continue to explore innovative techniques and technologies aimed at reducing the occurrence of iatrogenic peripheral nerve injuries during cosmetic surgeries. This may include the use of advanced imaging, surgical tools, and training methodologies. 5. Patient Education: emphasizing patient education about the potential risks and complications associated with cosmetic surgeries, including peripheral nerve injuries, can help patients recognize early symptoms and contribute to better prognosis. 6. Collaboration: collaboration between plastic surgeons, neurologists, and other medical specialties can lead to a more comprehensive understanding of peripheral nerve injuries, improved prevention strategies, and better treatment options.

In the realm of cosmetic surgeries, it is paramount that we emphasize the utmost care and precision to safeguard against possible nerve injuries. To minimize the risk of such injuries, practitioners should carefully assess the patient's anatomy, taking into consideration any potential variations or anomalies. During surgery, gentle tissue handling and a thorough understanding of the nerves' pathways are important to avoid inadvertent damage. Adequate lighting, magnification, and proper instruments can aid in preventing unintended injuries. Vigilance and meticulous attention to detail are

essential. Moreover, post-operative monitoring and communication with patients are equally crucial to promptly identify and address any signs of nerve impairment. By adhering to these principles and prioritizing nerve preservation, we can improve the overall safety of cosmetic surgical procedures.

Conclusion

Peripheral nerve injuries are rare but deserves special attention. Albeit the postoperative algorithm approaches prove effective, the waiting and treating processes can be lengthy and painful. Preventive measures are always preferable to postoperative remedies. Good mastery of surgical anatomy and meticulous dissection are the best weapons of prevention.

Author contributions

QC: Conceptualization, Formal analysis, Methodology, Funding acquisition, Software, Writing - original draft. PL: Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, review & editing. QZ: Project administration, Resources, Visualization, Writing - original draft. TT: Methodology, Supervision, Validation, Writing – review & editing. HL: Conceptualization, Formal analysis, Funding acquisition, Supervision, Writing – review & editing. WZ: Formal analysis, Funding acquisition, Resources, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The study received funding from the National Natural Science Foundation of China (grant number 81702135), Zhejiang Provincial Natural Science Foundation (grant numbers LY20H060007 and LS21H060001), Alibaba Youth Studio Project (grant number ZJU-032), Zhejiang Provincial Continuing Education Program (grant number 2022-04-07-001), and the Key projects by the province of Zhejiang Medical and Health Science and Technology Project (WKJ-ZJ-2101).

Acknowledgments

First, I'd like to show my sincere gratitude to my colleagues who provided me with invaluable help and support in carrying out the study. Also, I really appreciate all the funding programs for sponsoring our research. Last but not least, I want to thank all my families and friends, especially my mother who backed me all the way to where I am.

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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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 03 November 2023
DOI 10.3389/fneur.2023.1285659

OPEN ACCESS

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RECEIVED 30 August 2023
ACCEPTED 23 October 2023
PUBLISHED 03 November 2023

CITATION
Liu Z, Wen X, Shao Y, Wan Z, Liu B, Wang R and Liu H (2023) Efficacy of repetitive transcranial magnetic stimulation at different sites for peripheral facial paralysis: a prospective cohort study.
Front. Neurol. 14:1285659.
doi: 10.3389/fneur.2023.1285659

Efficacy of repetitive transcranial magnetic stimulation at different sites for peripheral facial paralysis: a prospective cohort study

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Background: There are very few studies on transcranial magnetic stimulation (TMS) therapy for facial paralysis and no studies comparing the efficacy of central and peripheral TMS in the treatment of peripheral facial paralysis (PFP).

Purpose: To observe the therapeutic effect and security of central and peripheral repetitive transcranial magnetic stimulation (rTMS) on PFP.

Methods: Patients with unilateral onset of peripheral facial paralysis within 1 month were prospectively recruited, 97 patients with PFP were divided into the peripheral group, central group, and control group. The control group was given common treatment (drug therapy and acupuncture), and the peripheral and central groups received rTMS in addition to conventional treatment. After 2 weeks of treatment, the House-Brackmann (HB) grading scale, Sunnybrook facial grading system (SFGS), and modified Portmann scale (MPS) were used to evaluate the facial muscle function of patients in the three groups.

Result: After 2 weeks of rTMS treatment, the HBGS/SFGS/MPS scores of the three groups were significantly better than before ($p < 0.05$), and the mean change values of HBGS, SFGS, and MPS scores were significantly higher in participants in Peripheral Group ($p < 0.001$; $p < 0.001$; $p = 0.003$; respectively) and Central Group ($p = 0.004$; $p = 0.003$; $p = 0.009$; respectively) than in Control Group. But the mean change values of HBGS, SFGS, and MPS scores showed no significant differences in participants in the Peripheral Group than in the Central Group ($p = 0.254$; $p = 0.139$; $p = 0.736$; respectively) after 2 weeks of treatment ($p > 0.05$).

Conclusion: Our study shows that rTMS can be a safe and effective adjuvant therapy for patients with PFP. Preliminary studies have shown that both peripheral and central stimulation can effectively improve facial nerve function, but there is no significant difference in the efficacy of the two sites.

KEYWORDS

repeated transcranial magnetic stimulation, cohort study, peripheral facial paralysis, peripheral facial neuritis, repetitive transcranial magnetic stimulation

1. Introduction

Peripheral facial paralysis (PFP) is a loss of function of the facial nerve-innervated tissues, which may be partial or total, presenting with facial muscle dyskinesia, often resulting in facial asymmetry persisting for many weeks or months (1). The exact cause of the disease is unknown (2, 3), it is reported to occur in about 20–30 cases per 100,000 people (4). Several treatments are usually used, including antivirals, Vitamin B drugs, steroids, surgery, physiotherapy, acupuncture treatment, and others (5). Although 70 percent of patients are cured within a year, 30 percent still suffer sequelae of varying degrees (6). This is still a high percentage, so finding new ways to improve outcomes is necessary.

Transcranial magnetic stimulation (TMS) is another promising technology that is attracting significant attention. As a noninvasive brain stimulation technique, repeated transcranial magnetic stimulation (rTMS) has been reported to accelerate recovery from peripheral facial neuritis (7). Few studies have focused on the application of rTMS intervention in facial paralysis. Most of the previous studies have focused on the clinical value of TMS in the electrophysiological diagnosis of PFP (8, 9). Through the preliminary experiment and clinical observation, we believe that rTMS has a certain rationality and value in the treatment of peripheral facial neuritis.

The purpose of this study was to determine the efficacy of repeated transcranial magnetic stimulation (rTMS) for peripheral facial neuritis and to compare the curative effects of peripheral stimulation and central stimulation.

2. Method

2.1. Study design

This study was a prospective, 3-arm, no-randomized controlled trial. Patients with PFP who participated in the study were either outpatients or inpatients between 2021 and June 2022 at Yuebei People's Hospital. Depending on the type of intervention, all patients were assigned to three parallel groups: peripheral, central, and control groups. All patients provided written informed consent. The clinical trials by Yuebei People's Hospital Medical Ethics Committee approval (approval number of KY - 2021-075), this research project has been registered in the Chinese clinical trial registry (http://www.chictr.org.cn/) (registration number: ChiCTR2100053550).

2.2. Participants

We prospectively enrolled patients aged 18–75 years who were diagnosed with peripheral facial neuritis at the Yuebei People's Hospital. The initial screening process includes tests and evaluations, including electromyography or electroneurogram examination, in addition, imaging and laboratory tests are performed to rule out brain damage or other causes of facial paralysis secondary to facial paralysis. All the patients we included were required to have the first onset and unilateral facial paralysis, and the course of the disease was required to be within 1 month, and the grading of House-Brackmann scale (10) was ≥3 level, willing to cooperate with the researchers for treatment and evaluation and sign the informed consent form. Exclusion criteria are facial paralysis due to stroke, encephalitis and Lyme disease and various tumors, intracranial metal foreign bodies, epilepsy, pregnancy, and other transcranial magnetic contraindications in patients, patients with other serious illnesses that were unstable or in the acute phase were also excluded, any other conditions that the investigator thought would affect the experiment may be considered excluded from the study.

2.3. Interventions

All three groups received conventional antiviral drugs and neurotrophic drugs, as well as the same acupuncture treatment, the medication regimen and adherence to medications did not change throughout the study. Both peripheral and central groups received repetitive transcranial magnetic stimulation (Jiangxi Brain Regulation Technology Development limited-liability company, NTK-TMS-II transcranial magnetic stimulation instrument), and the stimulus coil was a figure of 8 coil (size: 104∗196∗16 mm). The stimulation program has been used to treat facial paralysis (11). The peripheral and central groups received the same rTMS regimen, Magnetic Pulse Parameter Specifications: Stimulation frequency is 5 Hz, stimulation time of a single pulse string is 6 s, the interval between pulse strings is 14 s, so a pulse cycle is the 20 s, and the number of input pulses for each pulse cycle is 30; each time the treatment is repeated for 60 cycles, the treatment time of each transcranial magnetic stimulation is 1,200 s (20 min), and the total number of output pulses is 1,800 pulses. All patients in the central and peripheral groups received 10 sessions of rTMS over 2 weeks, for a total of 18,000 pulses, a maximum of one rTMS per day. The schematic diagram of the pulse is shown in Figure 1.

The stimulation site of the central stimulation group was the M1 area (7), Positioning caps were designed following the EEG 10–20 electrode placement system. The patient wears a cap that fits his/her head circumference, and the coil is placed in the corresponding position of the "face" in the cap pattern for stimulation (between the areas of F7/F3/T3/C3, the facial motor cortex area). This method is now more widely used in China, the positioning cap is clearly labeled, easy to use, and can be a good solution to the problem of rapid positioning during clinical treatment; in the peripheral group, the stimulation site was on the face of the injured side, located between the mandibular notch and the lower margin of the zygomatic arch (11), the coil stimulation site is shown in Figure 2.

2.4. Determination of the resting motor threshold

Resting motor thresholds (RMT) were measured before intervention in all patients receiving rTMS. The patient was asked to sit quietly and remain relaxed, approximately 3–6 CM from the apex is the center of the "8" coil, and a disposable electrode with 2 diameters of 1 cm was symmetrically fixed to the nasal muscle, recording nasal muscle complex muscle action potential (CMAP) after transcranial magnetic stimulation (TMS) (9, 11). RMT is determined by visual inspection of minor muscle contractions. We had a similar situation: in most subjects, it was not sufficient to contract the targeted muscle

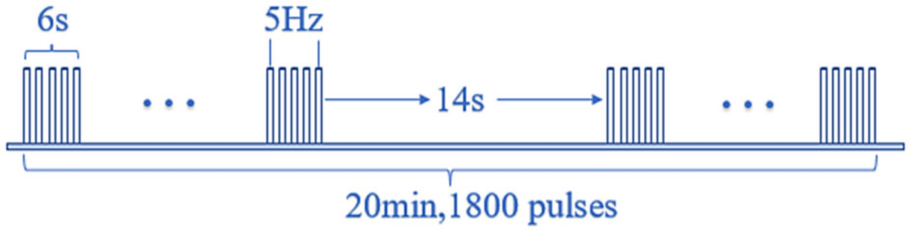

FIGURE 1
Schematic diagram of the pulse of rTMS.

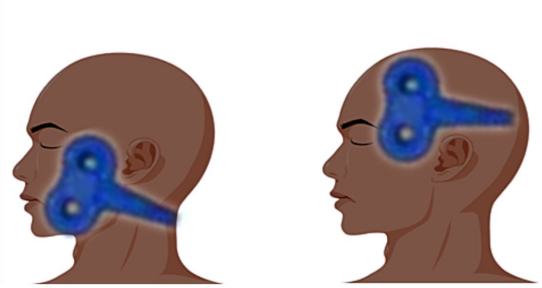

FIGURE 2
The image on the left shows peripheral stimulation and the image on the right shows central stimulation.

(nasal muscle) alone (12), and additional contraction of the tongue or masticatory muscle or both were required to obtain a response. To determine the intensity required for a maximal response, the healthy side was first stimulated (9). We referenced the RMT measured on the first day for only one measurement, and subsequent stimuli were referenced to this intensity. Perhaps due to our technique, only a small number of patients could measure the RMT of the nasolabial muscles, and the majority of patients could only test the FDI, so in practice both were present, and we understand that this may lead to some bias, but in most cases, the compound muscle action potentials of the first dorsal interosseus (FDI) muscles were recorded as well, FDI helps to localize the coil over the motor cortex and select the appropriate TMS intensity for each patient (13), this method widely used in stroke patients. The motor-evoked potential (MEP) of the FDI muscle was used as a reference to determine the strength only when the MEP of the nasal muscle is not fired or difficult to fire. During measuring FDI, the coil plane was attached to the scalp section and kept parallel, the coil handle was all oriented to the occipital side, and the coil was at a 45° Angle to the sagittal line of the subject. RMT was taken as the minimum stimulus intensity that caused a slight contraction of the target muscle in 5 out of 10 stimuli (14). Generally, the stimulation intensity of patients during treatment is between 80 and 120% RMT. However, in this study, we adjusted the percentage of RMT according to the patient's tolerance.

2.5. Outcome assessment

We used three different assessments of facial nerve function as outcome measures. It consisted of the Sunnybrook Facial Grading System (SFGS) (15), the House-Brackmann Grading Scale (HBGS) (10), and the Modified Portmann Scale (MPS) (16). The SFGS score ranges from 0 to 100, with higher scores indicating better facial nerve function, and measures static symmetry, voluntary symmetry, and synchronized facial movements. HBGS are graded from 1 to 6, with higher grades being more severe, and are assessed for facial symmetry at rest, forehead, eye, and mouth motor function during movement, and overall associated movement (11, 17). The MPS assesses the completion of six actions (raising eyebrows, closing eyes, widening nostrils, showing teeth, pursing mouth, bulging cheeks) on a scale of 0–20 across four dimensions, with higher scores indicating better facial function (7, 11, 18).

In addition, we recorded any adverse events that occurred during the study. The evaluators were not aware of patient groupings and interventions (blindness).

All patients were individually assessed by two professionals, and the average value of the two assessors was subsequently taken as a record, the evaluator did not know to which group the patient was assigned (blind). The intervention the evaluation and data analysis were all made up of different researchers, unaware of each other's specific work, and finally pooled by another researcher.

2.6. Statistical analysis

The data of this study were analyzed by SPSS 26.0 software. Using the Shapiro–Wilk test, we determined that the data distribution is normal. Continuous variables were measured using the mean or median of interquartile spacing; the Chi-square test was used for dichotomous variables such as gender in baseline data. One-way analysis of variance or nonparametric test was used according to whether the data were in line with normal distribution and homogeneity of variance. Paired *T*-test or rank sum test was used to compare the same data before and after the trial intervention. $p < 0.05$ was considered statistically significant.

3. Results

We recruited 227 patients with facial paralysis, of whom 122 did not meet the criteria and were excluded, and 105 met the inclusion criteria. An average of 35 patients in each group were assigned to central stimulation, peripheral stimulation, and control groups. In the early stages of the trial, eight people withdrew from the trial for reasons of force majeure (Lack of time, hospital transfer, etc), and

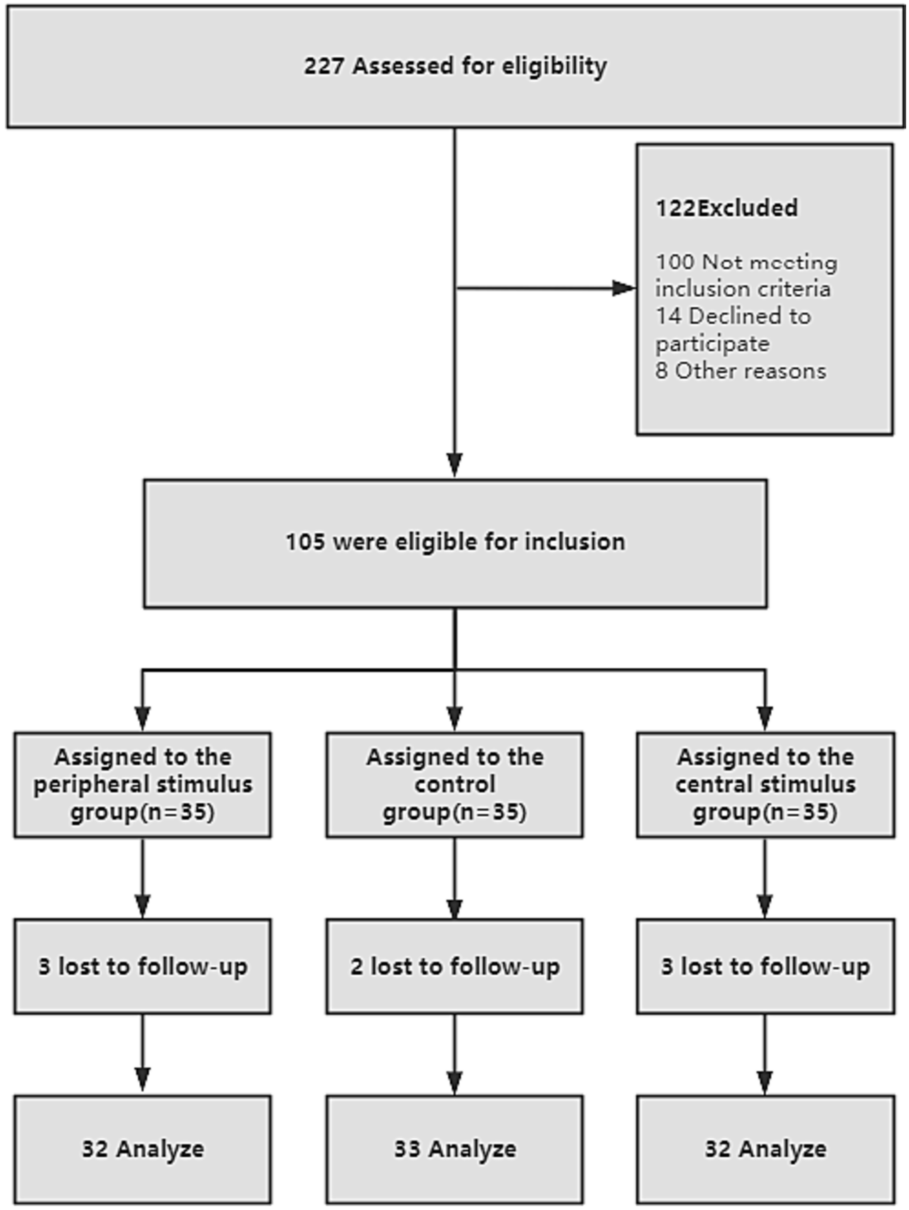

FIGURE 3
Participant flow diagram.

eventually, 97 completed all trials and were included in the analysis (Figure 3).

The baseline characteristics of the three groups are shown in Table 1. There were no significant differences in disease duration, age, sex ratio, hypertension, diabetes, and other characteristics among the three groups ($p > 0.05$), this suggests that the three groups are comparable.

The results showed that there was no significant difference in HBGS, SFGS, and MPS before treatment among the three groups (see Table 1). But After 2 weeks of transcranial magnetic therapy, there were significant improvements after treatment compared with before treatment, and the differences were statistically significant ($p < 0.05$, see Table 2).

Using the mean change before and after intervention as an indicator, we made a horizontal comparison of the three outcome indicators of the three groups and constructed a histogram. The mean change values of the HBGS score, SFGS score, and MPS score between pre-treatment and post-treatment of the three groups ($F = 8.847$, $p < 0.001$; $F = 10.690$, $p < 0.001$; $F = 5.410$, $p = 0.006$; respectively) were statistically significant. After 10 times of rTMS treatment, the mean change values of HBGS, SFGS, and MPS scores were significantly higher in participants in the Peripheral Group ($p < 0.001$; $p < 0.001$; $p = 0.003$; respectively) and Central Group ($p = 0.004$; $p = 0.003$; $p = 0.009$; respectively) than in Control Group (Table 3). However, the mean change values of HBGS, SFGS, and MPS scores showed no significant differences in participants in the Peripheral Group than in the Central Group ($p = 0.254$; $p = 0.139$; $p = 0.736$; respectively) after 2 weeks of treatment (Table 3).

None of the patients involved in this study experienced serious adverse events; two patients in the Peripheral group had a mild toothache, and no patients reported toothache when the placement of the stimulation coil was appropriately adjusted (11), This situation

TABLE 1 Baseline characteristics of the three groups.

Characteristics	Peripheral group (n = 32)	Central group (n = 32)	Control group (n = 33)	p
Sex (F/M)	19/13	14/18	16/17	0.439
Age (years)	45.6 ± 12.1	51.1 ± 14.6	49.6 ± 16.1	0.297
Facial paralysis side, (left/right)	16/16	15/17	14/19	0.827
The course of disease (day)	6.9 ± 5.3	7.0 ± 6.6	5.0 ± 3.9	0.250
Hypertension (yes/no)	7/25	9/23	7/26	0.772
Diabetes (yes/no)	5/27	5/27	4/29	0.897
Resting motor thresholds (RMT)	40.1 ± 10.3	40.3 ± 9.4	/	0.930
HBGS	4.7 ± 0.6	4.7 ± 0.5	4.5 ± 0.7	0.089
SFGS	23.3 ± 12.9	25.8 ± 11.4	31.8 ± 17.7	0.053
MPS	5.2 ± 2.2	5.3 ± 1.7	5.9 ± 2.9	0.509

HBGS, House-Brackmann grading scale; SFGS, Sunnybrook facial grading system; MPS, modified Portmann scale; IQR, interquartile range; SD, standard deviation.

TABLE 2 Comparison of efficacy before and after treatment among three groups.

Group	HBGS		SFGS		MPS	
	Pretreatment	Postreatment	Pretreatment	Postreatment	Pretreatment	Postreatment
Peripheral	4.7 ± 0.6	2.3 ± 0.9*	23.3 ± 12.9	74.5 ± 21.5*	5.2 ± 2.2	14.8 ± 4.0*
Central	4.7 ± 0.5	2.5 ± 0.8*	25.8 ± 11.4	71.0 ± 18.5*	5.3 ± 1.7	14.6 ± 3.1*
Control	4.5 ± 0.7	2.8 ± 0.8*	31.8 ± 17. 7	64.4 ± 23.1*	5.9 ± 2.9	12.9 ± 4.2*

HBGS, House-Brackmann grading scale; SFGS, Sunnybrook facial grading system; MPS, modified Portmann scale; *$p < 0.05$ (Pretreatment vs. Postreatment).

TABLE 3 Multiple comparisons of changes in the assessment of facial function among the three intervention groups.

Change in mean	Peripheral group vs. central group (p value)	Peripheral group vs. control group (p value)	Central group vs. control group (p value)
HBGS	0.254	<0.001	0.004
MPS	0.736	0.003	0.009
SFGS	0.139	<0.001	0.003

HBGS, House-Brackmann grading scale; SFGS, Sunnybrook facial grading system; MPS, modified Portmann scale.

occurs when the treatment is carried out once, mostly due to the coils of transcranial magnetism directly stimulate the teeth resulting in discomfort, and further retention will induce toothache, after adjusting the position of the coils, it will not directly stimulate the teeth, but stimulate the nerves and muscles around the face, so it is necessary for the treatment staff to adjust the coils in time. One patient had a mild headache in the central group, and the headache disappeared after reducing the intensity of TMS. No seizures, vomiting, or other adverse reactions occurred, and no other discomfort and withdrawal from clinical studies, indicating a better safety profile and high compliance with rTMS for PFP.

4. Discussion

This was a prospective cohort study of 97 patients with peripheral facial neuritis to compare the efficacy of central vs. peripheral rTMS. The results showed that after 2 weeks of treatment, the HBGS/SFGS/MPS scores of the three groups were significantly improved compared with those before treatment. The mean changes of HBGS/SFGS/MPS of the peripheral group and the central group were significantly higher than those of the control group, but there was no significant difference in the mean change before and after treatment between the central group and the peripheral group. This suggests that both central and peripheral stimulation had the same efficacy, and the efficacy of rTMS combined with conventional treatment was greater than that of conventional treatment alone. To the best of our knowledge, this is the first study to compare the efficacy of central rTMS and peripheral rTMS against PFP. Previous studies have only demonstrated the effectiveness of central stimulation (7) or peripheral stimulation (11) alone, and relevant studies in this field are lacking at present.

PFP is caused by a malfunction in the facial nerve that prevents facial muscles from being controlled (19), the clinical manifestations include difficulty frowning on the affected side, inability to close the eyes, air leakage from bulging cheeks, weakness in closing the lips, etc. Transcranial magnetic stimulation was used for this disease initially for electrophysiological diagnosis, Meyer et al. used TMS to measure facial nerve block in patients with facial paralysis (13), and Nowak et al. found TMS seems capable of localizing the site of the lesion within the Fallopian channel (9). Rimpiläinen et al. showed that TMS-induced facial motor responses predicted a good prognosis in early Peripheral facial neuritis (20). With the development of TMS and people learning more about facial paralysis, TMS is used as an intervention for the recovery of facial paralysis. Lan Shaoyong et al. used TMS combined with conventional treatment for PFP and found that the HBGS and the complete recovery rate of the observation group were significantly better than that of the control group (21). Liang and Qiang suggest TMS helped improve the clinical symptoms

and EMG metrics in patients with facial paralysis and improved the clinical efficacy and patient prognosis, along with good safety (22). Our previous study using rTMS on the affected face for peripheral stimulation found that peripheral rTMS could also significantly improve facial nerve function in patients with Bell facial paralysis (11).

Although we found that both central and peripheral stimulation improved PFP, the mechanism may be different. For peripheral TMS stimulation, the mechanism may be to improve the nutritional supply to the injured facial-related nerves (23) and promote blood flow (24), in addition, when the TMS coil is placed on the affected side of the face of a PFP patient, it produces muscle contractive vibrations. This mechanical vibration (25) and electrical stimulation stimulate the muscle spindles of the facial muscles and strengthen nerve control over the muscles. This peripheral electrical stimulation also activates sensory nerves, the trigeminal nerve plays an important role. Cheney et al. (26) and Martin and Helsper (27) have observed the possibility of *de novo* neuralization of the trigeminal nerve in paralyzed facial muscles, electrically induced orthodromic excitation of the trigeminal nerve fibers may promote the generation of terminal motor nerve twigs (28). In addition, another important explanation is that TMS relies on a magnetic field to generate induced current, and the magnetic field of the coil will touch the affected face, so peripheral TMS also has the effect of magnetic therapy on the affected face tissue. Magnetic therapy improves circulation, reduces inflammation, and reduces pain (29, 30). Different from the mechanism of peripheral TMS stimulation, the effective mechanism of central TMS stimulation may be the use of high-frequency (excitatory) TMS elicitation to guide the activation of the brain cortex representative area of facial movement, which is helpful to the remodeling of the facial muscle motor function, and the nerve impulse excited will also project to the facial nervous system, to accelerate the recovery of facial nerve function (31). There have been multiple studies showing that in patients with peripheral facial paralysis, the representative area of the cerebral cortex related to facial muscle decreases (32), the adjacent area (such as the forearm muscle cortex representative area) increases, and the functional remodeling of facial motor cerebral cortex representative area is closely related to the prognosis of patients with peripheral facial paralysis (20, 33, 34). Functional magnetic resonance imaging (fMRI) studies by Hu et al. suggested that cortical reorganization plays an important role in the recovery of Bell's facial paralysis (35). Facial nerve dysfunction has a destructive effect on the activity of sensorimotor areas, and the increased intensity of sensorimotor areas ipsilateral to the facial nerve injury in the middle stage of facial nerve dysfunction suggests that interhemispheric reorganization may be involved. Behavioral or brain stimulation techniques in this phase of treatment can be used to alter the reorganization of sensorimotor areas in facial functional rehabilitation, monitor treatment effects, and improve therapeutic interventions during rehabilitation (36).

For a look at the future, we have summarized some of the unresolved things. First, there is uncertainty regarding the optimal target of TMS for PFP, and our preliminary findings of no significant difference between central and peripheral stimulation are not absolute. Yang et al. used TMS to stimulate the outlet mastoid of the facial nerve and found that the percentage of R1 extraction rate and the percentage of CMAP amplitude decline of the facial nerve in the intervention group were significantly higher than those in the control group, suggesting that rTMS has a good clinical effect on the treatment of early PFP (37), more research will be needed to compare the efficacy of these different sites. Secondly, it is necessary to optimize the optimal treatment parameters of TMS. The current studies generally use stimulation frequencies of 5 HZ and 50 HZ (iTBS) (37), but there is no study to compare the efficacy difference of TMS with different frequencies. Finally, whether TMS is specific for PFP patients at different stages and how effective it is in the sequelae stage needs to be further explored. A point that needs to be discussed directly is this: if peripheral stimulation (and perhaps even the use of more convenient and less expensive electrical stimulators) is equally effective, is there a need for TMS, and is there a need to design a study comparing the effects of peripheral electrical stimulation with those of magnetic stimulation? We believe that this is a question that deserves in-depth research, and our answer is YES, we look forward to future studies that can compare the effects of peripheral electrical stimulation with magnetic stimulation or have a relevant systematic review to prove it.

This study has the following limitations: First of all, we did not use electrophysiological indicators such as electromyograms and only used HBGS, SFGS, and MPS as outcome indicators, which was somewhat subjective. Second, we did not calculate the sample size, and it was not randomly assigned, which may weaken the evidence quality of the study.

In conclusion, our study shows that rTMS can be used as a safe and effective adjuvant therapy for patients with PFP. Preliminary studies have shown that both peripheral and central stimulation can effectively improve facial nerve function, but there is no significant difference in the efficacy of the two sites.

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.

Ethics statement

The studies involving humans were approved by Ethics Committee of Yuebei People's Hospital. 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

ZL: Conceptualization, Investigation, Software, Writing – original draft, Writing – review & editing. XW: Methodology, Writing – original draft, Writing – review & editing. YS: Data curation, Formal analysis, Methodology, Project administration, Writing – original draft. ZW: Data curation, Formal analysis, Project administration, Writing – original draft. BL: Formal analysis, Project administration, Supervision, Validation, Writing – original draft. RW: Investigation, Methodology, Project administration, Writing – original draft. HL: Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Validation, Visualization, Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

Thanks for the help from other staff and interns of the Rehabilitation Medicine Department of YueBei People's Hospital. We would also like to thank all the patients for their participation and cooperation in completing all the evaluations and treatment of the trial.

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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frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 21 December 2023
DOI 10.3389/fneur.2023.1274384

OPEN ACCESS

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RECEIVED 08 August 2023
ACCEPTED 29 November 2023
PUBLISHED 21 December 2023

CITATION
Liu G, Zou X, Dong Y, Alhaskawi A, Hu L, Mao L, Qian J, Ying J, Abdalbary S, Alenikova O, Ma Y and Lu H (2023) Unilateral transforaminal lumbar interbody fusion through a modified hemilateral spinous process-splitting approach. *Front. Neurol.* 14:1274384. doi: 10.3389/fneur.2023.1274384

Unilateral transforaminal lumbar interbody fusion through a modified hemilateral spinous process-splitting approach

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Objective: To describe unilateral transforaminal lumbar interbody fusion (TLIF) via a modified hemilateral spinous process-splitting (MHSPS) approach and determine its effectiveness.

Methods: Sixty-five consecutive patients with the lumbar degenerative disease who underwent MHSPS TLIF between August 2020 and July 2021 were retrospectively analyzed. Japanese Orthopedic Association (JOA) score and visual analog scale (VAS) scores for back and leg pain were evaluated before surgery and at the last follow-up. Postoperative paraspinal muscle atrophy was evaluated on axial T2-weighted magnetic resonance imaging.

Results: Mean JOA score increased from 13.6 ± 3.21 before surgery to 24.72 ± 3.34 at last follow-up ($p < 0.001$). The mean recovery rate was 68.2% ± 5.68%. Clinical outcome was excellent in 22, good in 35, and fair in 8 patients. The VAS score for low back pain was significantly lower at the last follow-up than before surgery (1.18 ± 0.99 vs. 3.09 ± 1.35; $p < 0.001$). The VAS score for leg pain was also significantly lower at the last follow-up than before surgery (1.13 ± 0.91 vs. 6.61 ± 1.23; $p < 0.001$). The mean paraspinal muscle atrophy rate did not significantly differ between the symptomatic side (6% ± 3.8%) and asymptomatic side (4.8% ± 3.3%) at last follow -up ($p = 0.071$).

Conclusion: MHSPS TLIF is an effective minimally invasive surgical treatment for selected types of degenerative lumbar disease. This technique can achieve effective spinal decompression and interbody fusion. Its advantages include direct and adequate visualization, vast surgical working space, short operation time, and minimal muscle injury.

KEYWORDS

spinous process, multifidus muscle, surgical approach, lumbar spine, internal fixation

Introduction

Transforaminal lumbar interbody fusion (TLIF), first described by Harms et al. (1) in 1982, has become widely accepted as a standard surgical treatment for degenerative lumbar disk disease (2). Advantages of TLIF over posterior lumbar interbody fusion include minimal dural retraction, high surface area and sufficient blood supply for bony fusion, ability to maintain or restore intervertebral body height, and low risk of postoperative radiculitis (3). Although the conventional midline open approach provides good visualization and vast working space, it requires bilateral detachment and retraction of the paraspinal muscles, which may cause low back pain and atrophy of the muscles (4, 5). To mitigate these potential issues, surgeons have developed minimally invasive (MIS) techniques for TLIF. MIS procedures aim to minimize postoperative pain and preserve muscle integrity, and MIS TLIF using a tubular retractor (2) and TLIF via the Wiltse paraspinal approach (6) have been developed as alternatives. Other MIS-TLIF procedures have also been devised for specific and limited indications. Most MIS approaches require longer operation time and sacrifice surgical visualization and working space to minimize paraspinal muscle damage (6, 7). As a result, they are associated with higher risks of incomplete neural decompression and pseudarthrosis than the conventional open midline approach (7).

Watanabe et al. (8) introduced a spinous process-splitting approach for lumbar laminectomy in which the lamina is exposed by longitudinally splitting the spinous process into halves, while the soft tissue attachments to the spinous process are left intact. This procedure offers more expansive surgical working space and optimizes visualization while causing less muscular damage than the conventional approach (8). Because most lumbar degenerative disease patients suffer from unilateral lower extremity pain, bilateral splitting of the spinous process is unnecessary. Chatani et al. (9) described unilateral partial laminectomy using a hemilateral spinous process-splitting (HSPS) approach for lumbar spinal stenosis and reported satisfactory results. With this approach, the spinous process is split in the midline without stripping the attached muscles; then, the lateral half of the spinous process is resected at the base to expose only the ipsilateral lamina (9). This study aimed to describe unilateral TLIF via a modified HSPS (MHSPS) approach and report our experience with it in patients with lumbar degenerative disease and radiculopathy.

Methods

Patients

Clinical data from consecutive patients with unilateral symptoms who underwent MHSPS TLIF between August 2020 and July 2021 were retrospectively reviewed. A single experienced orthopedic surgeon performed all operations. The study protocol was approved by the Ethical Review Board of Ningbo No. 6 Hospital.

Patients who met the following criteria were eligible for inclusion: (1) diagnosis of lumbar degenerative lumbar disk herniation, stenosis, or spondylolisthesis in conjunction with unilateral lumbar radiculopathy; and (2) failure of at least 3 months of conservative treatment. We excluded patients with bilateral lower extremity symptoms, scoliosis, a history of previous lumbar spine surgery, and patients less than 18 years old or less than 12 months of follow-up. Those with incomplete data were also excluded.

Surgical technique

After induction of general anesthesia, patients were positioned prone on a radiolucent frame. Anteroposterior fluoroscopy was performed to mark the surgical level(s). A midline incision was made, and the spinous processes and interspinous ligaments cranial and caudal to the surgical level(s) were exposed. The subcutaneous tissue on the asymptomatic side was separated from the surface of the lumbodorsal fascia. The Wiltse interval between the medial multifidus and lateral longissimus muscles was identified and bluntly separated. Pedicle screws (Guanlong Co., Ltd., Jinan, Shandong, China) were then inserted.

On the symptomatic side, the lateral half of the spinous process and interspinous ligaments were longitudinally split and broken at the base. Next, they were retracted laterally along with the attached paravertebral muscles. Unilateral laminectomy, facetectomy, and discectomy were then performed under direct vision, followed by a standard TLIF (2). Adequately high cage (GN Tech Co., Ltd., Chengdu, Sichuan, China) was used for interbody fusion, which could allow contralateral indirect decompression. After the insertion of pedicle screws through the surgical field on the symptomatic side, the screw and rod system were locked with mild pressure. The retracted spinous process half was reattached to the portion of the spinous process left in place using transosseous sutures. The interspinous ligaments were repaired using sutures (Figures 1, 2).

Evaluation of clinical outcome

The Japanese Orthopedic Association (JOA) score for lumbar spinal disorders was determined before surgery and at the last follow-up (10). The recovery rate was calculated as (postoperative score − preoperative score)/(total score − preoperative score) × 100. Outcomes were defined according to recovery rate: excellent, recovery rate ≥ 75%; good, 50–74.9%; fair, 25–49.9%; and poor, <25%. Visual analog scale (VAS) scores for leg and back pain were also determined.

Radiographic evaluation

Preoperative and final follow-up lateral radiographs were reviewed for evaluating global lumbar lordosis and segmental lordosis (11). Postoperative computed tomography was used to assess interbody fusion and bony union of the split spinous process. Approach-related paraspinal muscle damage was evaluated by measuring a cross-sectional area of the paraspinal muscles at the surgical level on the symptomatic (decompression) side on axial T2-weighted magnetic resonance imaging performed before surgery and at the last follow-up (Magnetom Avanto; Siemens, Munich, Germany). The muscle atrophy rate was calculated as (1 − total postoperative area/total preoperative area) × 100^{8}. The paraspinal muscles on the asymptomatic side were used as a control (9). Radiographic evaluation was performed by two radiologists blinded to the study data. Any disagreements were resolved via discussion and consensus.

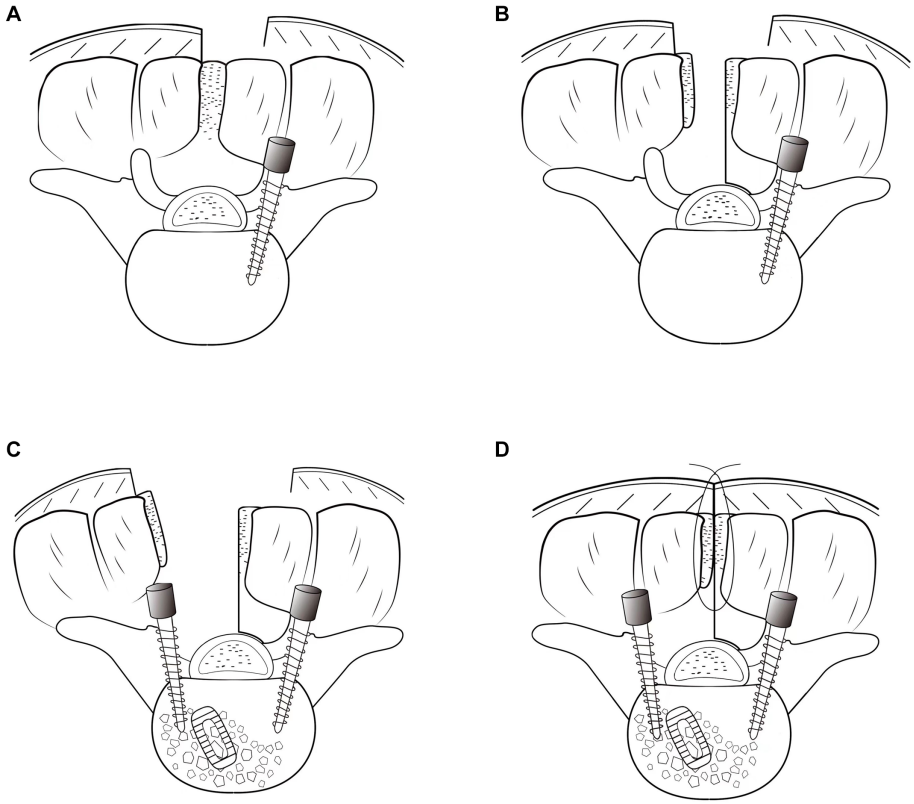

FIGURE 1
Illustration of the hemilateral spinous process-splitting transforaminal lumbar interbody fusion procedure. Pedicle screws on the asymptomatic side were placed using a Wiltse approach **(A)**. The spinous process was split in the midline with the attached muscles left intact and a hemilateral half of the spinous process for the decompression side was broken **(B)**. After unilateral decompression and interbody fusion were achieved, pedicle screws on the symptomatic side were inserted through the surgical field **(C)**. The spinous process was reattached **(D)**.

Statistical analysis

Statistical analyses were performed using SPSS software version 18.0 (IBM Corp., Armonk, NY, USA). Pre- and postoperative clinical results were compared using the two-sample *t*-test. Muscle atrophy rate was reached between the symptomatic (decompression) side and the asymptomatic side using the paired *t*-test. All tests were two-sided. $P < 0.05$ was considered significant.

Results

Sixty-five patients (43 men and 22 women) were included for analysis (Figures 3, 4). The mean age at the time of surgery was 52.27 ± 8.76 years. Preoperative diagnosis was degenerative disk disease with herniated nucleus pulposus in 39 patients, spondylolisthesis in 21, and lumbar stenosis in 5. The number of surgical levels was one in 49 patients and two in 15; three-level surgery was performed in one patient (Table 1).

The mean follow-up was 15.6 ± 3.7 months (range, 12–26). Mean operation time was 70.5 ± 15.6 min for one-level surgery, 120 ± 10.2 min for two-level surgery, and 160 min for three-level surgery.

All 65 patients experienced symptom relief after surgery. JOA score was significantly higher at the last follow-up than before surgery (24.72 ± 3.34 vs. 13.6 ± 3.21; $p < 0.001$, Figure 5). The mean recovery rate was 68.2% ± 5.68%. The outcome was excellent, good, and fair in 22, 35, and 8 patients. The VAS score for low back pain was significantly lower at the last follow-up than before surgery (1.18 ± 0.99 vs. 3.09 ± 1.35; $p < 0.001$). The VAS score for leg pain was also significantly lower at the last follow-up than before surgery (1.13 ± 0.91 vs. 6.61 ± 1.23; $p < 0.001$).

Lumbar lordosis and segmental lordosis slightly increased from preoperative (42.49 ° ± 8.1° and 14.96° ± 5.12°) to preoperative (43.78 ° ± 7.29° and 16.2° ± 4.78°), but there was no significant difference ($t = -0.955$ and -1.415, $p = 0.341$ and 0.159 respectively). Interbody fusion and fusion of the split spinous process were achieved in all patients. The mean paraspinal muscle atrophy rate did not significantly differ between the symptomatic (decompression) side (6% ± 3.8%) and the asymptomatic side (4.8% ± 3.3%) at the last follow-up ($p = 0.071$; Figure 6). Only one complication, a misplaced pedicle screw that required surgical repositioning, was observed; the patient experienced no neurological sequelae.

Discussion

Unilateral TLIF with bilateral pedicle screw fixation is a standard surgical treatment for lumbar degenerative disease (2, 3). The conventional open approach is widely used because of its safety, straightforward technique, and good visualization (1).

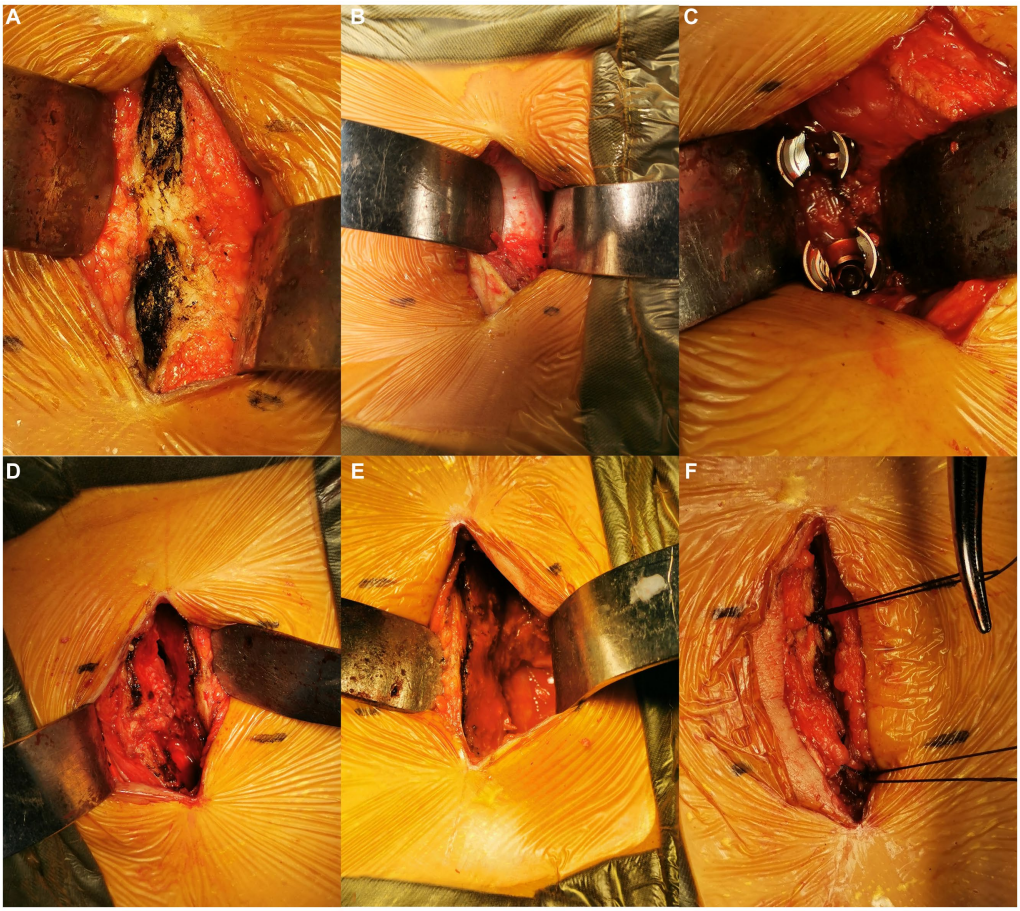

FIGURE 2
Intraoperative images. Exposure of the cranial and caudal spinous processes **(A)**. The Wiltse interval was identified **(B)** and bluntly separated for pedicle screw placement on the asymptomatic side **(C)**. The spinous process was longitudinally split and broken at the base on the symptomatic side, then laterally retracted **(D)**. The vertebral canal was exposed **(E)**. After the TLIF procedure, the spinous process was reattached by transosseous sutures **(F)**.

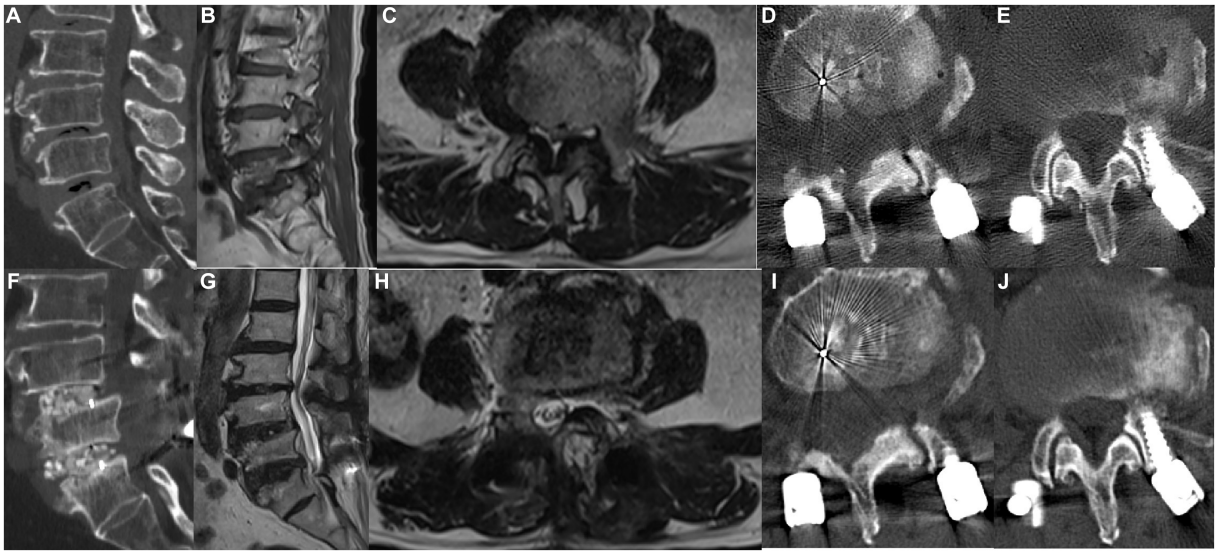

FIGURE 3
A 58-year-old woman underwent MHSPS TLIF for L4/5 lumbar spinal stenosis with instability and unilateral lower extremity pain. Preoperative sagittal computed tomography confirmed segmental instability **(A)**. Preoperative sagittal **(B)** and axial **(C)** T2-weighted magnetic resonance imaging shows lumbar spinal stenosis and instability. Three days after surgery, axial computed tomography shows the split spinous process of two levels **(D,E)**. Postoperative sagittal computed tomography 1 year after surgery shows a robust interbody fusion **(F)**. Axial **(G)** and sagittal **(H)** T2-weighted imaging 1 year after surgery shows good decompression and no marked difference in the cross-sectional area of the paraspinal muscles. Axial computed tomography 1 year after surgery shows a bony union of the spinous process of two levels **(I,J)**.

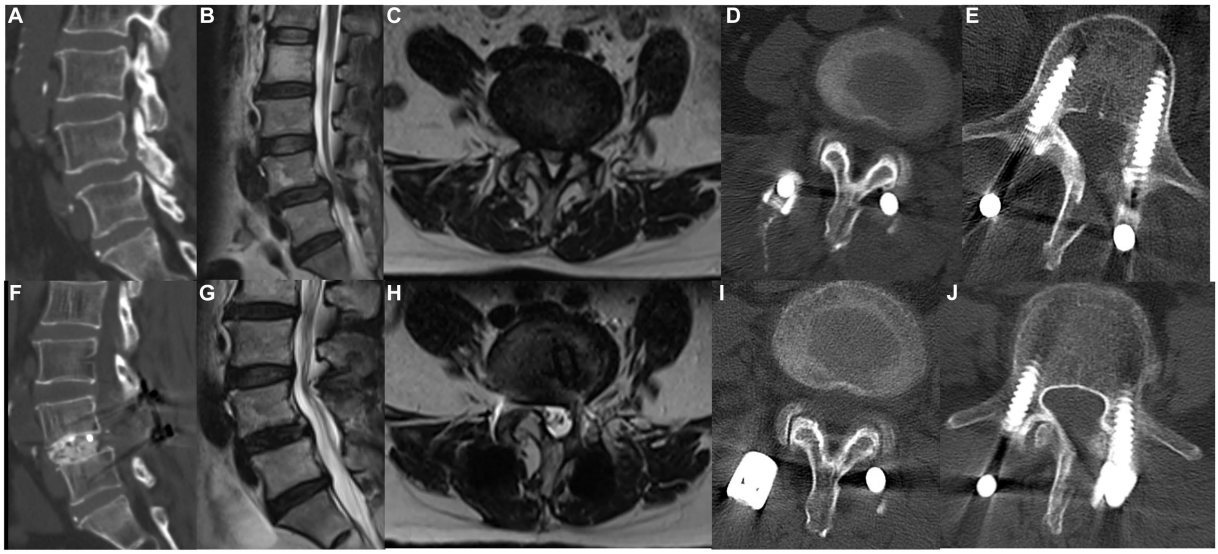

FIGURE 4
A 69-year-old man underwent MHSPS TLIF for L4/5 lumbar spinal stenosis with instability and unilateral lower extremity pain. Preoperative sagittal computed tomography demonstrates segmental instability **(A)**. Preoperative sagittal **(B)** and axial **(C)** T2-weighted magnetic resonance imaging shows L4/5 and L5/S1 spinal stenosis. Axial computed tomography 5 days after surgery shows the split spinous process at two levels **(D,E)**. Postoperative sagittal computed tomography demonstrates good interbody fusion **(F)**. Sagittal **(G)** and axial **(H)** T2-weighted imaging 1 year after surgery shows sufficient decompression and no marked difference in the cross-sectional area of the paraspinal muscles. Axial computed tomography 1 year after surgery demonstrates a bony union of the spinous process at two different levels **(I,J)**.

TABLE 1 Patient demographic data.

	Patient
Mean age (years) mean ± SD	52.27 ± 8.76
Gender (M/F)	43/22
BMI (kg/m2) mean ± SD	22.9 ± 3.5
Disease course (months) mean ± SD	10.3 ± 5.5
Preoperative diagnosis	
Herniated nucleus pulposus	39
Spondylolisthesis	21
Lumbar stenosis	5
Level of fusion	
L3–L4	3
L4–L5	28
L5–S1	26

BMI, Body mass index.

However, it requires extensive muscle stripping and retraction, which can cause iatrogenic muscle injury resulting in postoperative low back pain and/or failed back surgery syndrome (4, 5). MIS TLIF procedures are associated with less paraspinal muscle damage (6, 7). The Wiltse approach accesses the spine through the anatomic cleavage plane between the multifidus and longissimus muscles. Compared to the conventional approach, it causes less paraspinal muscle damage, blood loss, and back pain and is associated with better recovery of lumbar function (6, 12, 13). Although the Wiltse approach provides good exposure of the articular and transverse processes and enables pedicle screw placement, laminectomy can be challenging to perform because the medial multifidus impedes exposure of the lamina, especially in muscular or obese patients (6). A novel surgical retractor for specific use with the Wiltse TILF approach has recently been designed (6).

Watanabe et al. (8) compared lumbar stenosis patients who underwent lumbar laminectomy via the spinous process-splitting approach with those who underwent conventional laminectomy and reported that the latter approach provided adequate surgical working space and good visualization and caused less muscular injury than the conventional approach (8). Many other reports have confirmed the superiority of the spinous process-splitting approach (8, 9, 14–17). However, only some studies of this approach for TLIF have been previously reported. Mori et al. (18) studied patients who underwent single-level open pedicle screw fusion for degenerative spondylolisthesis (27 patients underwent the spinous process-splitting approach, and 26 underwent the conventional approach) and found the spinous process-splitting approach was less damaging to the paraspinal muscles; moreover, the patients who underwent the spinous process-splitting procedure had less low back discomfort 1 year after surgery. Our group recently compared a spinous process-splitting TLIF technique with conventional TLIF in patients with lumbar degenerative or isthmic spondylolisthesis and found that the spinous process-splitting technique allows for better visualization and a more expansive working space and minimizes damage to the paraspinal muscles (19). The present study modified the spinous process-splitting approach for unilateral TLIF to treat lumbar degenerative disease.

The MHSPS approach for TLIF combines the spinous process-splitting and Wiltse techniques. Unilateral laminotomy and pedicle screw insertion on the symptomatic (decompression) side are performed using the spinous process-splitting approach, while pedicle screw insertion on the asymptomatic side is performed via the Wiltse approach. Fusion was achieved in all patients and the lumbar lordosis

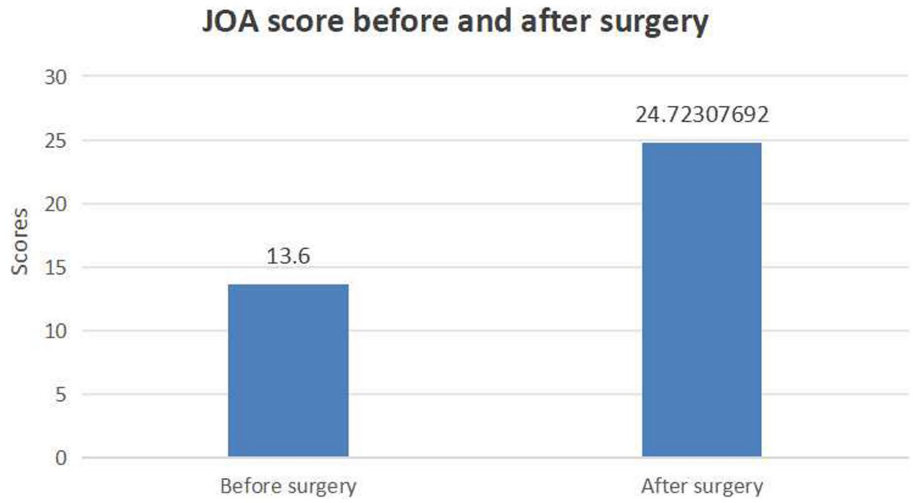

FIGURE 5
Bar graph showing the JOA score before and after surgery.

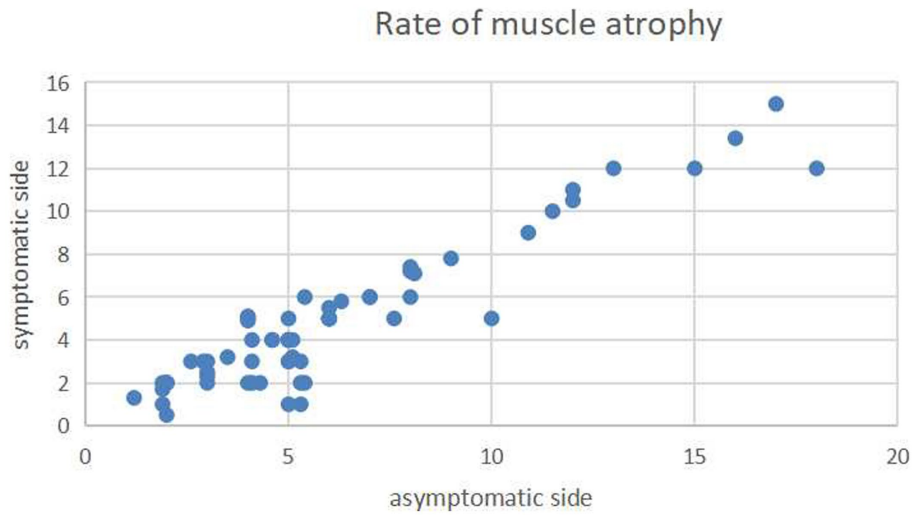

FIGURE 6
Scatterplot showing the mean atrophy rates of the paraspinal muscles on the axial T2-weighted imaging on the decompression (longitudinal axis) and nondecompression sides (horizontal axis). The atrophy rates did not significantly differ between the two sides.

was restored in our study. In addition, operation time was short and paraspinal muscle atrophy was negligible. Moreover, after surgery, the mean JOA score significantly increased and VAS scores for low back and leg pain significantly decreased.

Liu et al. (6) also reported improvements in JOA and VAS pain scores 12 months after Wiltse TLIF. In a study of 49 patients who underwent MIS TLIF for degenerative disk disease with a herniated disk, Schwender et al. (20) reported a decrease in VAS pain score from 7.2 before surgery to 2.1 at the last follow-up. The outcomes of our patients are comparable or superior to those reported in previous MIS TLIF studies.

MHSPS TLIF provides a clear surgical field and visualization, enabling a rapid operation. The mean operation time for one-level surgery in our study was 70.5 min; corresponding values were 120 min for two-level operations. These times are lower than those reported in previous MIS TLIF series (6, 12, 13). With the Wiltse and other MIS TLIF techniques, the multifidus is dissected and retracted medially before performing laminectomy. In contrast, with the MHSPS approach, the spinous process is split in the midline, and the lateral half is retracted laterally to expose the surgical field for laminectomy and discectomy. This approach can achieve similar functional outcomes with shorter operation time than the Wiltse TLIF and MIS TLIF without sacrificing visualization or working space.

Pedicle screw placement through the Wiltse approach is widely used and associated with less paraspinal muscle damage than the conventional approach (21, 22). Pedicle screws on the asymptomatic side in our study were placed through the Wiltse approach. Postoperative paraspinal muscle atrophy did not significantly differ between the asymptomatic and symptomatic sides where the

decompression was performed. This suggests that any postoperative paraspinal muscle changes were minor. Mori et al. (18) used the spinous process-splitting approach for interbody fusion combined with bilateral pedicle screw insertion using the Wiltse approach in single-level operations and found the degree of paraspinal muscle injury was less than that seen with the conventional open approach. Our surgical technique was similar; however, we inserted pedicle screws on the symptomatic (decompression) side through the surgical incision, not via the Wiltse approach. A potential disadvantage of the spinous process-bilateral-splitting approach is that the force of the multifidus muscle cannot be transmitted to the spine because of the floating spinous process (8). Only the lateral half of the spinous process is broken and retracted with our MHSPS TLIF technique, which might preserve muscle function.

The MHSPS TLIF has several limitations. First, spinous process anatomy can vary between individuals. The reported mean width of the spinous processes at L4 and L5 is 9 mm (range, 3–18) (23) and splitting may be difficult in some. Second, the unilateral approach technique is unsuitable for patients with bilateral lower extremity symptoms; these patients should undergo a bilateral lumbar spinous process-splitting laminectomy approach. Third, the pedicle screw entry point on the symptomatic (decompression) side should be located more medially than on the opposite side because the split spinous process may limit the proper axial screw angle. Forth, although the spinous process and interspinous ligaments are longitudinally split and then repaired, the long-term functional outcome of damaging the posterior midline complex is uncertain (24). Finally, other limitations of this study includ the study type-case series without a control group, as well as the fact that it is debatable whether midline incision surgery can be considered minimally invasive. Future long-term, large-scale randomized controlled studies are warranted to investigate.

Conclusion

MHSPS TLIF is an effective MIS surgical treatment for selected types of degenerative lumbar disease. This technique can achieve effective spinal decompression and interbody fusion. Its advantages include direct and adequate visualization, vast surgical working space, short operation time, and minimal muscle injury.

Author contributions

GL: Writing – original draft. XZ: Writing – original draft. YD: Writing – review & editing. AA: Writing – review & editing. LH: Writing – review & editing. LM: Writing – review & editing. JQ: Writing – review & editing. JY: Writing – review & editing. SA: Writing – review & editing. OA: Writing – review & editing. YM: Writing – review & editing. HL: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was financially supported by the Ningbo Public Welfare Research Plan critical project (No.: 2023S036).

Acknowledgments

We would like to acknowledge the hard and dedicated work of all the staff who implemented the intervention and evaluation components of the study.

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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frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 22 January 2024
DOI 10.3389/fneur.2023.1307883

OPEN ACCESS

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RECEIVED 05 October 2023
ACCEPTED 15 December 2023
PUBLISHED 22 January 2024

CITATION
Zou X, Dong Y, Alhaskawi A, Zhou H, Ezzi SHA, Kota VG, Abdulla MHAH, Abdalbary SA, Lu H and Wang C (2024) Techniques and graft materials for repairing peripheral nerve defects.
Front. Neurol. 14:1307883.
doi: 10.3389/fneur.2023.1307883

Techniques and graft materials for repairing peripheral nerve defects

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Peripheral nerve defects refer to damage or destruction occurring in the peripheral nervous system, typically affecting the limbs and face. The current primary approaches to address peripheral nerve defects involve the utilization of autologous nerve transplants or the transplantation of artificial material. Nevertheless, these methods possess certain limitations, such as inadequate availability of donor nerve or unsatisfactory regenerative outcomes post-transplantation. Biomaterials have been extensively studied as an alternative approach to promote the repair of peripheral neve defects. These biomaterials include both natural and synthetic materials. Natural materials consist of collagen, chitosan, and silk, while synthetic materials consist of polyurethane, polylactic acid, and polycaprolactone. Recently, several new neural repair technologies have also been developed, such as nerve regeneration bridging technology, electrical stimulation technology, and stem cell therapy technology. Overall, biomaterials and new neural repair technologies provide new methods and opportunities for repairing peripheral nerve defects. However, these methods still require further research and development to enhance their effectiveness and feasibility.

KEYWORDS

peripheral nerve injuries, graft materials, peripheral nerve defects, nerve regeneration, nerve gap

Introduction

Peripheral nerve injuries (PNIs) refer to damage to the peripheral nervous system, which includes all nerves outside of the brain and spinal cord (1). A variety of factors, such as trauma, compression, and disease, can lead to these injuries (2–5). The prevalence of PNIsis approximated to be within the range of 13 and 23 individuals per 100,000 annually in developed nations, causing either incomplete or complete deprivation of motor, sensory, and autonomic abilities in the affected regions of the anatomy (6, 7). The

importance of the nerve damage relies on the extent and intensity of the sensory or motor impairment, the length of time the clinical symptoms persist, and the individual affected by the nerve injury (1).

The nerves are encased by the epineurium, perineurium, and endoneurium, each playing a crucial role. The epineurium acts as a protective shield for the nerve against external stressors. Situated beneath the epineurium, the perineurium consists of a thin layer of flat cells with tight junctions, serving to control diffusion around individual fascicles and exhibiting high tensile strength. The endoneurium, which is characterized by a relaxed collagen matrix, envelops individual nerve fibers (8).

The process of nerve regeneration is intricate, encompassing multiple phases such as degeneration, sprouting, and reinnervation. In the wake of nerve injuries, axonal degeneration ensues, which is characterized by the disintegration of damaged axons and their myelin sheath. Schwann cells, located in the nerve's distal segment, initiate the catabolism of myelin and phagocytosis of the debris. Within a day post-injury, the axonal sprouting commences from the injured nerve's proximal stump. The growth cone of the sprouting axon progresses along the path of the unscathed basal lamina, a process influenced by neurotrophic and neurite-promoting factors. Assuming the endoneurial tube remains intact, the regenerating axon can follow a direct path to the end organ, migrating at an approximate rate of 1 mm per day. Neurotrophic factors are paramount in supporting peripheral nerve regeneration. Successful reinnervation activates both old and new motor end plates, facilitating muscle recovery. Given an appropriate route, peripheral axons have the capacity to regenerate and establish connections with their intended targets (9). However, in the absence of a suitable path, neuroma and scar tissue may form at the damaged nerve's proximal end, obstructing nerve regeneration progress. The perineurium plays an essential role in maintaining axonal integrity; without it, axon fibers fail to proceed as expected. Axons are likely to deviate from their path once the perineurium sustains damage. Neuroinflammation is another pivotal factor in this process. When axons reach the extraperineurial space – an area already subjected to tissue damage – inflammation ensues. Substances secreted during this inflammatory response can contribute to the development of neuromas (5). Schwann cells and stem cells in the area affected by injury can preserve their survival through autocrine circuits, which inhibit apoptosis in dense environments, thereby enhancing the probability of axonal growth from the proximal area towards the distal stump (10). Regardless of this regenerative potential, peripheral nerve regeneration often results in suboptimal functional outcomes, largely due to the significant gap between severed injured peripheral nerves and their intended targets, which hampers reconnection (10, 11) (see Figure 1).

Neurotmesis corresponds to Sunderland's classification of fifth-degree injury, which denotes the most extreme type of peripheral nerve damage characterized by a total interruption of the nerve (12). Surgery is always required to treat neurotmesis. A nerve defect, also known as a large nerve gap, cannot be directly repaired by suturing. The timely diagnosis of peripheral nerve injuries holds significant importance in their subsequent treatment. Conventional methods like MRI and ultrasound have been extensively utilized for diagnosing peripheral nerve injuries. Nevertheless, the intricate nature of MRI interpretation poses challenges, thereby restricting its practical implementation in clinical settings. In light of this, a recent study has introduced an end-to-end learning framework that leverages automatic image segmentation technology to streamline the process of MRI interpretation (13).

For peripheral nerve gaps that are small in size (<5 mm), the traditional method of suturing repair, without the use of grafted materials, can be employed (14). For longer nerve gaps, different methods of repair have been introduced in the medical field, with varying levels of achievement and acceptance among surgeons. This study aims to provide reference for clinicians in the field of repair techniques and graft materials (see Figure 2).

Graft materials

Autologous nerve

Autologous nerve grafts are considered the "gold standard" technique for repair of peripheral nerve defects. Up until now, auttologous nerve transplants have provided the most favorable outcomes in the regeneration of nerves under tension (15). A study reported that autologous nerve grafting provided functional motor recovery in mixed and motor nerve repairs, with meaningful motor recovery observed in 73% of cases (16). However, the availability of autologous nerve grafting is restricted due to limited tissue supply, the requirement for an additional surgical procedure to obtain graft tissue, morbidity at the donor site, loss of function and potential differences in tissue size and structure, etc. (17, 18).

To address the challenges associated with donor site complications, researchers (19) have been seeking an alternative that can match the efficacy of autologous nerves. In a study conducted on SD rats with a 1 cm nerve deficit, the use of vascularized neurotubes for peripheral nerve treatment was investigated. After an eight-week period following the nerve repair procedure, the results revealed that vascularized neurotubes were more effective in promoting nerve regeneration compared to non-vascularized biodegradable conduits and autologous nerve grafts. However, it is important to note that the study had a limited sample size and expanding it will be necessary to enhance the reliability of the research. Additionally, functional recovery was not assessed in this investigation; only histological and electrophysiological markers of nerve regeneration were evaluated. Furthermore, the study did not delve deeply into the vascularization mechanism of the neurotubes, warranting further exploration.

In another study (20), researchers investigated the effectiveness of using minced nerve tissue as a filler within venous grafts to repair 1 cm nerve defects. The study's findings concluded that incorporating minced nerve tissue into venous grafts significantly enhanced nerve regeneration, comparable to the outcomes of nerve transplantation, without causing complications at the donor site. Consequently, with additional support from experimental evidence and clinical trials, it can be considered a promising alternative for nerve defect repair, potentially replacing the need for autologous nerve grafts.

In peripheral nerve injuries, carefully selecting the most appropriate donor nerve is crucial for successful nerve reconstruction. Several key factors must be considered when choosing a donor nerve, including its function, location, number of branches, and axon count (21). The axon count is particularly important as it helps ensure the transferred nerve can adequately reinnervate the denervated muscle (22). Mackinnon et al. (23) underscored the importance of matching nerves of the appropriate size to optimize the functional outcome

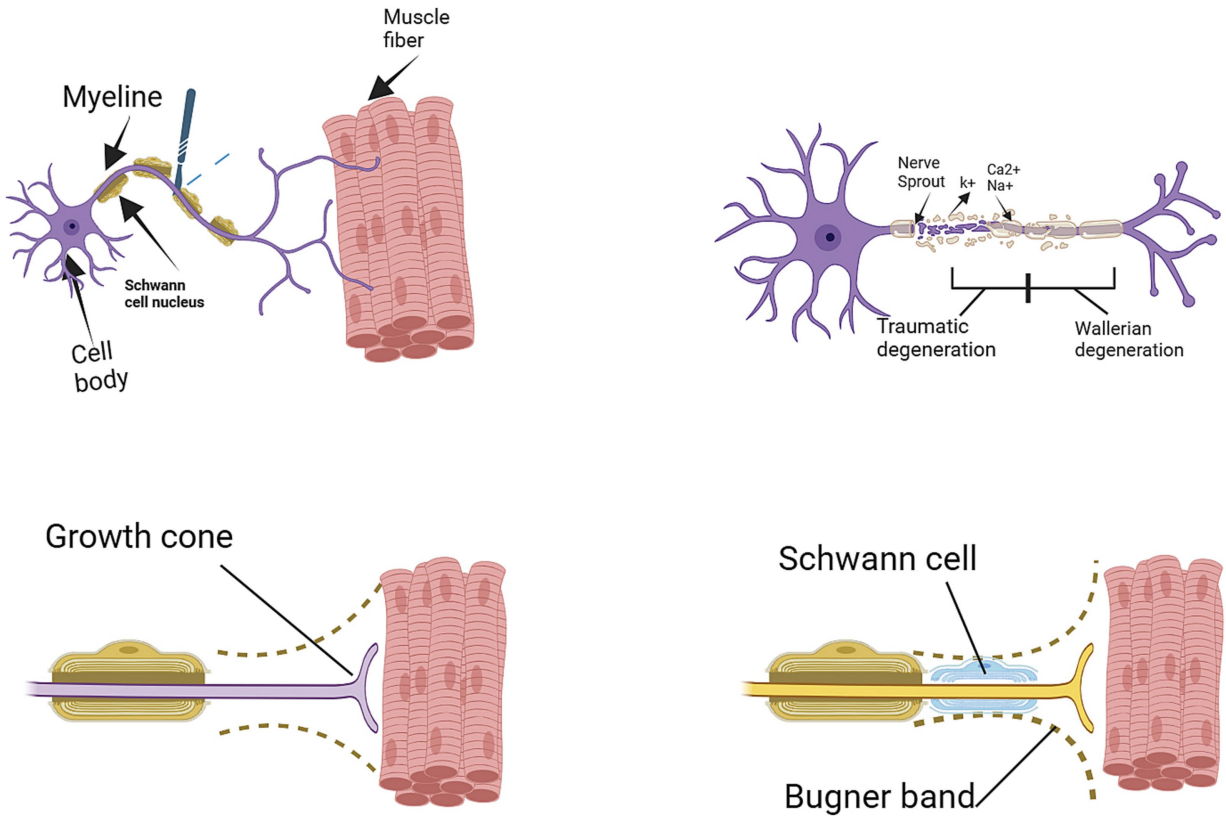

FIGURE 1
Degeneration and regeneration after peripheral nerve injury (11).

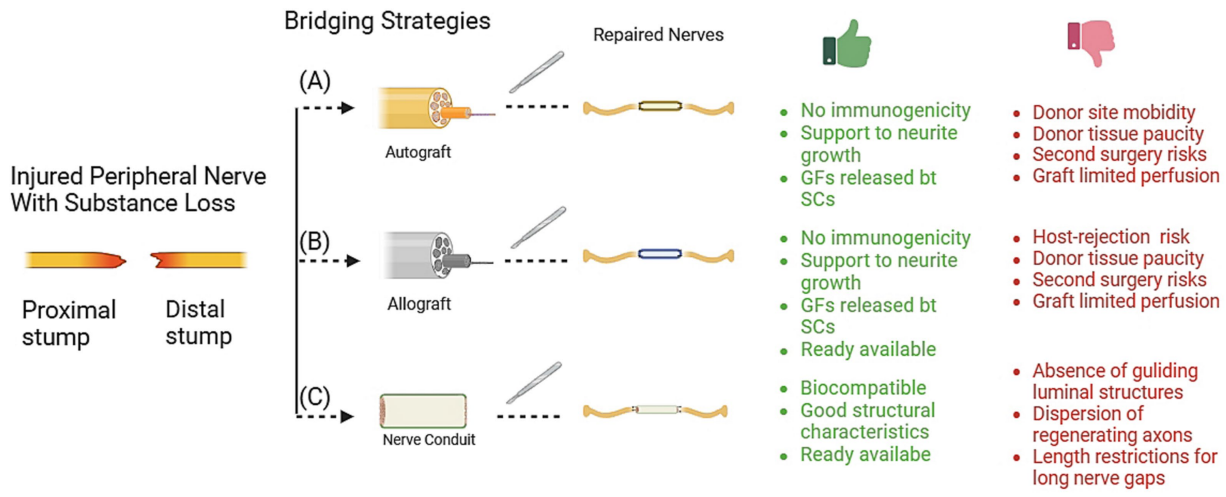

FIGURE 2
Techniques for bridging peripheral nerve defects. The graphic details the specific advantage (green words) and limitation (red words) for each technique, including (A) autograft, (B) allograft, and (C) nerve conduits. Gf, growth factors; SCs: Schwann cells. Graft materials.

following nerve repair, according to their study conducted on an animal model. The research involved nerve transplantation with precise ratios of 1:1, 2:1, and 2.5:1 (donor to recipient axon). In a detailed examination of the forearm, researchers reported [26] that the primary nerve branches of the flexor carpi radialis and the flexor carpi ulnaris had average axon counts of 746 and 659, respectively. These figures were found to align with the average axon counts of the extensor carpi radialis longus (704 axons) and brevis (745 axons). Within this group of wrist flexors and extensors, the extensor carpi ulnaris' main nerve branch posted the minimum average axon count,

at 543. Meanwhile, the primary nerve branches of the supinator, pronator teres, and pronator quadratus presented with average axon counts of 602, 625, and 824, respectively. Axon counts and cross sectional area for lower extremities also were also explored (Table 1).

Nerve allograft

In the past, allogenic nerve grafts need to utilize cadaveric or donor nerve tissue as an alternative to autologous nerve grafts (25). However, the disadvantage of using allografts is that it requires systemic immunosuppression lasting up to 18 months (26). In order to avoid the weak, Certain scientists have created modified nerve allografts, which have addressed certain limitations associated with allografts. Certain processing methods, such as multiple freeze–thaw cycles, radiation exposure, and prolonged storage, were utilized to render the allografts non-immunogenic (27). In certain instances, the procedure of identifying a suitable donor, preparing the graft, and subsequently scheduling the surgical intervention could be lengthy (28). Clinical data often suggests immediate surgical intervention yields better results compared to delayed nerve repair (29). Nevertheless, a research study (30) focusing on the application of processed nerve allografts (PNAs) in motor nerve repair unveiled that significant motor recovery was noted in 73% of subjects suffering from mixed and motor nerve injuries in the upper extremities, including the head and neck area. This recovery was observed regardless of whether the repair with processed nerve allografts was performed immediately or in a deferred manner. As an alternative to autologous nerve transplants, companies like Axogen are offering easily accessible frozen decellularized nerve allografts sourced from blood banks. These allografts, post-processing, are preserved at temperatures of either-80°C or 4°C. Recent research (31) suggests that the chosen preservation method could potentially influence motor recovery following nerve reconstruction, with allografts stored in cooler environments kick-starting regeneration earlier than their frozen counterparts. Moreover, the exploration of combining various processing and preservation techniques aims to create an optimal nerve allograft that boasts improved ultrastructural preservation and diminished immunogenicity (32). However, it's necessary to highlight that acellular allografts necessitate the repopulation of host cells, a process which could potentially result in a delay in axonal regeneration (33). Nevertheless, the regenerative capabilities of extended acellular nerve grafts (processed nerve allografts) are restricted, because SCs do not provide the necessary support for the formation of a basement membrane that contains extracellular matrix (ECM) proteins, which are crucial for axonal growth and the creation of endoneurial tubes that facilitate the growth of regenerating axons (34). However, in clinical applications, decellularized nerve grafts have shown comparable or even superior outcomes compared to other types of transplants. A study conducted on children with obstetrical brachial plexus injury compared acellular processed nerve allograft (ALG) with sural nerve autograft (AUG) and found no significant differences in motor strength and functional components between the two groups (35).

TABLE 1 Cross sectional area and total axon count of potential nerve donors (24).

Nerve donors	Area, mm^2	Axons, *n*
Tibialis anterior	0.255 ± 0.111	3,363 ± 1997
Extensor hallucis longus	0.197 ± 0.302	2062 ± 2,314
Flexor hallucis longus	0.234 ± 0.147	1,557 ± 735
Latissimus gastrocnemius	0.256 ± 0.105	2,352 ± 1,249
Medial gastrocnemius	0.309 ± 0.101	2,834 ± 718
Popliteus	0.309 ± 0.101	3,317 ± 1,467
Soleus	0.700 ± 0.222	4,941 ± 1994
Tibialis posterior	0.348 ± 0.253	3,039 ± 1,528
Data presented as mean ± SD		

Conduits

The rapid development of different materials as a substitute for nerve autografts in mending peripheral nerve injuries has been facilitated by advancements in biomedical techniques. Over the last few decades, research has primarily focused on the use of biomaterial-based nerve conduits for repairing peripheral nerves. These conduits can be made from various materials such as natural substances, non-degradable materials, and biodegradable synthetic material. These conduits possess a longitudinal arrangement that imitates the inherent composition of neural pathways. The conduits serve as pathways for axonal growth, directing regenerated axons to reconnect with their intended neurons. Nevertheless, the channels themselves do not significantly impact the result of neural restoration.

The successful healing of a damaged nerve relies on the gradual processof axonal regrowth and its accurate placement (26). The ideal nerve conduit should possess biocompatibility, biodegradability, flexibility, porosity, pliability, nerve inductivity, and neuroconductivity, with appropriate surface and mechanical properties (36). Most reports on series of nerve conduit reconstructions for digital nerve defects adhereto the boundary of 3 cm. Strauch et al. (37) conducted a study on rabbit sciatic nerve regeneration in which they compared the results of using vein conduits of lengths ranging from 1 to 6 cm. They found that regrowth and functionality were optimal for conduits of lengths ≤3 cm but deteriorated for lengths >3 cm. While nerve conduits are indeed widely used in the repair of certain peripheral nerve injuries, and are often considered effective for nerve gaps smaller than 3 cm, this does not mean that all types of nerve injuries adhere to this rule (38, 39). Firstly, the maximum effective length of a nerve conduit may vary depending on the type of nerve (sensory, motor or mixed) and the specific circumstances of the individual patient (39, 40). Secondly, the material, design, and manufacturing method of nerve conduit might also influence its efficacy in repairing longer nerve gaps (38, 39). Over the years, there have been notable progressions in the development of artificial nerve conduits. A diverse range of novel synthetic polymers and biopolymers have been assessed in terms of materials selection and design.

Natural materials

Extensive research has been conducted on the use of organic substances, such as muscle tissue or blood vessels for transporting materials. Natural materials provide greater biocompatibility, lower toxicity, and improved facilitation of cell migration in comparison to synthetic materials (41, 42). A study was conducted to determine whether Schwann cells migrate within nerve conduits used to repair substantial nerve gaps (43). The results revealed that endothelial cells formed a dense network of capillaries, which Schwann cells utilized for migration from both nerve stumps into the conduit. The

endothelial and Schwann cells gradually colonized the conduit. A week after the injury, a dense network of newly formed blood vessels was observed encircling both the proximal and distal stumps, with numerous Schwann cells in close proximity. The study concluded that angiogenesis was crucial within the nerve conduits, as it not only aided cell survival but also facilitated the migration of newly developed Schwann cells.

Abundant sources and a lower occurrence of acquired illnesses when collected are additional benefits of utilizing these organic substances. However, in longer nerve defects, the regenerative effects of these conduits on nerves may gradually decrease. In a retrospective case series, Jeon and colleagues assessed 11 patients, all of whom attained acceptable sensory restoration according to both SM2PD and Semmes-Weinstein monofilament examination (44). In their study, Stahl and colleagues examined 28 individuals (28) and discovered that 32% of Siemionow and Sonmez (28) participants attained a sensory improvement of 5–9 millimeters during two-point discrimination testing (45).

Peripheral nerve repair also utilizes non-biodegradable substances like silicone, elastomer hydrogel, or porous stainless steel. The drawbacks of these include inflexibility and instability, potential for causing long-term foreign body reaction and inflammation caused by the formation of scar tissue. These limitations restrict their application in peripheral nerve repair (6). In recent decades, increased attention has been directed towards naturally derived materials utilized in the development of nerve guidance conduits (NGC), peripheral nerve wraps (PNW), and membranes.

These materials should demonstrate biological functionality, sufficient compatibility with living organisms, and the ability to break down naturally (6). Moreover, it is imperative that these substances create structures that closely resemble the extracellular matrix (ECM) and facilitate accelerated tissue regeneration (15).

Collagen conduit

Studies have focused on the use of environmentally-friendly substances, including collagen, polyglycolic acid, polylactic acid, polyesters, and chitosan (46). Collagen, a structural protein, is present in the connective tissues of both humans and animals, serving as the main constituent of the extracellular matrix. Implants, such as wound dressings and artificial skin, have made use of it. Natural and biodegradable with low antigenicity, it promotes nerve sprouting, regeneration, and maintains cellular biological functions (17, 38, 47). Among its features are fibers inserted into conduit lumens to function as fillers, as well as hydrogel formulations for the delivery of cells, drugs, and growth factors (17).

A study finding (48) revealed no significant disparities in electrophysiological and hand function outcomes between the collagen conduit and microsurgical neurorrhaphy groups after a 24-month period. Yet, at the 12-month juncture, the collagen conduit group exhibited a statistically significant extension in distal motor latency and a noticeable reduction in compound muscle action potential. A broad-based recovery was observed in both motor and sensory conduction parameters from the 12th to the 24th month. The amplitudes of compound motor action potential regained about 50% of the control hand's level, the distal motor latency continued to be 50% extended, and a roughly 15% reduction was noted in the motor conduction speed between the elbow and wrist. In conclusion, the data indicates that both collagen conduit and microsurgical neurorrhaphy serve as effective strategies for peripheral nerve repair, delivering comparable outcomes at the 24-month benchmark. In a retrospective case study, Thomsen et al. (49) evaluated 10 patients with collagen conduits for nerves. In the SM2PD test, 50% of patients were classified as "excellent" or "good" in terms of sensation recovery. According to the Semmes-Weinstein monofilament test, at least 80% of patients had recovered light touch sensation. There were no complications reported.

Chitosan conduit

The second most abundant natural polymer after cellulose, chitosan is a cationic biopolymer derived from alkaline deacetylation of chitin (50, 51). Recent years have seen extensive use of chitosan in various biomedical fields (51–56), mainly because of its biocompatibility, biodegradability, low toxicity and non-immunogenicity, low cost and large availability. An analysis of chitosan hollow tubes and autologous nerve grafts for reconstruction of peripheral nerve defects was reported by Stenberg L (57). Using chitosan hollow tubes, the authors found that peripheral nerve reconstruction of sciatic nerve in rats was comparable to autologous nerve grafts, the gold standard. According to a study (58), chitosan-based nerve conduits can bridge nerve lesions up to 26 mm in the hand safely and effectively. During early regeneration, tactile gnosis improved significantly, and functional outcomes were similar to those obtained with autologous nerve grafts. Measurement of tactile gnosis using two-point discrimination was the primary outcome parameter. Additionally, a Semmens Weinstein Monofilament Test, self-assessed pain, and a patient satisfaction survey were used as secondary outcome indicators. As a result of complications associated with the chitosan nerve tube, one patient had to undergo revision surgery.

Polyglycolic acid conduit

Polyglycolic acid (PGA) is a synthetic polymer that is biodegradable and biocompatible. It has been used in various applications, including orthopedic implants, sutures, and nerve conduits (59). PGA is often used in combination with other materials to enhance its performance. Early studies on synthetic conduits were carried out with PGA. It is recycled, and considered to be more permeable and flexible compared to others, allowing diffusion to help with resorption and regeneration taking place in six months (60). In a prospective level IV case series, Mackinnon and Dellon (61) evaluated 15 patients with digital nerve gaps measuring 17 mm undergoing secondary nerve reconstruction. These researchers discovered that 53% of patients had a good recovery, 14% had a poor recovery, and 33% had outstanding sensory recovery. Sensory nerve grading scales from the British Medical Research Council were used for data collection. In order to qualify for excellent recovery, we required the static two-point discriminability level to be 6 mm, and the moving two-point discriminability level to be 3 mm. These criteria are identical to those used in the commonly used S4 grading system (S0–S4). Movement between 4 and 7 mm and static two-point discrimination between 7 and 15 mm was considered good recovery. The absence of either static or moving two-point discrimination constitutes a terrible outcome. In one case, extrusion was described by Mackinnon and Dellon5, who came to the conclusion that in some sensory lesions less than 3 cm, PGA tubes can produce outcomes

comparable to those of the traditional nerve transplant without donor morbidity.

Although several studies mention positive outcomes, some point out that PGA alone has an unfavorable degradation rate for bigger nerve gaps (>3 cm). The method employed to construct the conduit presents another issue. The surface of PGA conduits displayed poor quality when extrusion was applied (62). Additionally, when it breaks down, acidic chemicals are released, causing the pH at the implantation site to drop, which can set off an immunological response. Dehnavi et al. (63) recently reported the findings of a study on the application of a novel neural guidance channel including PGA/collagen/NBG for the enhancement of transected sciatic nerve in a rat animal model. According to the study, the manufactured conduit (bioglass conduit) is more successful in promoting nerve regeneration than PGA and PGA/collagen conduits and has the potential to enhance sciatic nerve regeneration.

The applications of biogradable materials mentioned above have shown similar effectiveness compared to traditional nerve grafts. However, it has been shown that the efficiency of nerve conduits for nerve repair is inferior to that of autograft and allograft when they are employed in digital nerve injury. Results of a systematic review and meta-analysis (64) on methods for repairing digital nerves revealed that all of them produce acceptable results. Nevertheless, autograft and allograft were both superior to conduit repair when treating digital nerve damage with gaps. For static 2-point discrimination (S2PD) outcomes, autograft repair outperformed all other forms of repair statistically, while allograft results generally exceeded neurorrhaphy and conduit repair but were not statistically significant.

Autograft repair statistically outperformed conduit repair and neurorrhaphy for Semmes-Weinstein monofilament testing (SWMF) results while being statistically comparable to allograft repair. Comparing moving 2-point discrimination (M2PD) performance to conduit repair, allograft performed statistically better. Nerve regeneration across large defect gaps has also been demonstrated to be facilitated by nerve conduit lumen fillers (15). As luminal fillers, natural polymers, such as fibrin, collagen, laminin, and agarose, are often used in solutions, hydrogels, filaments, and porous sponges due to their soft properties and biocompatibility. PNI repair and nerve conduit function can be effectively supported by these materials (65). The efficiency of luminal fillers can vary depending on the precise distance of the nerve lesion, despite the fact that many of them have been described. The fundamental criterion for them from the standpoint of clinical translation is that they be conveniently producible and injected into the conduit (65).

Conduits with supportive cells

The nerve conduits have recently been improved using a variety of research strategies that speed up nerve regeneration and bridge wide nerve gaps. Supporting cells have been added to nerve conduits, which has attracted the greatest research attention (66, 67). Cell-based therapy is an effective method for mending lengthy nerve defects and can foster the regeneration of peripheral nerves. There are several cell types of interest being studied in this project, including SCs, Olfactory ensheathing cells (OECs), bone marrow-derived mesenchymal stem cells (BMSCs), and adipose-derived mesenchymal stem cells (ADSCs) (68). Augmenting conduits with cells, such as Schwann cells or stem cells, can enhance nerve regeneration by providing cellular support, guiding new nerve fiber growth assisting in myelination, and modulating immune responses (69, 70).

Schwann cells are the most significant and natural seed cells for the healing of peripheral nerve damage. Because they are both structural and functional cells and play a critical role in peripheral nerve regeneration. SCs produce neurotrophic factors such as Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor, platelet-derived growth factor, and neuropeptide Y. These neurotrophic components may help injured axons survive longer and encourage their regeneration. It has been demonstrated that transplanting SCs seeds into a nerve conduit can improve axonal regeneration (71, 72). The utilization of autologous stem cells in clinical settings is limited due to various factors, such as the occurrence of morbidity at the donor site, challenges associated with acquiring and rapidly expanding a substantial quantity of stem cells, the requirement for sequential surgical procedures with short intervals (one for harvesting and expanding stem cells and another for nerve gap repair), and the decline in stem cell numbers with advancing age (73). There is a need for some readily available sources of seed cells having SCs properties. The current focus of cell-based therapy research for peripheral nerve injuries is on finding other approaches to SC usage.

It has been demonstrated that astrocytes and SCs share characteristics with olfactory ensheathing cells. Like SCs, OECs produce a variety of neurotrophic substances. In customary conditions, oligodendrocyte precursor cells (OECs) are present in both the peripheral and central nervous systems. Oligodendrocyte precursor cells (OECs) have been employed in clinical trials for the purpose of treating spinal cord lesions in individuals, as well as improving functional recovery in adolescents and young children affected by cerebral palsy. Until recently, their regeneration-promoting function for the peripheral nervous system was unknown (74, 75). The transplantation of olfactory ensheathing cells (OECs) at the time of microsurgical intervention was found to enhance axonal regeneration and improve functional outcomes, as assessed by the sciatic functional index (SFI), in the adult rat sciatic nerve (75). OECs exhibit greater migratory capabilities compared to SCs, and unlike SCs, they do not accumulate proteoglycans, which can result in the collapse of growth cones. As a result, OECs rather than SCs may make a better choice for cell-based regenerative therapy. However, more preclinical and clinical studies are required before OEC transplantation can be used to treat human peripheral nerve injuries (76). Due to their rapid multiplication and ability to integrate into the host in an immunologically safe manner, stem cells are a promising clinically viable alternative to cell-basal therapy for PNI (77). Although embryonic stem cells have the potential to develop into any form of cell, including SC, there are moral questions regarding their usage in medicine. Therefore, researchers have looked for an effective replacement for embryonic stem cells. A more appealing alternative for stem cell therapy is adult stem cells.

A variety of adult tissues can be used to produce mesenchymal stem cells (MSCs), including skin, adipose tissue, bone marrow, and umbilical cord blood. The ability of MSCs to develop into neurons makes them a potential therapeutic target for neurogenesis and neuroprotection. The impact of pre-induced mesenchymal stem cells (MSCs) coated cellulose/collagen nanofibrous nerve conduits on facial nerve regeneration was investigated in a rat model through *in vitro*

and *in vivo* experiments, as determined by Cho et al. (78) in their published study.

The findings demonstrated that the regeneration parameters were greatly enhanced by the extra coating of pre-induced MSCs in the cellulose/collagen nanofibrous conduit. According to functional and histological evaluations, Group II, which underwent treatment with the pre-induced MSC-coated cellulose/collagen nanofibrous nerve conduit, exhibited the highest level of recuperation. In each of the three groups, the nerve gap was effectively restored in every rat, and after a period of eight weeks following the surgical procedure, observable degradation of the cellulose/collagen nanofiber commenced. Group II showed a slightly larger nerve diameter than the control group, but there were no neuromas formed, and there was no statistically significant difference in nerve thickness.

Studies have been done on the use of brain-derived neural stem cells (NSCs), in addition to MSCs, in the regeneration of damaged peripheral nerves. An NSC-loaded silicon conduit, which spans the 10-mm gap between the nerve stumps in the study (79), was used to investigate the effects of neural stem cells on sciatic nerve injury in rats. The findings of this study indicate that neural stem cells (NSCs) possess the potential to promote the regeneration of the injured sciatic nerve. Consequently, incorporating NSCs into clinical trials for individuals suffering from nerve injuries could potentially yield improved clinical outcomes, as NSCs have the ability to enhance the expression of nerve growth factor (NGF) and hepatocyte growth factor (HGF) within the sciatic nerve.

Cell-based therapy holds substantial promise, but significant challenges persist in its application in current and future clinical contexts. One such challenge is ensuring the safety of cell transplantation, particularly concerning potential adverse reactions and issues arising in the brain, especially in the case of stem cell transplantation. These issues warrant further investigation. Another obstacle is the extended waiting period required to prepare these autologous cell sources, which could potentially result in missing the critical treatment window (68, 69). SCs and OECs appear to be the most promising due to their inherent roles in nerve function, but limitations include their availability and inconsistent results (80, 81). Mesenchymal stem cells (MSCs) offer a convenient source of cells, but their regenerative capabilities require further exploration (82). The potential of combinatorial approaches utilizing multiple cell types is also under investigation. More comparative research is still necessary to identify the optimal cell therapy approach (see Table 2).

A study (85) embarks on an exploration of chemical substances that could potentially foster peripheral nerve regeneration. It seeks to unravel methodologies that could amplify the capacity for nerve repair and regeneration. In addressing this complex issue, the research team meticulously combed through existing literature and experimental data, distilling a selection of chemical agents believed to be conducive to nerve healing, such as neurotrophic and growth factors, and cytokines. The conversation further delves into the realm of cell and tissue engineering therapies, spotlighting the use of nerve scaffolds and conduits, and the innovative application of stem and nerve cells. The culmination of this research is the illumination of clinical applications and future investigative paths, advocating for multidisciplinary and integrated treatment approaches and the exploration of varied therapeutic strategies tailored to different nerve injury scenarios. These research efforts aim to advance the field by enhancing the capacity for nerve regeneration and fostering the progression of nerve repair.

The field of nerve regeneration is witnessing significant advancements in the design and application of implantable biomaterials. Key strategies include the integration of neurotrophic factors, chemical guidance agents, and auxiliary solute factors to foster nerve tissue repair, as well as pioneering bioartificial nerve conduits as novel therapeutic avenues (86). Moreover, the refinement of therapeutic proteins through precise dosage control, optimized release kinetics, and targeted delivery is gaining momentum. Research is also delving into the distinct patterns of angiogenesis and the regeneration across different nerve fiber types. Collectively, these innovations aim to bolster the success rate of nerve regeneration therapies and present enhanced solutions for clinical deployment.

Technologies to stimulate nerve regeneration

Electrical stimulation

Electrical stimulation (ES) improves the intrinsic ability of neurons to regenerate in a clinically applicable manner (87, 88). Studies on the peripheral nervous system strongly imply that electrical stimulation has benefits for regenerating sensory and motor neurons (89). In one investigation, DRG cells from chick embryos exposed to an electric field exhibited enhanced neurite development (90). The enhanced growth of peripheral neurons is believed to be attributed to the upregulation of nerve growth-associated genes (such as GAP-43, preprotachykinin A, VEGF, NGF, ANGPT1, CCL11, VEGFC, and Myc proto-oncogene) (91–94), neurotrophic factors such as BDNFs

TABLE 2 Summarization of various nerve conduits (39, 83, 84).

Material	Advantages	Disadvantages	Animal trials	Clinical application
Vein grafts	Biocompatible, natural structure	Risk of adhesion/Compression	Dog, primate	Clinical use as grafts
Silicone	Inert, flexible stable	Not biodegradable	Rat, primate	FDA approved
Collagen	Biodegradable, supports regeneration	Potential Immunogenicity, poor strength	Rat, rabbit dog	Limited
Chitosan	Biocompatible antimicrobial	Poor mechanical strength	Rat, rabbit, dog	None
Polyglycolic acid (PGA)	Biodegradable, available in fibers/tubes	Acidic degradation products	Rat, rabbit, dog, monkey	Limited
Nerve conduits with supportive cells	Biocompatible, Supports Regeneration, secrete neurotropic and growth factors	Cell transplant safety, unfavorable reactions	Rat	Limited

(95), and glial cell line-derived neurotrophic factor (GDNF) (96) in dorsal root ganglia (DRGs). In an randomized controlled trial (RCT) (97), ES demonstrated significant postoperative improvements in all sensory modalities within 5–6 months for patients ($n = 16$) with completely transected digital nerves compared to those who underwent surgery alone (control subjects, $n = 15$). The cold detection threshold for ES patients nearly normalized, achieving 14.33 ± 0.46 just-noticeable difference (JND) units, which was significantly lower than the control group's 17.22 ± 0.44 JND ($p < 0.001$). Enhancements were also observed in tactile discrimination and pressure detection. Furthmore, the static two-point discrimination in ES patients improved to 4.71 ± 0.90 mm, notably better than the control group's 8.69 ± 1.05 mm ($p < 0.001$). The duration of electrical stimulation can indeed impact the regenerative capacity of neurons. This is particularly relevant in the context of peripheral nerve injuries, where electrical stimulation has been shown to enhance the intrinsic molecular pathways involved in regeneration, leading to accelerated axonal outgrowth and reinnervation of target tissue (98). However, the timing of electrical stimulation also plays a crucial role. For example, immediate onset of electrical stimulation following surgery has been found to improve functional recovery in cases of large nerve defects in diabetic animals (99). In the field of tissue engineering, electrical stimulation has demonstrated its influence on the behavior of adipose tissue-derived progenitor cells (ATDPCs) in 3D cultures. It promotes the formation of well-connected cellular networks and reduces the diameter of tissue constructs, all while maintaining cell viability and connectivity (100).

In summary, research has demonstrated that electrical stimulation (ES) plays a significant role in promoting axonal regeneration and functional recovery, as well as modulating the biological activity of Schwann cells (SCs), which are essential for nerve regeneration. ES enhances this process by promoting neuronal differentiation, proliferation, neurite outgrowth, and axonal elongation/regeneration, leading to varying degrees of functional recovery in both animals and humans (101). Furthermore, ES influences the behavior of SCs, encouraging their migration, adhesion, elongation, and enhancing their neuronal expression. Interestingly, some studies have found that a direct current of 10 mV is particularly beneficial for the growth and proliferation of SCs (102). It's important to note, however, that although these studies provide valuable insights, the optimal physical parameters for electrical stimulation, including frequency, intensity, and duration, may vary depending on the specific circumstances and are still subjects of ongoing research (103). Therefore, further studies are needed to establish standardized protocols for the application of electrical stimulation in the context of neuronal regeneration.

Optogenetic stimulation

In neuroscience engineering, optogenetic stimulation has become a powerful technique. Its great selectivity and lack of invasiveness may exceed the stimulation methods used by its competitors. According to the evidence from various groups, optogenetic activation encourages neurite development (104). Optical pulses and exposure time influence neurite outgrowth and axonal regeneration (104). The study conducted by Park et al. (105) involved the examination of optogenetics, specifically utilizing transgenic Thy1-ChR2-YFP mice expressing ChR228 to generate light-sensitive entire DRGs. The objective of this investigation was to assess the potential enhancement of neurite outgrowth through optically induced neural activity. The researchers explored the impact of various optical stimulation frequencies and exposure durations on neuronal development. In addition, they discovered that the development of optically sensitive neurites was enhanced and skewed in one direction, demonstrating the cell-specific targeting of optogenetics. Indeed, a significant challenge in the application of optogenetic stimulation is its restricted penetration depth, a factor that becomes particularly limiting when addressing peripheral nerve injuries. The ability of light to penetrate tissue is inherently limited, confining the use of optogenetics primarily to superficial structures unless invasive techniques are employed to direct light towards deeper tissues. This constraint becomes especially formidable when trying to stimulate peripheral nerves, which often reside deep within the body. Consequently, while optogenetics presents substantial potential for investigating and treating a range of neurological conditions, its utility in the context of peripheral nerve injuries is presently constrained by the limited depth of light penetration (106).

Conclusion

For nerve reinnervation, autografts continue to be superior to all bioengineered grafts. However, the drawbacks that result from this point to the requirement for the creation of substitute strategies. In short nerve gaps, the performance of nerve guide conduits made from various materials is comparable to autologous nerve grafts. Most of the bioengineering approaches have been found to focus only on the development of nerve conduits that promote neuronal guidance and growth.

Repairing long nerve gaps remains a significant challenge in the field of nerve regeneration. While there have been advancements in the development of nerve conduits made from various novel materials and the addition of supportive cells, these methods have not yet resulted in a breakthrough for long nerve gap repair.

Additionally, peripheral nerve regeneration techniques using electrical, optogenetic, and magnetic stimulation are showing promise. One possibility is electrical stimulation. However, the standardized parameters for ES have not been established.

While the precise mechanisms underlying the beneficial effects of magnetic stimulation on neurons are not fully understood yet, this technique holds promise as a non-invasive therapy for various neuronal disorders. Furthermore, combining nerve conduits with other peripheral nerve regeneration techniques, such as electrical or magnetic stimulation, could potentially improve the outcomes of long nerve gap repair. However, further research is still needed to optimize these combination approaches, fully elucidate their mechanisms of action, and translate the findings to viable clinical therapies.

Author contributions

XZ: Writing – original draft. YD: Writing – original draft. AA: Writing – review & editing. HZ: Writing – review & editing. SE:

Writing – review & editing. VK: Writing – review & editing. MA: Writing – review & editing. SA: Writing – review & editing. HL: Writing – review & editing. CW: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The study was funded by Zhejiang Provincial Natural Science Foundation Academic Exchange Program (grant number: LS21H0600010). The funding bodies had no role in the design of the study; in the collection, analysis, interpretation of data and in drafting the manuscript.

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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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 29 January 2024
DOI 10.3389/fneur.2024.1325464

OPEN ACCESS

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RECEIVED 21 October 2023
ACCEPTED 11 January 2024
PUBLISHED 29 January 2024

CITATION
Chen Q, Zou X, Xia Y, Hu Y, Chen C and Zheng P (2024) B-Mode ultrasound imaging in diagnosing carpal tunnel syndrome: an auxiliary diagnostic tool for hand surgeons. *Front. Neurol.* 15:1325464. doi: 10.3389/fneur.2024.1325464

B-Mode ultrasound imaging in diagnosing carpal tunnel syndrome: an auxiliary diagnostic tool for hand surgeons

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Objective: The purpose of this article is to explore the effectiveness of B-Mode ultrasound as an auxiliary diagnostic tool for carpal tunnel syndrome (CTS). It aims to demonstrate the advantages of B-Mode ultrasound, including its non-invasive nature and its ability to provide real-time imaging, in localizing nerve compression and predicting postoperative outcomes.

Methods: The study included 40 patients who were subjected to preoperative B-ultrasonography. The approach focused on evaluating the consistency of B-Mode ultrasound results with intraoperative findings. It also assessed the importance of employing standardized imaging techniques and emphasized the need for cooperation between hand surgeons and sonographers for accurate diagnosis.

Results: B-Mode ultrasound findings in the study were consistent with intraoperative observations, indicating its reliability. Additionally, B-Mode ultrasound was able to identify other anatomical abnormalities within the carpal canal that may contribute to CTS symptoms, such as persistent median arteries, median nerve bifurcation, and space-occupying lesions like cysts and tumors.

Conclusion: The article concludes that B-Mode ultrasound should be considered a valuable supplementary diagnostic tool for CTS, particularly in instances where clinical signs and electrophysiological studies do not offer clear results. However, it should not replace established diagnostic methods for CTS.

KEYWORDS

B-ultrasound diagnosis, flattening ratio, carpal tunnel syndrome (CTS), carpal canal volume, surgery

Introduction

Carpal tunnel syndrome (CTS) is the most common disease that compresses the nerves of the upper limb and causes neuropathy of the limb. Common causes of CTS include thickening of the transverse carpal ligament or a reduction in carpal tunnel volume. Surgical incision of the transverse carpal ligament and median nerve decompression is the most common surgical procedure (1, 2). In recent years, with the improvement of B-Mode ultrasound equipment and doctors' technology, B-Mode ultrasound has emerged as a valuable tool for evaluating CTS, offering unique advantages. As a convenient examination method, B-Mode ultrasound can be performed immediately on the same day in the outpatient department, is non-invasive, and is cost-effective, making it well-received by patients. It can measure the carpal tunnel volume, track changes in the median nerve's circumference, assess the stenosis or enlargement of the median nerve, pinpoint the location of nerve entrapment, and facilitate the statistical analysis of nerve changes before and after surgery. Compared to other examinations, B-Mode ultrasound has a prominent advantage in distinguishing between the acute and chronic phases of CTS during sonographic examinations (3). During the acute phase, there can be extravasation of fluids within the endoneurial compartment, which occurs due to the disruption of the blood-nerve barrier and increased permeability of the endoneurial capillaries. The fibrous structure of the endoneurium makes it porous and ineffective as a barrier to the passage of chemicals. As a result, intra-fascicular edema leads to a localized, hypoechoic swelling that can be observed during a ultrasound examination (4). During the chronic phase, Schwann cells are gradually replaced by fibroblasts that produce collagen fibers, and the endoneurial edema is gradually replaced by fibrotic tissue. As a result, the echogenicity of the nerve fascicles may gradually increase, leading to a hyperechoic texture (5). Additionally, dynamic ultrasound enables the evaluation of the median nerve's mobility or gliding within the carpal tunnel during the post-operative phase (6). This modality is particularly useful for assessing the success of median nerve decompression following a minimally invasive carpal tunnel release procedure (7). By instructing the patient to flex and extend their fingers, clinicians can observe the median nerve's dynamic movements (7). In postoperative ultrasonography studies of the carpal tunnel, the most commonly analyzed parameters include the median nerve's cross-sectional area at its widest point along with pre- and post-operative comparative measurements of these values (8).

Although electromyography is still the gold standard for the diagnosis of CTS, B-ultrasonography is being used more and more widely in clinical diagnosis (9, 10). This article reports our experience in diagnosing CTS using B-Mode ultrasound as an additional tool. This included, history and physical examination, electromyography, preoperative B-Mode ultrasound findings, intraoperative direct control, and postoperative findings. To determine the potential role of B ultrasonography in diagnosing CTS.

Materials and methods

Forty newly diagnosed patients, 12 male and 28 female, average 40.2 aged from 34 to 56 years old, were randomly selected to visit our hospital. Six cases had bilateral symptoms and 34 patients had unilateral symptoms. All patients Complain of numbness of thumb, index finger and middle finger and underwent comprehensive history, physical examination, electrophysiological diagnosis, and B-ultrasonography before operation. Six patients underwent bilateral surgeries for transverse carpal ligament release, and the rest of the patients underwent unilateral surgery. The postoperative follow-up was 10 to 18 months.

Group A was formed by randomly selecting 20 patients from a pool of 34 individuals who were scheduled to undergo unilateral surgery and the diagnosis of CTS was confirmed during surgery. Group B consisted of 20 healthy volunteers randomly selected. The details of Flattening ratio of the median nerve (MN), cross-sectional area of the MN, thickness on the cross-section in both groups are recorded. The details were compared to demonstrate the significance of B-mode ultrasound in diagnosing CTS (Table 1).

Criteria for Diagnosis of Carpal Tunnel Syndrome: (1) Complaints of numbness in the thumb, index finger, and middle finger, consistent with median nerve sensory distribution, (2) Physical examination tests are positive, such as Tinel's sign, Phalen's maneuver, Durkan's test, (3) Electrophysiological Tests: Slowing of median nerve sensory and motor conduction velocity across the carpal tunnel, and (4) Ultrasound Imaging: increased cross-sectional area of the median nerve at the proximal carpal tunnel and Swelling of the median nerve or changes in its echotexture.

Exclusion Criteria: (1) Symptoms0020consistent with other conditions such as cervical radiculopathy, peripheral neuropathy, or tenosynovitis, (2) Previous carpal tunnel release surgery on the affected hand, and (3) Severe trauma to the affected wrist or hand.

In this study, we utilized SPSS software (version 27) for data analysis and statistical processing. To assess the differences and correlations between research variables, we employed the *T*-test.

Instruments and methods

Siemens ACUSON SEQUOIA color ultrasonic diagnostic instrument with linear array probe was used at a frequency of 5–12 MHz. Routine ultrasound examination: The subjects were seated, the upper arm was placed flat on the examination bed, the palm was up, and the wrist joint was slightly extended. The probe was placed vertically on the proximal end of the carpal tunnel. The ulnar lentiform bone, radial scaphoid bone and posterior lunate bone were used as bone markers. The flattening rate of median nerve was calculated (left and right diameters/anteroposterior diameters).

TABLE 1 Sonographic findings for two groups.

	Group A (n = 20 wrists)	Group B (n = 20 wrists)
Flattening ratio of the MN (FR)	2.95 ± 0.42	2.41 ± 0.23
Cross-sectional area of the MN (CSA, cm^2)	0.15 ± 0.04	0.08 ± 0.02
Thickness on the cross-section of the MN (TCL, mm)	4.45 ± 0.38	3.52 ± 0.51

Group A vs. Group B, p-value<0.05. Group A: patients with CTS; Group B: control group.

Additionally, the cross-sectional area also measured (Measured structures include nerve fascicles, epineurium, and perineurium). Keeping the fingers semi-extended in a neutral position. A high-resolution ultrasound scanner with a linear array transducer, with a frequency of around 13 MHz, is used to measure the CSA at the carpal tunnel inlet.

The surgeon and attending radiologist discussed in detail the B-Mode ultrasound images of each case, combined with relevant clinical data, structural anatomy, and previous radiography, to arrive at the final interpretation of the B-Mode ultrasound imaging study. The median nerve was examined by carpal tunnel using tourniquet under general anesthesia or brachial plexus anesthesia in 40 patients. After the anesthesia takes effect, the patient is laid on the operating table. The upper arm is positioned flat on a support, with the palm facing up and the wrist joint slightly extended. In the surgical area, routine disinfection was performed and sterile drapes were placed. A small incision is made in the palm of the hand near the wrist. The transverse carpal ligament is visualized by carefully dissecting through subcutaneous tissue and palmar fascia. The transverse carpal ligament is carefully cut, releasing the pressure on the median nerve.

Intraoperative findings were observed subjectively and recorded with photos or images and score according to symptoms during postoperative follow-up.

Results

The history and physical findings of all 40 patients suggested persistent compression median neuropathy. All patients complained of persistent numbness. In 40 cases, symptoms progressed to areas where patients complained of persistent numbness. Other symptoms include pain and weakness. Postoperative symptoms disappeared completely in 35 patients and numbness and tingling were relieved in 5 patients, but there were still varying degrees of pain.

Preoperatively, sonographic imaging was instrumental in diagnosing carpal tunnel syndrome in our patient cohort. B-Mode ultrasound consistently identified abnormalities within the carpal tunnel, such as swelling and deformation of the median nerve or a reduction in the surrounding space, which could indicate the presence of a persistent compression neuropathy. These findings were present in all 40 patients and were found to accurately reflect the intraoperative state of the median nerve. Postoperatively, sonographic images demonstrated a reduction in median nerve swelling and a return to normal carpal tunnel architecture in 35 patients, correlating with the resolution of symptoms. In the remaining five patients, although there was an improvement in nerve morphology, minor persistent changes were observed, aligning with the patients' residual symptoms.

Surgical exploration and decompression of the carpal tunnel revealed a consistent pattern of median nerve compression among the patients studied. The intraoperative findings confirmed the preoperative sonographic observations, with the transverse carpal ligament contributing to nerve compression in all cases. During surgery, the ligament was released, which was expected to alleviate the pressure on the median nerve. For the majority of patients, this procedure was successful, as evidenced by the resolution of preoperative symptoms. However, in five cases, despite the release, patients experienced ongoing pain post-surgery, suggesting that while the mechanical aspect of nerve compression was addressed, other factors contributing to pain may persist or develop.

Electrophysiological studies conducted before surgery were consistent with the diagnosis of carpal tunnel syndrome in all patients. Nerve conduction studies and electromyography confirmed the presence of median neuropathy characterized by slowed conduction velocities and altered sensory and motor responses. These findings complemented the clinical presentation of numbness, pain, and weakness in the areas innervated by the median nerve. Postoperative electrophysiological assessments showed significant improvement in nerve conduction, which was in line with the symptomatic relief reported by 35 patients. The remaining five patients showed some electrophysiological improvement, which was not as pronounced, paralleling their partial clinical improvement (Figures 1, 2).

Discussion

Carpal tunnel syndrome (CTS) is a condition that falls under the category of cumulative trauma disorder (CTDs) and is the most common compression neuropathy of the upper extremities At least 50 percent of cases usually occur in patients between 40 and 60 years of age. Although no research has adequately documented the harmful effects of CTS on the workforce, it is indeed so well known that CTDS are caused by repetitive forceful movements of the upper limbs and, as a result, are relatively common in the workplace (11). Other elderly people are also susceptible to carpal tunnel syndrome after holding grandchildren for long periods of time. Diagnosis of carpal tunnel syndrome depends on history, physical examination, and electrophysiological examination, with electrophysiological examination being the gold standard (12, 13). The application of MR In the diagnosis of carpal tunnel syndrome has also been reported, but it is accompanied by shortcomings such as slow appointment, high cost, and non-real-time measurement (14). With the development of high resolution B-Mode ultrasound, B-Mode ultrasound is more and more accepted by hand surgeons as an auxiliary diagnostic tool for carpal tunnel syndrome. It has the advantages of rapid and non-invasive examination, which can identify the location of nerve entrapment before surgery, and predict the postoperative effect of carpal tunnel release through data analysis (15).

A notable limitation of this study is the small sample size, which may not fully represent the broader population and could limit the generalizability of the findings. Our findings support the utility of preoperative B-Mode ultrasound, which revealed anatomical changes correlating with persistent median nerve symptoms in each of our 40 cases. These changes included a thickened transverse carpal ligament, often exceeding 5 mm, and various manifestations of fascicle edema to the median nerve. Enhancements in nerve echogenicity were also noted, suggesting alterations in nerve characteristics due to compression. Additionally, instances of proximal neural edema exceeding 2 cm were observed. The median nerve flattening rate, measured by comparing the left/right and anteroposterior diameters, provided a precise indicator of compression when showing a statistically significant difference from the healthy side. Moreover, volume changes in the carpal tunnel, particularly at the pisiform and hamate bone levels where the cross-sectional area is less than 0.1 cm^2, were critical in our assessments. Our standardized imaging techniques and the collaboration between hand surgeons and sonographers have

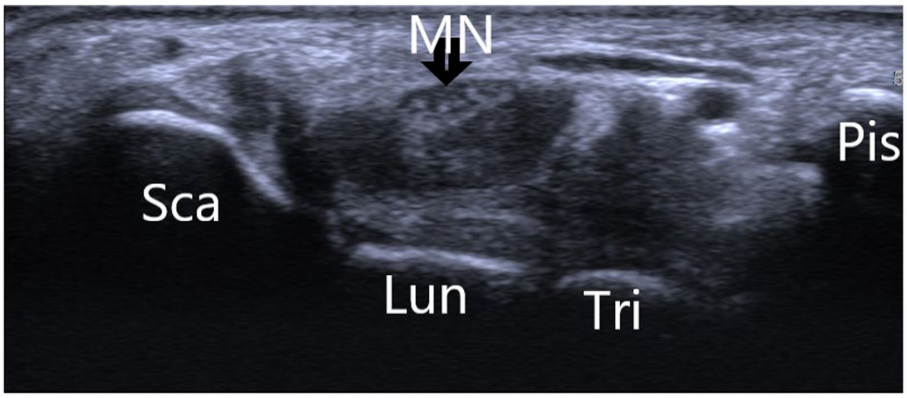

FIGURE 1
Showing the normal wrist B-ultrasonography image of a 30-year-old asymptomatic male volunteer. *Sca, scaphoid bone; Lun, lunate bone; Tri, triquetral bone; Pis, pisiform bone; MN, median nerve.

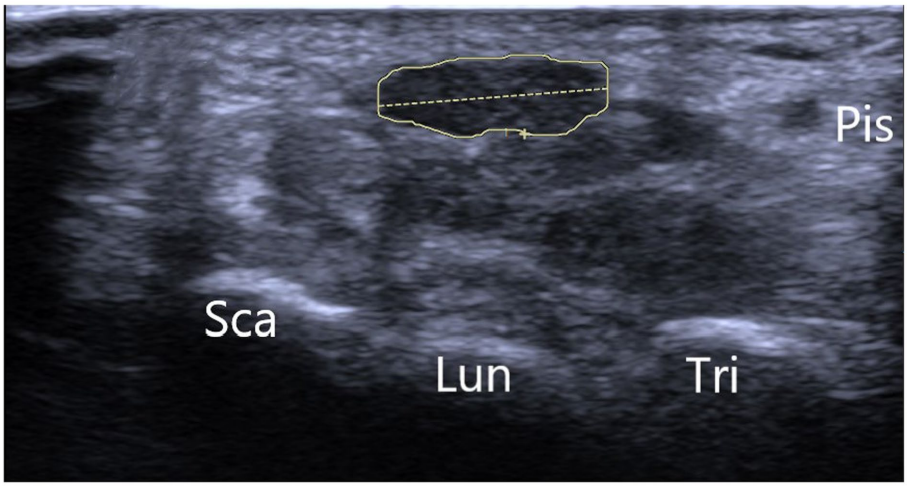

FIGURE 2
Depicting the B-ultrasonography image of typical carpal tunnel syndrome. *Sca, scaphoid bone; Lun, lunate bone; Tri, triquetral bone; Pis, pisiform bone.

been paramount. For accurate diagnosis, patients should have symptoms lasting more than a month, high-resolution ultrasound equipment must be utilized, and surgeons should engage in detailed discussions with sonographers regarding clinical anatomy (Figure 3).

Images are made by the radiologist to ensure that the entire extent of the carpal tunnel and the transverse ligament are visible. As previously stated, Presazzi A et al. showed a direct relationship between preoperative B-Mode ultrasound and intraoperative findings in 8 patients who did not have carpal tunnel release. We were able to demonstrate a direct relationship between preoperative imaging abnormalities and the scanning and location of intraoperative anatomic compression. We are not saying that ultrasound should replace the standard diagnosis of carpal tunnel syndrome. Ultrasound can also detect abnormal anatomical structures in carpal canal, such as persistent median artery, median nerve bifurcation, variation of motor and palmar cutaneous branches of median nerve, retrograde palmar longus muscle, Martin-Gruber anastomoses, Limburg-Comstock syndrome, etc. (15).

Space-occupying lesions in the carpal canal are also one of the causes of CTS, such as ganglion cysts, fibromas, tenosynovitis and tumors involving the median nerve itself. Depaoli et al. reported two patients with CTS who still had local pain and paresthesia after decompression surgery. Ultrasound examination showed that there was a schwannoma related to the median nerve in the carpal canal, and the patients' symptoms were relieved after surgical resection (16).

Conclusion

It can be seen that ultrasonography plays an important role in the etiological diagnosis of CTS. Currently, most sonographers have limited experience in interpreting median nerve compression and neuropathic images of CTS, which also limits the therapeutic techniques of this method. However, we believe that ultrasound can be useful as an adjunct to hand surgeons especially when the physical examination of CTS and the electrodiagnostic evidence is equivocal.

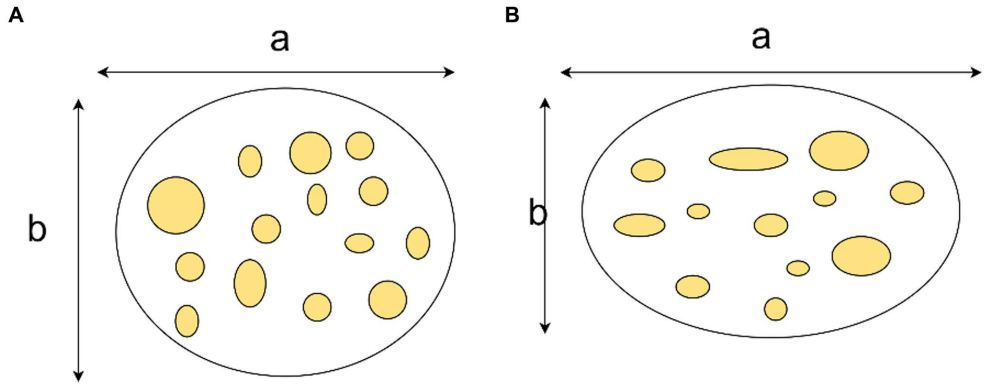

FIGURE 3
Demonstration of median nerve flattening rate. The median nerve flattening rate equals the ratio of the transverse diameter (a) to the anteroposterior diameter (b). **(A)** Present a normal median nerve. **(B)** Show a median nerve with CTS.

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.

Ethics statement

The studies involving humans were approved by Ethical Review Board of Zhejiang Provincial People's Hospital. 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

QC: Writing – original draft. XZ: Writing – review & editing. YX: Writing – review & editing. YH: Writing – review & editing. CC: Writing – review & editing. PZ: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Key Projects of Medical and Health Science and Technology Project of Zhejiang Province (WKJ-ZJ-2101). Zhejiang Traditional Chinese Medicine Research Program (Grant Number 2019ZA008).

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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frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 08 March 2024
DOI 10.3389/fneur.2024.1330224

OPEN ACCESS

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RECEIVED 30 October 2023
ACCEPTED 22 February 2024
PUBLISHED 08 March 2024

CITATION
Xu G, Zou X, Dong Y, Alhaskawi A, Zhou H, Ezzi SHA, Kota VG, Abdulla MHAH, Alenikova O, Abdalbary SA and Lu H (2024) Advancements in autologous peripheral nerve transplantation care: a review of strategies and practices to facilitate recovery. *Front. Neurol.* 15:1330224. doi: 10.3389/fneur.2024.1330224

Advancements in autologous peripheral nerve transplantation care: a review of strategies and practices to facilitate recovery

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Autologous peripheral nerve transplantation, a pioneering technique in nerve injury treatment, has demonstrated remarkable progress. We examine recent nursing strategies and methodologies tailored to various anatomical sites, highlighting their role in postoperative recovery enhancement. Encompassing brachial plexus, upper limb, and lower limb nerve transplantation care, this discussion underscores the importance of personalized rehabilitation plans, interdisciplinary collaboration, and innovative approaches like nerve electrical stimulation and nerve growth factor therapy. Moreover, the exploration extends to effective complication management and prevention strategies, encompassing infection control and pain management. Ultimately, the review concludes by emphasizing the advances achieved in autologous peripheral nerve transplantation care, showcasing the potential to optimize postoperative recovery through tailored and advanced practices.

KEYWORDS

peripheral nerve injuries, autologous nerve transplantation, nursing care, functional impairments, rehabilitation

Introduction

Peripheral nerve injuries (PNIs) pose a significant clinical challenge, often leading to severe functional impairments and disability (1, 2). Treatment options for peripheral nerve injuries (PNIs) vary based on the specific type and severity of the injury, including surgical repair, nerve transplantation, physical therapy, medication, and rehabilitation aids (3–5). Autologous nerve transplantation, also known as nerve grafting, is a surgical procedure that entails using a segment of nerve tissue to bridge the gap between the ends of a damaged nerve.

While autologous nerve grafts are considered the gold standard due to their exceptional regenerative capacity, they are constrained by donor site length limitations and the potential for neuroma formation. Autologous nerve transplantation primarily finds application in repairing peripheral nerve injuries that leave gaps too extensive for simple nerve end suturing. Critical factors such as nerve parameters (e.g., location, length, and shape), donor nerve cross-sectional area, and its compatibility with the damaged nerves need careful consideration during the donor selection phase. Patient preferences also demand assessment since nerve harvesting may result in impairment, attenuation, or complete loss of function at the donor site in a significant number of cases. Consequently, autologous nerve transplantation remains the cornerstone for treating segmental nerve defects that are unsuitable for primary repair. In a study focusing on eight patients with complete high sciatic nerve injuries featuring extended defects (6) (>10 cm), a surgical intervention was performed involving autologous nerve grafting using the tibial nerve. Postoperative assessments conducted over a 36-to-60-month follow-up period included muscle strength and sensory function evaluations. Motor recovery was classified as "good" or "very good" (M3–M4) in 62.5% of the cases, with five out of the eight patients exhibiting such improvement. However, plantar flexion remained suboptimal in the remaining three patients. Sensory function was similarly encouraging, with "good" or "very good" (S2–S3) recovery noted in six patients, while two patients experienced "inadequate" (S4) sensory outcomes. Data on 4,331 patients who underwent reconstructive surgery for peripheral nerve abnormalities between 2015 and 2020 was gathered for a study (7). The results showed that after 2018, allograft utilization grew dramatically from 21.5 to 29.6%, while conduit utilization reduced from 60 to 54.7% and nerve autograft utilization dropped from 18.6 to 15.8%.

The rapid development of different materials as a substitute for nerve autografts in mending peripheral nerve defects has been facilitated by advancements in biomedical techniques. Research has focused on the use biomaterial-based nerve conduits for repairing the peripheral nerve defects.

Compared to autologous nerve grafting, nerve conduit repair of nerve defects eliminates the risk of donor site morbidity and achieves comparable results (8). However, its use is constrained by an optimal length, which may limit its applicability in certain scenarios. Studies found that regrowth and functionality were optimal for conduits of lengths ≤3 cm but deteriorated for lengths >3 cm (9).

In order to speed up nerve regeneration and bridge wide nerve gaps, supporting cells, such as stem cells or growth factors, have been added to the nerve conduits, which have attracted the greatest attention. Cell-based nerve conduits holds substantial promise in studies. However, significant challenges exist in its application in current and future clinical contexts. One is ensuring the safety of cell transplantation. Another obstacle is the extended waiting period required to prepare these autologous cell sources, which could potentially result in missing the critical treatment window.

To expedite nerve regeneration and span extensive nerve gaps, adjunctive cells, like stem cells or growth factors, have been incorporated into nerve conduits, garnering considerable interest (10). Cell-based nerve conduits exhibit considerable potential in research (11). Nonetheless, their clinical application, both present and prospective, is beset with noteworthy hurdles. Ensuring the safety of cell transplantation stands as one primary challenge. Another significant obstacle is the protracted preparation time for these autologous cell sources, which may risk surpassing the crucial treatment window (12, 13) (Figure 1).

Recent years have witnessed remarkable progress in the field of autologous nerve transplantation. Advances in surgical techniques, nerve graft harvesting, and postoperative care have contributed to improved outcomes and enhanced nerve regeneration. Nursing care plays a pivotal role in the success of autologous nerve transplantation, encompassing preoperative evaluation, meticulous surgical assistance, and comprehensive postoperative management. From monitoring nerve regeneration to implementing tailored rehabilitation plans, nursing care ensures the best possible outcomes for patients undergoing this intricate procedure. This review aims to explore the nuances of nursing care in autologous peripheral nerve transplantation across different anatomical sites. By examining the latest strategies and methodologies, we seek to shed light on how nursing care can optimize postoperative recovery and empower patients to regain functional independence.

Brachial plexus nerve transplantation care

Brachial plexus nerve transplantation is commonly used for severe upper limb nerve injuries, often resulting from high-energy traumas like car crashes, predominantly affecting young adults. The avulsion of the brachial plexus nerve origins causes significant motor neuron destruction and muscle function impairment (14–16). Traumatic total brachial plexus avulsion (TBPA) presents difficulties as extra plexal nerves must regulate functions for the shoulder, elbow, wrist, and hand. Nerve transfer and free functional gracilis transplantation (FFGT) are current therapies, but complete hand function restoration remains a challenge (17). Recent approaches involve nerve transfer alongside FFGT or double FFGT to enhance hand function (18, 19). Nerve repair often involves suturing the adventitia/intima directly, suitable for acute, localized injuries. Extensive nerve deficiencies may require transplantation, with options like the sural nerve, medial brachial cutaneous nerve, and medial forearm cutaneous nerve. While nerve transplantation avoids donor region cortical remodeling and provides motor bundles, it unavoidably causes donor area injury, and inherent issues like muscle atrophy and neuromuscular dysfunction persist (20–24).

Preoperative nursing emphasis

Preoperative depression is considered one of the important factors affecting the BPI. The World Health Organization (WHO) reports that more than 17 million Americans (5.9% of the population) suffer from depression (25). Patients experiencing shoulder, hip, and knee replacements have an increased risk of depression when compared to the rest of the population (26–28). A preoperative assessment of depression can be linked with a higher possibility of medical complications (29–31), infection (32), readmission (33), transfusions (34), non-home discharge (35), and length of stay (LOS) for individuals experiencing hip and knee replacement (36, 37). Delays in

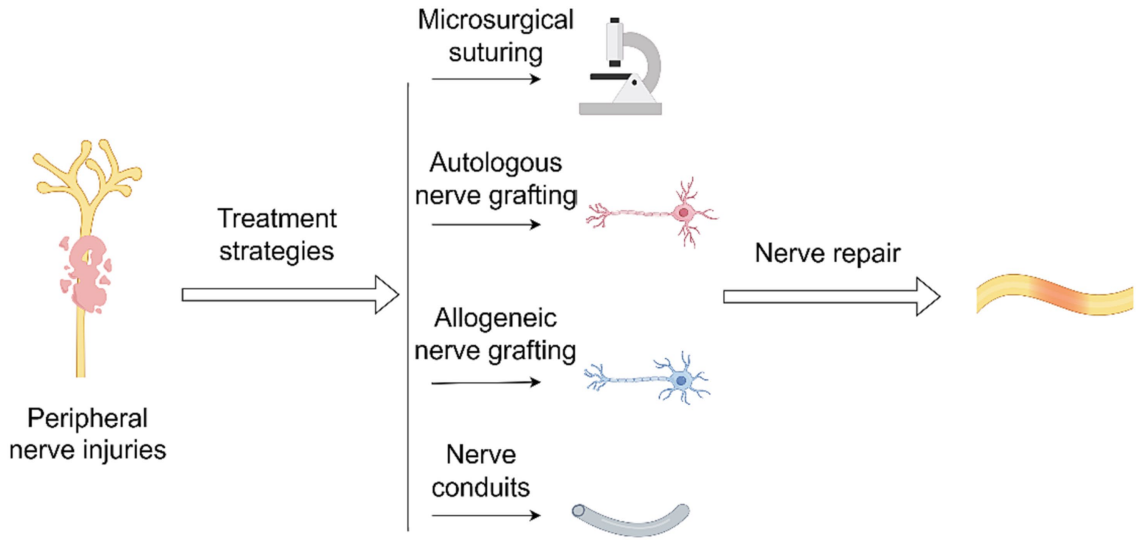

FIGURE 1
Treatment strategies for peripheral nerve injuries.

reconstructive surgery are the primary cause of poor prognosis (38, 39), so the majority of surgeons employ preoperative magnetic resonance imaging (MRI) and neurophysiological tests. Vargas et al. (40) to identify patients with avulsion injuries. Wade et al. (41) mentioned that preoperative (MRI) is used to identify root avulsions, but investigations on its diagnostic efficacy have produced contradictory results. Their survey studies reflected that a minority of diagnosed patients with BPI will not have received a surgical examination for a variety of reasons, including refusal of surgery, hazardous anesthesia, or treatment of other injuries taking precedence. If the percentage of false-negative results is underestimated, this would increase the degree of sensitivity of MRI. Conversely, the diagnostic precision of MRI may be influenced to the downside due to the possibility that patients received treatment based on imaging results rather than the existence of symptoms alone. In addition, they anticipated that the majority of research would be retrospective and some investigations may have obtained a non-representative sample of individuals, which could prejudice the diagnostic precision and raise concerns regarding relevance (41).

Postoperative nursing emphasis

Efficient pain management post-brachial plexus nerve transplantation is crucial. Nurses assess and address pain intensity, customizing individualized treatment strategies, including opioids, regional anesthesia, and non-pharmacological therapies. It's essential to ensure correct medication dosages. Regarding splinting techniques, nurses play a vital role in their administration and maintenance, ensuring graft stability and preventing complications (42). Educating patients on three key principles is important:

(a) Examination: check for erythematous indications after removing a splint. Temporary disappearance within 30 min is acceptable; enduring marks require splint adjustment. Engage in joint exercises if joint stiffness occurs.

(b) Washing Instructions: avoid exposing heat-sensitive splints to hot water or heat-emitting sources. Clean splints with cold or lukewarm water and mild soap.

(c) Adjustments: for non-self-constructed splints, avoid attempting modifications. Consult the therapist or center responsible for the splint. Children and adolescents should have orthoses tailored for ongoing growth, necessitating regular follow-up appointments (43).

Special considerations

In the case of pan-brachial plexus injuries, major functional impairment can result. However, surgical advancements, such as free-functioning muscle transfers, have led to significant improvements in functional ability. However, individuals with brachial plexus injuries still face challenges post-surgery, including persistent pain, occupational changes, appearance concerns, dependence on others, and difficulties with daily tasks (44). To enhance healthcare services for BPI patients, several considerations should be followed post-transplantation surgeries:

(A) Psychological support: BPI patients may experience diverse emotional responses, including worry and dissatisfaction. Nurses play a crucial role in offering emotional assistance and facilitating counseling services as needed.

(B) Family involvement and education: Family engagement is vital for patient rehabilitation. Nurses provide families with education on postoperative care, including wound care, splint management, and prescribed exercises.

(C) Occupational therapy: This plays an essential role in helping patients regain independence in daily activities. Nurses collaborate with occupational professionals to ensure a smooth transition from rehabilitation to occupational therapy (45).

Brito et al. (46) examined the experiences of individuals who received free-functioning muscle transfers for Pan-BPI. Despite access

to extensive medical resources, patients faced challenges related to physical impairments, changes in relationships, reliance on pain medication, self-concept adjustments, and resuming important roles like employment. Providers must address personal and social needs, including pain management, depression, adapting to a new self-identity, and re-engaging in life roles. The Continuity of healthcare professionals is crucial for effective therapy. Therefore, a broader application of continuity of care for BPI individuals and relevant community support initiatives is essential. Strategies should be explored to improve care for patients in areas with limited access to specialized BPI treatment. Occupational health practitioners are well-positioned to provide services for adaptation, pain management, psychological effects, and societal reintegration. This study provides valuable insights for healthcare practitioners, planners, and funders supporting BPI individuals (46).

Donor nerve requirements

There are some vital requirements for donor nerve transplantation in BPI surgery as follows: (i) the selection of a suitable and compatible donor nerve is a crucial factor in the transplantation of brachial plexus nerves. Ideally, the selection of the donor nerve should align with the specific type of nerve fibers needed for the recipient's place (it will be for sensory or motor purposes). (ii) The factor of proximity has played an essential part in minimizing graft length and tension, hence influencing the success of the transplant. It is better to have a nerve in close proximity to the site of injury. (iii) Functional significance at donor location: the selection of a donor nerve should prioritize minimizing the functional consequences associated with its loss at the donor site. Generally, sensory nerves in areas of less significance are favored. (iv) Surgical access: the practical aspects of accessibility and convenience of harvesting the donor nerve are important factors to be taken into account. Surgeons must possess the capability to efficiently and effectively obtain and extract the donor nerve while causing minimal disturbance (47, 48).

A nerve transfer for elbow extension is recommended in cases where grafting is not possible, such as root avulsions. A variety of nerves are used in these transfers, including the suprascapular, phrenic, contralateral C7 root, partial medial or ulnar, spinal accessory, or intercostal nerves. Restoration of elbow flexion is the first priority, followed by shoulder external rotation and grasp function. Elbow extension is considered less often but becomes relevant when using a functional free muscle transfer that crosses the elbow to enhance grasp capabilities (49). In Nagano (50) documented the use of multiple nerve transfers for lesions specifically affecting the C5-6 region, including the utilization of intercostal nerves to reinnervate the musculocutaneous nerve.

Upper limb nerve transplantation care

Upper limb nerve transplantation is a highly specialized intervention designed to restore both sensory and motor capabilities in the hands and arms. Its main goal is to address the impaired finger movement resulting from nerve damage or loss. Nerve transfer presents a viable approach for the restoration of function, with the primary objective of revitalizing the paralyzed muscles in the upper limbs (51). The basic justification for implementing nerve transfer procedures in individuals with tetraplegia is the redirection of intact nerve axons originating proximal to the site of injury toward paralyzed muscle-nerve cells located below the site of injury. This process effectively circumvents the damaged region of the spinal cord. Axons that are in healthy condition and subject to voluntary control have regenerative properties, wherein they undergo a process of restoration by extending from the donor's nerves. This regenerative phenomenon aims to reinstate the ability to control muscles that were previously rendered immobile due to a spinal cord injury (SCI) (52).

In our case, a 41-year-old male complained of numbness in the left thumb, index finger, and middle finger and was characterized by abnormal palmar opposition of the thumb. His motor nerve conduction and sensory nerve conduction studies indicated a lesion of the median nerve. After administering general anesthesia, the patient underwent tumor resection in the median nerve and received a sural nerve graft. After 1 month, the sensation in the fingertips had recovered. The function of palmar opposition of the thumb returned to completely normal within 6 months (Figures 2, 3).

Preoperative nursing emphasis

The successful outcome of upper limb transplantation is contingent upon both the meticulous care provided to the patient post-operation and the efficacy of the treatment itself. In order to preserve the viability of the transplanted part, it is imperative to implement a comprehensive regimen consisting of vigilant pharmacological therapy, intensive physical therapy, essential psychological support, and regular testing. Certain medicines are required to be administered continuously over the lifespan of the graft (53). In order to adequately prepare for the postoperative care of patients receiving hand transplantation, it is essential to establish a select group of nurses who possess clinical knowledge in the specialized care of hand and microsurgery individuals. In addition, these nurses must receive specialized educational training pertaining to the provision of care for patients enduring transplantation procedures. The patient is admitted to the designated medical facility prior to the surgical procedure and assigned to a room equipped with a high-efficiency particle air filter.

In order to foster a sense of security and contentment, it is recommended that the nurse greets the patient and their family in a kind, engaged, caring, and non-judgmental manner (54, 55). An unhurried attitude should characterize this approach. The patient and their family are provided with a comprehensive orientation to the unit and call framework, with an emphasis on promoting open communication with the nursing staff and physicians. Nurses conduct an initial evaluation of the patient and their family, including a comprehensive psychosocial assessment. In anticipation of the surgical procedure, hand transplant preoperative requirements are recorded and completed (56, 57).

Postoperative nursing emphasis

Nurses conduct a comprehensive physical examination of the recipient after the recipient is transferred from the postoperative care unit to the hospital ward. Furthermore, the circulation condition of

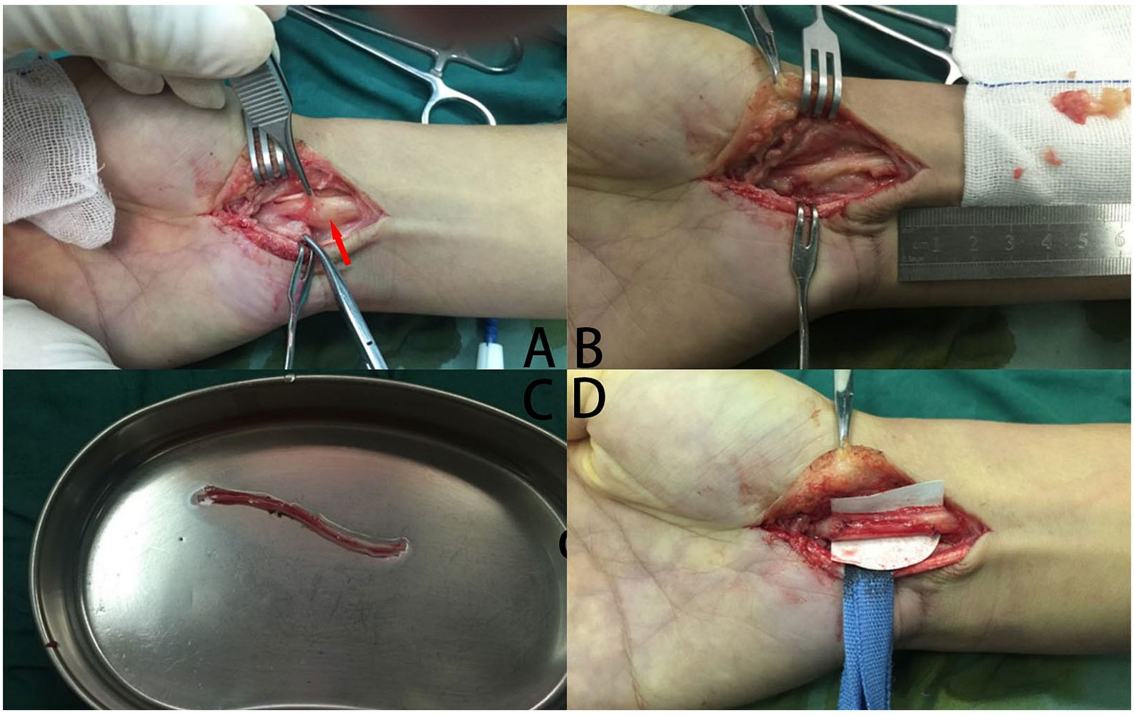

FIGURE 2
The procedure of tumor resection in the median nerve and a sural nerve graft. **(A)** A tumor (red arrowhead) grew in the median nerve, which was encased by the nerve tissue. **(B)** The tumor was excised, which causes the median nerve defects. **(C)** The sural nerve has been incised. **(D)** Postoperative images of autologous nerve transplantation.

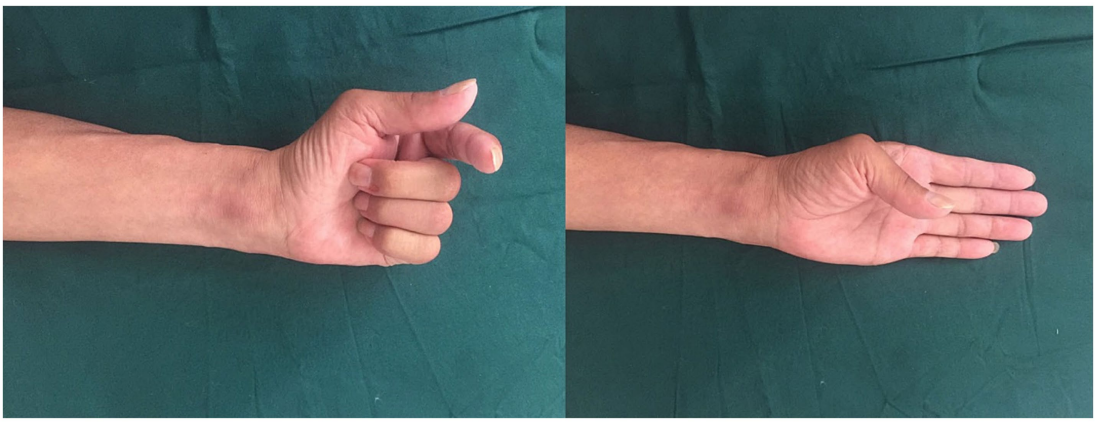

FIGURE 3
Postoperative functional assessment at 6 months.

the transplant is evaluated on an hourly schedule. During transplant surgery and afterwards, a pulse oximeter is used to monitor the unaffected and transplanted limbs' blood flow. Using a device for measuring skin temperature, the surface of the transplanted hand's fingers is compared with those on the unaffected limb (58). Temperature measurements should be recorded at a minimum of 30°C or above. It is imperative to promptly notify the attending physician immediately of a decrease in body temperature or alteration in the circulatory condition. Keeping the recipient's room at 24°C is recommended. The consumption of caffeine is contraindicated for the patient, and smoking is strictly restricted. The family is advised to refrain from smoking before their visits to the beneficiary. Nurses evaluate pain management, nutritional status, physical activity level, bowel and bladder function, and anti-embolic measures regularly following surgery (54). A specific pharmaceutical regimen facilitates immunosuppression, after which the transplant physician and transplant coordinator monitor the progress. The coordinator conducts regular trips to the recipient, providing education to both the recipient and their family on topics such as medications, activity levels, environmental considerations, and other relevant variables (59, 60). Due to the recipient's immunosuppressed condition, it is imperative for the nurse responsible for their care to exert utmost

effort in coordinating visits from family members and pertinent personnel, with the aim of reducing the frequency of individuals entering the room. The discharge nurse is responsible for providing a comprehensive explanation of surgical discharge guidelines, including (1) the time of administration for all medications, including information on pharmaceutical types, dosages, and the corresponding profiles of adverse effects. (2) Timetable for mandatory laboratory examinations. (3) The scheduling of physician follow-up visits. (4) Wound care. (5) The evaluation of hand color, warmth, and capillary refill. (6) The surveillance of blood pressure and temperature. (7) The importance of hygiene and the prevention of opportunistic infections (61, 62).

Special considerations

Effective communication between the hand transplantation hospital and the hand therapist and/or orthotist involved in the recipient's care is crucial. Physical and occupational therapists should actively view real-time video recordings of therapy to understand potential variances in tendon architecture and surgical intricacies affecting rehabilitation (27). Additional electrodes can be placed along the median and ulnar nerves above the transplant site after surgery. Transcutaneous electrical nerve stimulators can be used when needed, either in the recovery room or at the initial dressing change. The recipient should undergo daily hand rehabilitation for at least 3 months, followed by ongoing care from a local hand therapist (63, 64). Using a dynamic crane outrigger splint and an extension block at the metacarpophalangeal joint can significantly improve functional outcomes, similar to hand replantation (65, 66). Exercise programs are based on robust tendon weave repair techniques. Scar care, including compression materials, can start around 4 weeks post-transplantation. Hand-based anti-claw splints may be used intermittently after 3 weeks. For functional assessment, Carroll's test and the Disability of the Arm, Shoulder, and Hand (DASH) questionnaire are used (67). Immunosuppressive treatments for limb transplantation include drugs for induction and maintenance. Induction phase drugs typically include a calcineurin inhibitor, an antimetabolite, a monoclonal antibody, and steroids. Maintenance therapy involves lower doses of steroids, antimetabolites, and calcineurin inhibitors. Steroid-free maintenance therapy has shown promising results (68–70). The hospital should maintain an adequate supply of antibiotics, antihistamines, opioids, gastrointestinal prophylaxis medications, and laxatives for surgery. Anticoagulation requires aspirin, low molecular weight dextran, and heparin. Local anesthetic drugs like bupivacaine and ropivacaine, with epinephrine, should be available for potential nerve blocks (54).

Donor nerve requirements

To achieve optimal results in sensory and motor restoration for the recipient's hand, several key factors must be considered in selecting donor nerves. Compatibility with the specific type of fibers needed is crucial for successful integration and functional recovery. Proximity to the recipient site is also essential to minimize graft length and the stress associated with it. Choosing nerves close to the damaged site increases the chances of successful transplantation (71). Careful selection of donor nerves is imperative to minimize adverse effects on the functionality of the donor location. It's generally preferable to choose sensory nerves in less vital regions to reduce negative impacts on the donor site (72, 73). A study by Javeed et al. (51) reported that upper extremity function could be restored using single, double, or triple nerve grafts. Various nerve transfers were performed based on injury severity, remaining motor function, and electrodiagnostic signs of motor neuron damage. The Medical Research Council graded donor nerves 4–5 on their clinical motor strength. In the context of nerve transfer pairings, the supinator branch of the radial nerve was combined with the posterior interosseus nerve to facilitate hand opening, finger, and wrist extensions. Similarly, the brachialis branch of the musculocutaneous nerve was paired with the anterior interosseus nerve fascicle of the median nerve to enable pinch and finger flexion. Additionally, the spinal accessory nerve was linked with the posterior deltoid motor branch of the axillary nerve to support elbow extension (51).

Lower limb nerve transplantation

Patients with severe trauma may experience discomfort and functional impairment due to PNI. A prevalence rate of 1.2% has been observed in lower extremity injury patients developing PNI, which increases the risk of chronic pain and the need for therapy (74). In the past, upper extremity peripheral nerve reconstruction has received more attention than lower extremity peripheral nerve reconstruction. Nerve transfers in the lower extremities pose challenges due to longer nerve lengths, potentially leading to unfavorable outcomes (75). Lower limb nerve transplantation aims to restore sensory perception and motor control. Sensory deficiencies can affect proprioception and balance, while motor impairments can reduce muscle strength and alter gait (76). Treatment for lower extremity nerve injuries varies based on severity and nerve gap length. Nerve conduits are utilized for nerve gaps measuring less than three centimeters, while direct healing is favored for smaller gaps. Autografts or allografts are employed for gaps exceeding 3 cm; nevertheless, their utilization may be limited due to factors such as scar tissue, hemostasis, and infection (77).

Individualized approaches considering the advantages and limitations of each therapeutic intervention are essential for managing lower extremity nerve injuries.

Preoperative nursing emphasis

A variety of essential nursing interventions characterize the preoperative period of lower limb nerve transplantation. The purpose of these treatments is to enhance patients' empowerment via the acquisition of knowledge, provision of emotional support, and the facilitation of physical preparedness for surgical procedures. The primary focus throughout this stage is on comprehensive care, acknowledging the interconnectedness of the patient's physical and mental health. For example, in the context of patients with fractures, normal nursing care mostly centers on the observation of their health and the provision of general recovery instructions, sometimes falling short of meeting customized needs. Fast-track surgery (FTS) aims to expedite the rate of postoperative recovery, reduce physiological and psychological stress (78), and facilitate early discharge from the

hospital for patients (79). This is achieved by the use of various optimal perioperative nursing interventions, such as less invasive surgical procedures.

The perioperative phase encompasses several key components, such as pre-hospitalization education, preoperative fasting guidelines, postoperative vital sign monitoring, and the provision of analgesics as needed. Participants were permitted to consume water and food once the gas had gone through the anus, to have the catheter removed when spontaneous urination had been regained, and to engage in recovery activities at their discretion. The nursing intervention, as described by Chen et al. (80), includes comprehensive patient education using various methods such as verbal, visual, and written materials covering topics like hospital procedures, surgery concepts, pain management, fracture diagnosis, and healing processes. Nutritional guidance involves reducing preoperative food and water restrictions, closely monitoring vital signs post-anesthesia, and gradually introducing meals. Pain management is tailored to the patient's pain severity, using the visual analog scale (VAS) for assessment and administering appropriate analgesics. Additionally, patients receive guidelines for functional exercises, including passive and active routines post-surgery, ensuring comprehensive care and support.

Postoperative nursing emphasis

The nurses engaged in effective communication with patients who expressed reluctance to participate in post-surgical recovery exercises owing to intense pain. They employed a patient and empathetic approach, elucidating the significance of early engagement in functional exercises for rehabilitation. The researchers implemented suitable methodologies to alleviate the discomfort experienced by the patients, followed by guiding and engaging in functional exercises. Following the dissipation of the anesthetic, the leg in concern was raised at an angle of 15° to facilitate the systematic massaging of the toes and pulps. Patients performed toe flexion and extension exercises for 10 s, as directed by the nursing staff, followed by a 5-min rest period. Post-operative exercises consisted of ankle pump exercises, relaxation, and a contraction of the quadriceps femoris on the first day, contraction of the gluteus maximus on the second day, calf muscle contraction and exercise of the back muscles on the third day, straight leg raising on the fourth day, knee joint bending and extending on the fifth day, and hip joint movements on the sixth day (80). Postoperative care includes the following key aspects:

Swelling Assessment: Swelling in the affected limb was evaluated before surgery and at 1, 2, 3, and 4 weeks post-surgery, categorized into three levels: Level I (modest swelling), Level II (evident swelling with increased skin temperature), and Level III (brilliant swelling with tension blisters).

Pain Evaluation: Pain intensity was measured using the VAS scale before surgery, immediately after surgery, and at 6, 24, and 72 h post-surgery, with higher scores indicating more severe pain.

Complications Monitoring: A 6-month follow-up assessed the occurrence rates of constipation, urinary tract infection (UTI), lung infection, and lower limb deep vein thrombosis. Deep vein thrombosis diagnosis used color Doppler ultrasonography, checking for blood flow absence and sound. Lower Extremities Function: Kostuj et al. (81) assessed ankle and knee joint function at 3 and 6 months post-surgery using the AOFAS Ankle Hindfoot Scale and Lysholm criteria. The AOFAS scale comprises nine components, each with a maximum score of 100 points, evaluating pain levels, functional abilities, independent movements, limitations in everyday activities, gait patterns, forefoot and backfoot activities, ankle and heel stability, and foot alignment. Scores range from ≤50 (poor) to 90–100 (exceptional). The Lysholm criteria cover factors like discomfort, swelling, crouching, encouragement, instability, limping, and interlocking, with scores >84 (normal), 66–84 (acceptable), and <65 (poor).

Special considerations

Both amputation and limb salvage therapies for lower limb injuries have limitations. Functional and psychological outcomes often remain unsatisfactory compared to the patient's initial condition 2 years post-injury (82). Despite uncertainties regarding the applicability of upper extremity allotransplantation outcomes to lower extremity cases due to various factors, there is hope for lower extremity allotransplantation based on an examination of upper extremity transplantation advantages and disadvantages (83). Potential outcomes for lower extremity allotransplantation encompass several factors. First, lower limb anatomy is simpler, with fewer intricate structures, reducing operative complexity and anesthesia time, likely resulting in fewer complications (83). Second, intrinsic muscle reinnervation's significance is lower in the lower limbs compared to the upper limbs. The restoration of proximal thigh muscle function, essential for ambulation, is prioritized over intrinsic reinnervation, making lower extremity allotransplantation potentially beneficial for converting above-knee to below-knee amputations (84). Third, while concerns about immunosuppression exist, lower extremity allotransplants, especially above the knee, may contain hematopoietically active bone marrow, potentially reducing the need for immunosuppressive medications (85, 86). Finally, lower limb allotransplantation is expected to significantly improve recipients' quality of life by restoring sensation, function, and integrity, similar to the benefits observed in upper extremity transplant recipients. These improvements may also enhance body image, autonomy, and social reintegration (87, 88).

Donor nerve requirements

Primary repair is recommended when the nerve damage is complete, without significant gaps, and can be reconnected without tension. Autogenous nerve grafts like the sural nerve are ideal when the nerve cannot be repaired without tension. This method requires intact proximal and distal nerve targets and a donor nerve with expendable functionality (89). Nerve conduits can guide nerve regeneration but are limited to shorter segment abnormalities. When direct repair or grafting is not feasible, nerve transfers, connecting a functional donor nerve to a non-functional recipient nerve, can be used. Nerve transfers have gained attention in lower extremity PNI due to the long distances involved, potentially avoiding the zone of injury. For common peroneal nerve injuries, neurolysis restored useful function in about 88% of cases. Direct repair achieved similar results in 84% of patients. However, the recovery probability decreased with longer grafts (90). Nerve transfer is recommended in cases meeting specific criteria: no motor function between 3 and

TABLE 1 Nursing care summary for nerve transplantation.

Injured area	Preoperative nursing	Postoperative nursing
Brachial plexus injury	◆ Assess for depression ◆ Educate on surgery process ◆ MRI and tests to ID avulsion injuries	◆ Pain management ◆ Splinting education ◆ Psychosocial support
Upper limb nerve damage	◆ Specialized nurse training ◆ Patient/family education ◆ Comprehensive assessments	◆ Frequent graft monitoring ◆ Immunosuppression management ◆ Rehab and testing
Lower limb nerve injury	◆ Patient education ◆ Nutrition guidance ◆ Pre-op preparation	◆ Swelling and pain checks ◆ Functional exercises ◆ Complication monitoring

12 months post-injury, too great a gap for primary repair or grafting, and unavailability of the proximal nerve end for repair. Rehabilitation aims to establish a stable hip joint, normal walking patterns, and a protective feeling in the plantar region of the foot (91). Nerve transfers in the lower extremities are used to provide protective sensation to the foot's plantar side and address painful neuropathies and neuromas. Nerve transfers are not preferred when other surgical methods might yield similar results with less morbidity. Motor nerve transfers aren't recommended if there's a delay of more than 12–18 months since the injury or if donor nerve strength is below BMRC grade M4 (92). Transferring motor nerves requires direct end-to-end coaptation, verifying no muscle contraction in the recipient nerve. In sensory nerve transfers, either end-to-end or end-to-side transfers can be used effectively. Sensory nerve transfers aim to regain essential sensations using a donor nerve lacking vital sensations (93–95). Nerve transfers from the proximal motor branches of the tibial nerve to common or deep peroneal nerve injuries have shown promise. In one study, seven out of nine pediatric patients with common peroneal nerve palsy achieved at least M4 rehabilitation in ankle dorsiflexion over 6 months after the transfer (96). Overall, primary repair, grafts, conduits, and nerve transfers are valuable tools in addressing peripheral nerve injuries, each with its own indications and considerations (Table 1).

Application of new care approaches

Personalized rehabilitation plans

The primary objectives of Rehabilitation Medicine are to enhance a patient's overall quality of life, physical and psychological functioning, especially in the context of disabilities or illness. Rehabilitation Medicine adopts a comprehensive approach known as the biopsychosocial interdisciplinary and multimodal approach (97).

Rehabilitation after hand and upper limb transplantation, which is the focus here, involves a multi-stage process:

(i) Early Stage (0–6 weeks): The primary goal is to educate patients about safeguarding and adopting the right posture for the insensate limb. A thermoplastic volar resting splint is used to protect bone fixation and soft tissues. It's worn for 6 weeks, except during physical activity and certain maintenance tasks. Edema is managed using circumferential measures, posture, massage, mobilization, and compression. Active and passive movements are initiated between three and 5 days post-transplantation to prevent joint stiffness and tendon adhesions. Sensory-motor re-education is encouraged through the prehabilitation motor imagery plan.

(ii) Intermediate Stage (6–12 weeks): Motor and sensory restoration are closely monitored, and necessary adjustments to splinting and exercises are made. The volar resting splint is used mainly at night, while daytime splints facilitate functional tasks. Motor relearning is incorporated, with a focus on achieving a complete passive motion range within 12 weeks. Strengthening exercises are introduced, and massage and compression are used for scar and edema management.

(iii) Late Stage (12 weeks and more): Outpatient visits are gradually reduced based on individual needs. Patients are encouraged to maintain their home exercise routine. The treatment evolves to enhance muscular strength, endurance, and overall functional autonomy. Sensory re-education continues, including static and dynamic localization, texture and form discrimination, immersion, and stereognosis. Patients are advised to integrate sensory re-education into their daily routines and experience various sensory stimuli. Rehabilitation focuses on identifying and pursuing long-term therapeutic goals (98).

This rehabilitation process is tailored to patients undergoing hand and upper limb transplantation, considering factors such as the level of transplantation and individual health conditions.

Integration of advanced techniques

Peripheral nerve regeneration after injury is challenging, especially for proximal nerve injuries where axons must cover long distances at a slow rate of 1 mm/day (99).

Nerves severed in experimental injuries may regenerate if repaired within 3 months (100). Delaying repair for four to 6 months significantly reduces regeneration capacity to only 33% of normal levels (99). Despite progress in peripheral nerve restoration, satisfactory clinical outcomes remain elusive, often resulting in long-term sensorimotor impairment and neuropathic pain in patients (101, 102). An effective approach to expedite peripheral nerve regeneration is electrical stimulation (ES) applied directly to the injured nerve. ES enhances early regeneration processes, promoting neuronal survival and axonal sprouting (103). In rodent injury models, ES has shown potential in enhancing neuron regeneration in various nerve injuries (104–106). *In vitro* studies suggest that ES

increases intraneuronal cyclic adenosine monophosphate (cAMP) levels and nerve growth factor (NGF) levels, aiding regeneration (107). The specific cellular mechanisms of ES in axonal regeneration are not fully understood. ES mimics normal calcium influx after nerve damage, providing a retrograde signal that activates regeneration-promoting processes (108, 109). ES accelerates axonal growth and upregulates regeneration-related genes (105, 110, 111). ES also influences cAMP, linked to neurite outgrowth and axonal guidance (112, 113). ES triggers cAMP production, activating pathways promoting brain-derived neurotrophic factor (BDNF) and neurite development (114). BDNF inhibits cAMP breakdown, maintaining elevated levels (109, 115). Recent research explores ES's impact on downstream pathways, including PTEN downregulation, a growth inhibitor (116). PTEN inhibits the PI3-K/Akt pathway crucial for regeneration (117, 118). Inhibiting PTEN facilitates peripheral nerve regeneration (119), suggesting ES promotes the PI3-K/Akt pathway (116). Additionally, using growth factors (GFs) to facilitate nerve regeneration is explored. GFs activate signaling cascades, but their short effectiveness and quick inactivation are limitations. Nerve conduits with controlled GF release support axonal regeneration and functional recovery (120).

Conclusion

Autologous peripheral nerve transplantation care is experiencing substantial progress across various anatomical sites. Through the adoption of personalized rehabilitation plans, advanced techniques, and effective complication management, enhanced postoperative recovery can be achieved, providing patients with clearer pathways toward functional restoration.

Author contributions

GX: Writing – original draft. XZ: Writing – review & editing. YD: Writing – review & editing. AA: Writing – review & editing. HZ: Writing – review & editing. SE: Writing – review & editing. VK: Writing – review & editing. MA: Writing – review & editing. OA: Writing – review & editing. SA: Writing – review & editing. HL: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 26 March 2024
DOI 10.3389/fneur.2024.1372168

OPEN ACCESS

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RECEIVED 17 January 2024
ACCEPTED 27 February 2024
PUBLISHED 26 March 2024

CITATION
Jiang M, Chen M and Liu N (2024) Interactions between Schwann cell and extracellular matrix in peripheral nerve regeneration.
Front. Neurol. 15:1372168.
doi: 10.3389/fneur.2024.1372168

Interactions between Schwann cell and extracellular matrix in peripheral nerve regeneration

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Peripheral nerve injuries, caused by various reasons, often lead to severe sensory, motor, and autonomic dysfunction or permanent disability, posing a challenging problem in regenerative medicine. Autologous nerve transplantation has been the gold standard in traditional treatments but faces numerous limitations and risk factors, such as donor area denervation, increased surgical complications, and diameter or nerve bundle mismatches. The extracellular matrix (ECM) is a complex molecular network synthesized and released into the extracellular space by cells residing in tissues or organs. Its main components include collagen, proteoglycans/glycosaminoglycans, elastin, laminin, fibronectin, etc., providing structural and biochemical support to surrounding cells, crucial for cell survival and growth. Schwann cells, as the primary glial cells in the peripheral nervous system, play various important roles. Schwann cell transplantation is considered the gold standard in cell therapy for peripheral nerve injuries, making ECM derived from Schwann cells one of the most suitable biomaterials for peripheral nerve repair. To better understand the mechanisms of Schwann cells and the ECM in peripheral nerve regeneration and their optimal application, this review provides an overview of their roles in peripheral nerve regeneration.

KEYWORDS

axon biomaterials, extracellular matrix, myelin sheath, peripheral nerve regeneration, Schwann cells

1 Introduction

It is well-known that the nervous system possesses strong stability, and once damaged, spontaneous repair becomes extremely challenging (1). Peripheral nerve injuries are a common type of neurological damage in clinical practice, leading to varying degrees of autonomic dysfunction, sensory or motor impairments, localized paralysis, and chronic neuropathic pain, thereby diminishing patients' quality of life (2). In the United States, the annual incidence rate of upper limb peripheral nerve injuries is 16.9 per 100,000 people, with an average emergency care cost of $5,779 per person. Calculated accordingly, the total annual medical expenses due to upper limb peripheral nerve injuries in the U.S. reach nearly $300 million (3). Therefore, peripheral nerve injuries represent a significant clinical and public health concern.

The causes of peripheral nerve injuries are complex, including cutting injuries, tearing injuries, traction injuries, compressive injuries, and iatrogenic injuries. Among these, traction-related peripheral nerve injuries are the most common, followed by tearing injuries and compressive injuries that can cause complete transverse damage to the affected nerves (4).

Clinically, the Seddon or Sunderland classification methods are often employed. Seddon classifies the severity of nerve injuries into neurapraxia (temporary functional changes with preserved axonal continuity), axonotmesis (loss of axonal continuity with varying degrees of endoneurial disruption, temporary loss of function), and neurotmesis (complete loss of axonal and endoneurial continuity, incomplete nerve regeneration, and incomplete functional recovery) (5). Sunderland refines the Seddon classification into five degrees, corresponding to varying degrees of severity from concussion (first degree) to rupture (fifth degree), providing a more detailed assessment of overall injury severity and recovery difficulty (4).

Different nerve repair methods are adopted based on the varying degrees of nerve injury. Autologous nerve transplantation is the most widely used bridging technique for repairing peripheral nerve defects, currently considered the "gold standard" for treating long-distance peripheral nerve defects (6, 7). However, autologous nerve transplantation comes with numerous limitations and risk factors, such as denervation of the donor area, increased surgical complications, and diameter or nerve bundle mismatches. With the development of tissue engineering, tissue-engineered nerve grafts (TENG) have become an important potential alternative to autologous nerve grafts (8).

The ECM is a complex molecular network synthesized and released into the extracellular space by cells residing in tissues or organs (9). Its main components include collagen, proteoglycans/glycosaminoglycans, elastin, laminin, fibronectin, etc., providing structural support and attachment sites for cells (10). Schwann cells, as the primary glial cells in the peripheral nervous system, play various crucial roles and are considered the gold standard in cell therapy for peripheral nerve injuries (7, 11). Therefore, ECM derived from Schwann cells has become one of the most suitable biomaterials for peripheral nerve repair (7). To explore new approaches for peripheral nerve injury repair, this article provides a review of the key histological foundations of peripheral nerve regeneration - Schwann cells and ECM, as well as their interactions.

2 Neural repair after injury

Although the peripheral nervous system possesses strong regenerative potential, spontaneous regeneration rarely occurs in cases of nerve transection, and the outcomes of treatment interventions are often unsatisfactory (12). Conservative treatment and surgical intervention are the two main approaches for peripheral nerve injury (2). Conservative treatment involves non-surgical methods to protect damaged neurons, promote nerve regeneration and maturation, thereby facilitating the recovery of nerve function (13). Surgical treatment, depending on the type and severity of peripheral nerve injury, may employ direct nerve anastomosis or bridging repair as two repair strategies (14). For injuries with a small nerve defect distance (5 mm), surgical suturing is generally considered the best repair method, while nerve transplantation is required for larger defects (≥5 mm) (15). Autologous nerve transplantation is the most widely used bridging technique in clinical practice for repairing long-distance peripheral nerve defects and is currently considered the "gold standard." Autologous nerve transplantation has advantages such as good regeneration effects (higher vascularization, an elevated degree of anastomosis), minimal immune rejection impact, etc. However, it comes with inevitable drawbacks, including limited availability of autologous nerve grafts, denervation of the donor area, nerve tumor formation, increased infection risk, diameter mismatch, etc. Therefore, optimization and exploration of alternative solutions are crucial (16–21).

In recent years, with the advancement of tissue engineering research, tissue-engineered nerve grafts are considered promising alternatives to autologous nerve grafts (22). Tissue-engineered nerve grafts encompass tissue-engineered neural biomaterial scaffolds, mainly including nerve conduits and their fillers, with diverse structural forms. They can be tailored to repair peripheral nerves of different diameters and defect lengths, making them a current hotspot in peripheral nerve repair and regeneration (23). Tissue-engineered nerves consist of three elements: scaffold, seed cells, and soluble regulatory factors. The core idea is to use living cells to combine with ECM or scaffold material in a certain way, and add factors that induce and promote growth to form neural tissue *in vitro*, replacing damaged tissue (24).The neural scaffold or conduit provides a foundational space for nerve regeneration, guiding axonal regeneration and preventing scar formation. However, seed cells and soluble regulatory factors face various limitations. Therefore, there is an urgent need to find an alternative biomaterial that can support cells and growth factors, leading to the construction of a novel tissue-engineered nerve graft (25). ECM possesses various characteristics, promoting axonal regeneration while avoiding the limitations of supporting cells and growth factors. Hence, it holds the potential to replace seed cells and growth factors, becoming a crucial biomaterial in the construction of innovative tissue-engineered nerves (26, 27).

3 Significance of Schwann cells

Undoubtedly, Schwann cells play a dominant role in the regeneration and development following peripheral nerve injuries (16, 28–32). Derived from the neural crest, Schwann cell precursors (SCPs) can generate various polarized cells, including Schwann cell precursors (33, 34). These precursors proliferate rapidly, developing into immature SCs, which subsequently differentiate into two mature types of SCs: myelinating SCs and non-myelinating SCs (35). In recent years, scholars have discovered another subset of mature Schwann cells (SCs), termed repair Schwann cells, which are formed through adaptive cell reprogramming following nerve injury (36). Although non-myelinating SCs do not produce myelin, they still play important roles in the peripheral nervous system, such as maintaining axonal metabolism and preventing neuropathic pain. Non-myelinating SCs still possess the potential for myelination. After axonal or nerve injury, SCs trigger defense mechanisms involving inflammation and immune responses, activate Wallerian degeneration, and promote the survival of damaged neurons and axon regeneration (7). At this stage, both myelinating and non-myelinating SCs transition to repair Schwann cells to initiate the repair process (37). This phenotypic change requires adaptive cell reprogramming of SCs, including dedifferentiation of myelin and activation of axon repair and regeneration functions (36). These characteristics indicate that SCs are highly plastic and can undergo conversion between different subtypes in response to environmental signals.

Recent studies have found that Schwann cells have functions such as migration, adhesion, ECM production, secretion of various

neurotrophic factors, and bioactive substances (38, 39). Neurotrophic factors include NGF, BDNF, CNTF, FGF, NT, GAP-43, etc. (40). Secreted ECM components include FN, LN, IV collagen, V collagen, heparin sulfate proteoglycan (HSPG), and entactin (38). These ECM components are deposited outside Schwann cells to form the basal lamina. Schwann cells also synthesize cell adhesion molecules (CAMs), which affect cell adhesion. CAMs include neural cell adhesion molecule (N-CAM), neural glial cell adhesion molecule (NG-CAM), MAG, peripheral myelin protein, etc. ECM and CAMs, in the early stages of nerve regeneration, regulate the initial extension of nerves, growth rate, and maturity, promote cell adhesion, maintain the stability of growth cone advancement, and accelerate axonal initiation and growth (41).

Myelinating Schwann cells, the focus of this discussion, exhibit radial and longitudinal polarization. As myelination progresses, Schwann cells organize into distinct domains, each with a unique protein array and a set of interconnected cytoplasmic compartments. Longitudinal polarity is prominently manifested in the overall organization of myelinating Schwann cells and axons, forming distinct nodal, paranodal, and internodal compartments. Radial polarity is evident on different inner and outer membrane surfaces, present at opposite ends of the cell; the compact myelin sheath inserts between these two domains (42). Myelinating Schwann cells express many typical genes in an immature state under normal physiological conditions and many newly expressed genes (such as EGFL8 gene, H3K27 gene, Oct6 gene, and Krox20 gene). These genes regulate and drive the process of neuron survival, damaged axon breakdown, and the regeneration process. The regeneration process involves myelin clearance, axon regeneration, guiding regenerated axons to their normal physiological locations, and ultimately remyelinating the regenerated axons (35, 43, 44). Therefore, elucidating the various biochemical mechanisms influencing Schwann cell growth, proliferation, function, and apoptosis is undeniably crucial for peripheral nerve regeneration research.

4 Schwann cell-related growth factors and pathways

Macrophages secrete interleukin (IL)-1 after injury, inducing Schwann cells to release neurotrophic factors and transforming them into a regenerative phenotype. The jun gene transcription product c-jun plays a crucial role in this process, regulating the expression of 172 genes in Schwann cells. Prolonged denervation after injury leads to a decrease in the expression of this key factor, affecting Schwann cell phenotypic differentiation. Therefore, one potential direction is to add chemical stimulants to scaffolds to upregulate c-jun expression, thereby activating more Schwann cells with the Remak Schwann cell (RSC) phenotype (30, 45). Research has shown that the guidance receptor Plexin-B2 also plays a crucial role in this process. The expression of this receptor is significantly upregulated in infiltrating macrophages of damaged nerves, and it can guide the alignment of macrophages and Schwann cells, thereby preventing collisions with axons. Conditional deletion of Plexin-B2 in the myeloid lineage not only leads to misplacement of macrophages but also results in matrix disarray and Schwann cell disintegration, consequently causing axonal misguidance and delayed functional recovery (46). Additionally, another critical cellular factor, Exendin-4, has been found to promote Schwann cell proliferation and migration by activating the Jak–STAT pathway, thereby effectively promoting the repair process after nerve injury (31).

Research has focused on improving the efficiency of basic fibroblast growth factor (bFGF) transmission in the process of nerve regeneration. bFGF is a crucial growth factor for nerve injury repair, promoting Schwann cell proliferation. In one study, a specific collagen-binding domain (CBD) was fused to the N-terminus of bFGF. This fusion complex was then combined with a linearly ordered collagen fiber scaffold. The modified scaffold was transplanted into the cut end of the rat sciatic nerve, effectively enhancing bFGF factor transmission efficiency and regeneration outcomes (30). Tomokazu Fukuda and colleagues combined a controlled release system of basic fibroblast growth factor (bFGF) with biodegradable nerve conduits. They used enzyme-linked immunosorbent assay (ELISA) to measure the release of bFGF and investigated its effects on neurovascularization and Schwann cell proliferation in a mouse sciatic nerve model. The results indicated that compared to the control group, the experimental group with the addition of the controlled release system exhibited slow release of bFGF, leading to improvements in neurovascularization and Schwann cell proliferation (47).

It has been found that beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) weakens Schwann cell-mediated peripheral nerve regeneration. Inhibiting its activity can promote muscle nerve redenervation (48). MicroRNA (miRNA) is a short endogenous RNA with the potential to regulate and silence the expression of any RNA. Injecting miRNA into ECM during the regeneration process to silence the mRNA encoding BACE1 in Schwann cells might promote nerve regeneration and muscle nerve redenervation.

Osteopontin (OPN) is a glycoprotein containing the RGD (arginine-glycine-aspartic acid) sequence, exhibiting cytokine-like, chemotactic, and pro-adhesive properties. It is expressed in Schwann cells in the degenerated distal nerve stump and is regulated by axon-derived signals, significantly reducing severe axonal multifocal neuropathy (49). OPN is crucial for the secretion of type I collagen during dentin repair, improving the microenvironment for dental nerve regeneration (50). Application of OPN in the healing of replanted mouse teeth resulted in reduced inflammation and better reinnervation of blood vessels and nerves compared to the control group (51).

The main challenge in Schwann cell research is the inability to determine to what extent *in vitro* cultures of human Schwann cells reflect the changes and development of Schwann cell phenotypes in the actual human peripheral nerve environment after injury. This awaits the emergence of new research methods.

5 ECM and its connection with Schwann cells

5.1 Overview of ECM structure in the Schwann cell environment

The normal growth of Schwann cells relies on a well-established ECM environment. All tissues and organs contain a mixture of cells and non-cellular components, where the non-cellular component forms a well-organized network known as ECM. The ECM is composed of various matrix macromolecules, and its precise

composition and specific structure vary between tissues. The main components include fibrous proteins such as collagen, elastin, fibronectin (FN), laminin, glycoproteins, proteoglycans (pg), and glycosaminoglycans (GAGs), which are highly acidic and hydrated molecules. This extensive meshwork system provides structural support to cells and regulates intercellular communication. The 3D arrangement of cells through the ECM creates physical paths for cell movement. Additionally, ECM can interact with various molecules, such as growth factors, signal receptors, and adhesion molecules, influencing a range of cellular behaviors and functions, including cell growth, migration, differentiation, survival, homeostasis, and morphogenesis (52–54). Undoubtfully, this interaction is particularly crucial for axon regeneration and the redirection of nerve fibers.

Next, we will provide an overview of the major components of ECM and their impact on Schwann cell growth.

5.1.1 Collagen

Collagen is the most abundant protein in mammals. The collagen family includes 28 members, each containing at least one triple helical structure domain. Collagen is deposited in the ECM, where most form supramolecular assemblies, aiding in tissue organization and shaping. Collagens also interact with cell surface receptors, regulating cell proliferation, differentiation, and migration. In the differentiation process of peripheral nerves, Schwann cells predominantly express a member of the V-type collagen family, α4(V) collagen. This collagen protein has high affinity with heparan sulfate through a unique binding motif in the non-collagen N-terminal domain (NTD). The primary α4(V) collagen-binding protein on the Schwann cell surface is heparan sulfate proteoglycan-1. In co-culture, α4(V) collagen binds with fibronectin on the polarized Schwann cell surface, forming tubular ECM structures, crucial sites for myelin sheath formation. Inhibiting glypican-1 or alpha4(V) collagen expression significantly inhibits myelin sheath formation, highlighting their critical role in peripheral nervous system myelination. Furthermore, it has been found that type VI collagen is crucial for the migration and polarization of macrophages during peripheral nerve regeneration. Nerve injury induces a strong upregulation of type VI collagen. *In vitro* studies have demonstrated that type VI collagen promotes macrophage migration and polarization through the AKT and PKA pathways, regulating macrophage function and consequently modulating peripheral nerve regeneration (55–57).

5.1.2 Elastin

Elastin is a crucial, long-lived ECM protein primarily found in major arteries, lungs, ligaments, tendons, skin, and elastic cartilage. Secreted by the Eln gene, elastin is organized into elastic fibers, providing elasticity and resilience to various vertebrate tissues. Elastin represents a class of heat-triggered phase separation thermosensitive peptide polymers with a low critical solution temperature, exhibiting good tissue compatibility (58, 59). Elastin can enhance the elasticity and flexibility of myelin sheaths after peripheral nerve regeneration.

5.1.3 Fibronectin

Fibronectin (FN) is a 500 kDa dimer glycoprotein with variable molecular conformations and splice variants. Each FN molecule consists of three types of repeating subunits. FNI and FNII are stabilized by disulfide bonds in beta-sheets, while FNIII is a mechanically deformable seven-stranded beta-barrel structure. The FNIII9-10 domain contains the synergy-binding site (PHSRN) and the RGD-binding site, regulating integrin adhesion. FN can be classified into various types based on molecular conformation and splice variations, preferentially binding to cells through integrins, other FN subunits, collagen, heparin, fibronectin, matrix metalloproteinases (MMPs), and growth factors. FN is classically divided into two types: plasma-soluble and cellular (60). In the peripheral nervous system, fibronectin is primarily secreted and produced by Schwann cells, sparsely distributed along the cell surface, and mainly located within the perineurium (61).

Fibronectin binds to the cell surface through receptor-ligand interactions and transmits signals into the cell, thereby mediating the growth of neuronal axons (62). *In vitro* experiments have demonstrated that fibronectin can promote Schwann cell proliferation and stimulate their directed migration and chemotaxis (63). During the early stages of peripheral nerve regeneration, fibronectin has been observed to regulate axonal growth and positively influence crucial cells involved in nerve repair, including Schwann cells and macrophages (64).

In the peripheral nervous system, the interaction between neurons and fibronectin is primarily mediated by β1 class integrin heterodimers. During neural development, fibronectin and α5β1 integrin are expressed at relatively high levels in neurons (65). In mature nerve injuries, both fibronectin and α5β1 integrin are upregulated. Therefore, it can be observed that fibronectin and its receptor α5β1 may mediate functionally important interactions during the development and regeneration of the peripheral nervous system (66). α5 integrin is localized in adhesion complexes within the growth cones and protrusions of injured peripheral nerves, and injured sensory nerves exhibit a stronger response to fibronectin compared to normal nerves (67). Thus, in injured nerves, enhanced axonal growth mediated by fibronectin is largely facilitated by α5β1 integrin.

Studies by Mosahebi et al. suggest that adding fibronectin to a bioengineered nerve conduit scaffold based on alginate hydrogel promotes nerve regeneration, supports Schwann cell vitality, and enhances its influence on axon growth during nerve conduit transplantation, emphasizing its crucial role in axon regeneration (68).

5.1.4 Laminin

Laminin is a high-molecular-weight glycoprotein composed of three disulfide-bonded peptides, α, β, and γ chains. The human genome encodes 11 genes for different laminin chains. Different laminin isoforms can bind to different molecules, and laminin is present on all basement membranes. Laminin can interact with type IV collagen, nidogen, perlecan, and heparan sulfate proteoglycans, assembling into the basement membrane (69, 70). A common and crucial function of laminin is its interaction with receptors anchored on the cell membrane near the basement membrane. In this process, laminin regulates various cellular activities and signaling pathways. Structurally, laminin consists of several independently folded, distinct domains, the number, location, and size of which, as well as their interaction with other molecular components of the basement membrane, vary among laminin members (71). It has been found that in models of nerve regeneration after peripheral nerve injury, the additional addition of cross-linked laminin complexes can lead to the

observation of many new capillary-like structures around regenerating nerves, suggesting its potential to promote nerve regeneration by inducing angiogenesis (72).

5.1.5 Glycoproteins and proteoglycans

These components have diverse compositions and are not detailed here.

5.1.6 Glycosaminoglycans

Glycosaminoglycans (GAGs) are long linear polysaccharides composed of repeating disaccharide units, typically consisting of uronic acid and amino sugar. The repeating disaccharide units, except for keratan sulfate, where glucuronic acid is replaced by galactose, consist of a sugar aldehyde and an amino sugar (73). GAGs are present in vertebrates, invertebrates, and bacteria (15). Due to their high polarity, GAGs attract water, serving as lubricants or shock absorbers in the human body. In the ECM environment after peripheral nerve injury, GAGs may play a role in shaping and guiding Schwann cell growth. A study suggests that incorporating a synthetic collagen substrate matrix containing chondroitin sulfate 6 into the lumen significantly improves bridging and functional recovery in a rat model of nerve injury (74).

5.2 Scaffold material selection

The materials used to construct nerve scaffold conduits can be classified into two major categories: natural and synthetic. Compared to synthetic materials, natural materials exhibit higher compatibility, faster degradation, non-toxic degradation products, and the ability to provide cell adhesion factors and their binding sites, making them more promising for applications. To promote the structural and functional repair and regeneration processes after peripheral nerve injury, exploring and improving natural biomaterials that closely mimic the highly directional native ECM can be crucial. These materials can bridge the gap in injured nerves, provide guidance for regenerating axons, and support a protective microenvironment, thereby facilitating better cell growth and reducing the probability of nerve tumor formation. The closer the microstructure of a good nerve scaffold conduit material is to natural tissue, the greater the success rate of regeneration transplantation (10, 29, 75–77).

As mentioned earlier, collagen is the most abundant protein in humans and animals, accounting for 25–35% of total proteins. It is also a major inherent component of the ECM in peripheral nerves, playing a crucial role in nerve development and maintenance of nerve function. Collagen's fibrous structure, close to natural nerve tissue, and its better revascularization effects make it an important alternative material. It can deposit in the ECM of Schwann cell basement membranes and peripheral nerves to provide structural support, and through surface receptors, aid in myelin regeneration and functional recovery. However, collagen has the disadvantage of poor mechanical and physical properties (75, 78, 79).

To improve its performance for better scaffold construction and transplantation, attempts have been made to modify collagen by adding SiO2. The results showed a significant reduction in the scaffold's porosity, swelling rate, and degradation rate, and a notable improvement in mechanical and physical properties. Schwann cell viability and DNA content increased initially with SiO2 concentration and then declined. The optimum concentration for the lowest cytotoxicity was found to be 25 μg/mL [59]. Another approach involves combining collagen with chondroitin sulfate using electrospinning technology to build a scaffold. The fiber orientation of the scaffold was observed under scanning electron microscopy to assess its impact on cell tissue growth. The results showed that the fiber orientation and tensile strength of the scaffold were close to normal nerve tissue. Additionally, using a centrifuge produced more orderly oriented fibers (75).

Some researchers proposed using nanosilver particles combined with collagen to significantly increase the adsorption capacity of fibronectin (a crucial protein for stabilizing nerve morphology and adsorbing seed cells) and achieve better morphological and functional recovery. It was observed that in the animal model of 10 mm peripheral nerve injury, compared to the control group without nanosilver, the silver-containing group had thicker myelin, faster conduction speed, and higher maximum nerve potential. Moreover, it could avoid the negative effects of the traditional polyglycolic acid (PGA) scaffold's degradation process, which leads to a decrease in pH and further damages the residual scaffold structure, triggering a positive feedback effect that accelerates degradation and harms the cell microenvironment. The team successfully used type I collagen combined with nanosilver to promote the regeneration of rabbit sciatic nerves (29). In addition to collagen, chitosan is another alternative material in the field of nerve regeneration. Chitosan is derived from chitin extracted from crustaceans, insects, and mushrooms. Similar to collagen, it exhibits good biocompatibility but has limitations in terms of plasticity and mechanical properties. The binding of chitosan with Schwann cells can increase the probability of damaged nerve connections, producing more ECM components similar to natural scaffolds (mainly collagen, proteoglycans/glycosaminoglycans (PG/GAGs), elastin, etc.). This stimulation further induces the secretion of fibronectin, a key protein in ECM that regulates tissue homeostasis and controls core cell processes and participates in the regulation of axon myelination. This secretion can lead to the formation of vascular basement membranes and peripheral myelinated axon regeneration. Chitosan's unique physicochemical composition allows it to mimic the physiological multilayer structure of peripheral nerves, making it suitable for biomimetic structures (80–82).

Researchers led by Florian Neubrech attempted to use chitosan nerve conduits to repair acute human hand sensory nerve injuries. The results showed that the additional use of chitosan nerve conduits significantly reduced the occurrence of painful neuromas. Moreover, there was a correlation between clinical improvement in function (static two-point discrimination ability) and the use of chitosan conduits (83). The team led by Yuval Shapira conducted a comparative study between chitosan hollow tubes and autologous nerve grafts. After 90 days, there were no statistically significant differences in electrophysiological indices, muscle function, and morphology-related indicators between chitosan hollow tubes and autologous nerve grafts, suggesting its potential application prospects (84). Rachel Sarabia-Estrada and colleagues implanted chitosan nerve conduits loaded with progesterone to regenerate the sciatic nerves of rats. The results indicated that, after 90 days, rats with chitosan conduits containing progesterone showed better recovery in knee joint angle displacement, stride length, movement

speed, and hindlimb lift-off the ground compared to the regular chitosan group (85). Chitosan biodegradation can form chito-oligosaccharides (COS), which possess neuroaffinity and neuroprotective effects. Yanpei Gong found that COSs can accelerate peripheral nerve regeneration after rabbit sciatic nerve crush injury (86).

Apart from collagen and chitosan, some niche materials are worth mentioning. A team led by A E Carolus used bovine pericardium as a wrapping material for nerve scaffolds transplanted to patients with peripheral nerve injuries. The results showed improvement in both function and pain for all patients. The material used showed no adverse reactions, and compatibility tests indicated seamless integration with the environment without causing nerve reformation scars, suggesting that bovine pericardium is a promising allogeneic material for nerve wrapping (87).

5.3 Improvement in the manufacturing process of nerve conduit scaffolds

In the context of nerve conduit scaffolds, material selection is not the only crucial factor; the manufacturing process also plays a key role in determining the final performance and effectiveness. Traditional processes, including electrospinning, freeze-drying, and centrifugal casting, have limitations in replicating the structure, fiber alignment, and physicochemical parameters of natural ECM. A newer production process for scaffolds, high-resolution 3D printing, has entered the animal experimentation stage. The scaffolds produced using this method demonstrate superior effects in promoting axonal directional growth and myelin sheath formation compared to simple cell transplantation. This is attributed to the ability of 3D printing to generate a complex and intricate internal structure that closely resembles natural ECM. The goal of 3D printing in peripheral nerve regeneration is to automate the manufacturing of structures inside nerve conduits, potentially rivaling autologous nerve grafts in cases of large gap injuries, and allowing for precise customization for patients (16, 88).

Another approach to improving the ECM condition after nerve conduit transplantation involves constructing acellular nerve grafts (ANG) with ECM derived from homologous dental pulp stem cells (DPSCs). In ANG, cells and myelin from DPSCs are removed, preserving the original ECM. This promotes Schwann cell attachment and proliferation without triggering a strong immune response. However, the effectiveness of ANG is still weaker than that of autologous nerve transplantation (89).

The products obtained after decellularization of neural tissue and processed through specific procedures to create tissue-derived ECM and applied in neural regeneration research are also of significant importance (9, 27). Chen et al. prepared decellularized ECM and polydopamine (PDA)-coated 3D-printed poly(ε-caprolactone) (PCL) conduits. The results showed that dECM/PDA-coated PCL conduits exhibited favorable mechanical properties compared to nerves from humans or animals. The dECM/PDA-coated PCL nerve conduits could serve as a practical and clinically feasible tool to promote the regeneration of longer peripheral nerve defects (90).

From the above studies, it is evident that nerve conduits are moving toward greater diversity in materials, combining organic and inorganic components. The manufacturing process is becoming more sophisticated, gradually approaching the goal of creating an environment similar to natural ECM. This direction aims to provide an environment more conducive to the growth and proliferation of Schwann cells, ultimately improving the success rate of nerve regeneration.

5.4 Complex interactions between ECM and Schwann cells

Further research is underway to explore the intricate interactions between ECM and Schwann cells (SCs). The team led by Peng Yu found that laminin (LN), fibronectin (FN), and type IV collagen (IV-Col) possess the ability to promote early adhesion of SCs in 2D culture. However, there are significant differences in the proportion of early cell adhesion, and the expression levels required for maintaining cell morphology vary markedly with different ECM proteins (10). Stephanie J Armstrong's earlier study on the impact of ECM molecules on SC adhesion and proliferation on poly(3-hydroxybutyrate) (PHB) nerve conduit material yielded similar findings, highlighting the role of LN in enhancing synaptic growth by activating NF-kappaB in SCs (91, 92). Taogen Gong's team, using single-cell RNA sequencing (scRNA-seq), revealed strong interactions between ECM and SC-related subgroups, possibly mediated by the SEMA3C signaling pathway and MK/PTN gene family, which are crucial for promoting SC proliferation and migration, thus facilitating earlobe scar nodule formation (93). Regulating and activating these pathways during peripheral nerve regeneration can accelerate SC proliferation and migration, promoting the regeneration process.

Xu and colleagues analyzed the impact of ECM hardness and cell morphology on SC plasticity, finding that increased ECM hardness and SC spreading downregulated regenerative proteins through the activation of Rho GTPase and YAP/TAZ. At the same time, cell elongation promoted unique SC regenerative abilities through the upregulation of Rac1/MKK7/JNK, essential for the ECM and morphological changes observed in nerve regeneration (94). Natural and synthetic enhancer-promoter (EP) systems can induce gene transcription through time, space, or environmental signals, providing a means for finely regulating expression. Constructing SCs with artificial EP promoter carrier systems to further enhance the expression intensity of pathways like Rac1/MKK7/JNK might better promote ECM regulation and peripheral nervous system regeneration. Eva Sonnenberg-Riethmacher's team found that the neural regulatory protein ligand and its ErbB3 receptor are crucial for SC development. Defective ErbB3 expression leads to complete loss of SCs in peripheral nerve axons, muscle bundle tremors, and neuronal cell death. ECM gene periostin was significantly downregulated in ErbB3-deficient pseudo-unipolar neurons (DRG), suggesting a pathway where ECM interacts with neurons to intervene in SC gene expression (ErbB3 receptor activation-periostin gene-periostin secretion-SC migration). Feng-Chun Yang's team, studying neurofibromas, discovered that mast cells in the ECM can infiltrate neurofibromas and secrete proteins that reshape the ECM and initiate vascularization, establishing a new interaction between Nf1−/− (homozygous mutation of the Nf1

TABLE 1 Overview of Schwann cell and extracellular matrix (ECM) interactions.

Acting factors	Routes of action/effects	References
Laminin Fibrin Type IV collagen	Promote early adhesion of SCs in two-dimensional culture, with obvious difference in adhesion ratio.	(89, 91)
Laminin	Activating NF-kappaB in Schwann cells to enhance synaptic growth.	(92)
MK/PTN gene family	Promote Schwann cell proliferation and metastasis through the SEMA3C signaling pathway, thereby promoting earlobe keloid formation.	(93)
Increase in ECM stiffness and SC diffusion	Downregulation of SC regeneration-related proteins through activation of RhoGTPase and YAP/TAZ	(94)
Cell elongation	Promotes unique SC regeneration capacity through upregulation of Rac1/MKK7/JNK, contributing to changes in cell morphology and ECM.	(94)
Neuregulin ligands and their ErbB receptors	Promote the expression of ECM gene periostin, induce the production of periostin, and promote the formation, proliferation and migration of Schwann cells.	(96)
Nf1+/− Mast cell migration	Overactivation of the Ras-like IA-PI3K-Rac2 pathway triggers the interaction between Nf1−/− Schwann cells and Nf1+/− mast cells, ultimately promoting the secretion of a type of protein that can remodel the ECM and promote angiogenesis, causing neurofibromas.	(95)

tumor suppressor gene) SCs and Nf1+/− (heterozygous mutation of the Nf1 tumor suppressor gene) mast cells. This interaction is characterized by increased migration of Nf1+/− mast cells, closely related to the overactivation of the Ras class IA-PI3K-Rac2 pathway and significant for the formation of neurofibromas during regeneration (95).

In summary, after peripheral nerve injury conduit transplantation, the newly formed ECM will activate a series of signaling pathways through a range of growth factors, leading to complex interactions with Schwann cells. Adjusting materials and manufacturing methods, altering the physicochemical properties of ECM, and properly regulating these pathways will be crucial in promoting better recovery of structure and function after peripheral nerve injury, representing a key focus in future research in this field (Table 1).

6 Summary and future outlook

This review has outlined one of the key focuses in the field of peripheral nerve regeneration: Schwann cells, ECM, and their intricate interactions. It is evident that the quality of the ECM environment directly determines the proliferation and developmental processes of Schwann cells, thereby influencing the prognosis of peripheral nerve regeneration after injury. By improving the materials and manufacturing processes of nerve conduits to alter the physicochemical properties of the ECM, and by supplementing with exogenous growth factors or modulating the expression of specific genes, we can enhance Schwann cell growth, proliferation, and directionality. This approach aims to achieve nerve structures that closely resemble normal states, maximizing functional recovery and overcoming the inconveniences associated with autologous nerve transplantation.

However, the effectiveness of tissue-engineered nerve conduits relying on the interplay between the ECM and Schwann cells for repairing peripheral nerve injuries is not consistently uniform. From the literature covered in this review, future prospects involve the use of collagen-SiO2-chitosan composite materials, employing electrospinning and 3D printing to mimic the intricate internal structures of natural peripheral nerves. Additionally, the injection of exogenous growth factors such as bFGF, along with the use of gene editing techniques to introduce enhancers, miRNA, and other methods to activate/silence specific genes necessary for maintaining the complex interaction between Schwann cells and the ECM, holds promise. This approach is expected to establish a comprehensive and precise medical industry chain for peripheral nerve injuries – one of the most common and challenging surgical injuries. This development could bring significant economic benefits and health improvements, profoundly impacting the fundamental research in neuroscience.

Author contributions

MJ: Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. MC: Writing – original draft, Writing – review & editing. NL: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 09 April 2024
DOI 10.3389/fneur.2024.1357476

OPEN ACCESS

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RECEIVED 18 December 2023
ACCEPTED 28 March 2024
PUBLISHED 09 April 2024

CITATION
Zhou B-b, Chen X, Zhang C, Wang Y-p, Ma P-p, Hao S-j, Hui L and Bai Y-f (2024) Analysis of spinal muscular atrophy carrier screening results in 32,416 pregnant women and 7,231 prepregnant women.
Front. Neurol. 15:1357476.
doi: 10.3389/fneur.2024.1357476

Analysis of spinal muscular atrophy carrier screening results in 32,416 pregnant women and 7,231 prepregnant women

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Objectives: Spinal muscular atrophy (SMA) is an autosomal recessive disease that is one of the most common in childhood neuromuscular disorders. Our screenings are more meaningful programs in preventing birth defects, providing a significant resource for healthcare professionals, genetic counselors, and policymakers involved in designing strategies to prevent and manage SMA.

Method: We screened 39,647 participants from 2020 to the present by quantitative real-time PCR, including 7,231 pre-pregnancy participants and 32,416 pregnancy participants, to detect the presence of SMN1 gene EX7 and EX8 deletion in the DNA samples provided by the subjects. To validate the accuracy of our findings, we also utilized the Multiplex Ligation-dependent Probe Amplification (MLPA) to confirm the reliability of screening results obtained by quantitative real-time PCR.

Result: Among the 39,647 participants who were screened, 726 participants were the carriers of *SMN1*. The overall carrier rate was calculated to be 1.83% (95% confidence interval: 0.86–2.8%). After undergoing screening, a total of 592 pregnancy carriers were provided with genetic counseling and only 503 of their spouses (84.97, 95% confidence interval: 82.09–87.85%) voluntarily underwent SMA screening.

Conclusion: This study provides crucial insights into the prevalence and distribution of SMA carriers among the female population. The identification of 726 asymptomatic carriers highlights the necessity of comprehensive screening programs to identify at-risk individuals and ensure appropriate interventions are in place to minimize the impact of SMA-related conditions.

KEYWORDS

SMA carrier screening, genetics counseling, *SMN1*, pre-pregnancy, pregnancy

1 Introduction

Spinal muscular atrophy (SMA) is one of the most common neuromuscular diseases in children, with muscle weakness and muscle atrophy caused by the defects of α-motor neurons in the anterior horn of the spinal cord as the main clinical features. In 1995, scientists made a significant breakthrough by identifying a survival motor neuron (*SMN1*) gene which is located

in the chromosomal region of 5q11.2-q13.3 (1), as the culprit for SMA, an autosomal recessive disorder. *SMN1* is responsible for encoding the vital survival motor neuron protein in motor neurons, thus playing a crucial role in maintaining their proper functioning (2). SMA is identified as the second most common inherited cause of infant mortality, with an estimated incidence of 1/6000 ~ 1/11000 live births, and the carrier frequency is 1/47 ~ 1/72 (3, 4).

SMA is a disease that manifests itself in varying degrees of severity, and patients can exhibit a wide spectrum of clinical symptoms. To classify the disease and its various manifestations, clinicians generally divide SMA into four distinct clinical types based on their diagnostic criteria (5): (1) Type I is the most severe and common type, which accounts for about 50% of patients diagnosed with SMA, and is usually characterized by an inability to walk unaided, weakness in the neck, and an inability to care for oneself. (2) Type II is relatively mild compared to Type I. Patients can sit without support and in some cases, they may even be able to stand up, but they do not gain the ability to walk on their own. (3) Type III is relatively milder compared to Type II. Patients with this condition may exhibit clinical heterogeneity, meaning they can present with varying symptoms and severity. However, most patients with type III exhibit muscle atrophy and loss of ambulation. (4) Type IV is characterized by mild symptoms and typically appears after the age of 30. Patients with Type IV are usually able to walk without any issues related to breathing or eating (4, 6). Approximately 95% of SMA patients are caused by loss of function in the *SMN1* due to E7 lost or both E7 and E8 lost, while the remaining individuals may exhibit a genetic variation where one copy of the gene is lost and the other copy contains a mutation within the gene (7). The disease severity is mainly influenced by the copy number of survival motor neuron 2 (*SMN2*), a nearly identical gene and highly similar to *SMN1*, which produces only less functional protein (8). The *SMN1* and *SMN2* are very similar in terms of their DNA sequences, with only five nucleotides differentiating them. Of these nucleotides, the four nucleotides are located in the non-coding region (2), and a special site (c.840C > T) in the coding region is used to distinguish *SMN1* from*SMN2* in the next-generation sequencing technology (9).

Considering the severity of clinical symptoms, high mortality rate, and strong genotype–phenotype correlation, for a long time, screening for SMA carriers has been of interest to clinicians. In 2008, the American College of Medical Genetics (ACMG) recommended that individuals be screened for SMA carrier status regardless of their race or ethnicity. This population screening is intended to identify carriers of the SMA gene, which can help with family planning and early detection of symptoms in affected children. By identifying carriers in the general population, healthcare providers can better inform individuals and couples about the risks of passing on the SMA gene to their children. This recommendation reflects the importance of early detection and prevention of genetic diseases like SMA (10). In 2016, the American College of Obstetrics and Gynecology (ACOG) recommended that all women who are planning to become pregnant or are already pregnant should undergo screening for SMA carriers. This recommendation was made to identify carriers of SMA, a genetic disorder that can be passed on to offspring, and to provide appropriate counseling and care to affected families. Therefore, it is important for women to be aware of this recommendation and to discuss SMA carrier screening with their healthcare provider (11). The therapeutic medication for SMA, nusinersen, has been available in mainland China since 2019, and an expert consensus on genetic diagnosis of SMA has been published (12, 13). Through meticulous and thorough screening, it is feasible to detect people who possess *SMN1* mutations in a heterozygous condition, which denotes that they are carriers of SMA. If both partners of a couple are SMA carriers, there is a 25% possibility that their offspring may inherit SMA. It is advisable to undergo prenatal diagnosis of SMA with standard genetic counseling. Currently, most countries and regions, including some parts of China, routinely screen parents and newborns for SMA mutations (14–19). In this study, we report our SMA carrier screening data for >30,000 individuals without a family history of SMA in Lanzhou City, Gansu Province, Northwest China, which was performed using technical criteria and guidelines for SMA testing and conducted using real-time quantitative polymerase chain reaction (real-time PCR, or qPCR). Our findings highlight the significant impact of the ACMG guidelines, which led to an increase in the adoption of rapid testing and the identification of SMA carriers in the area. Additionally, this study sheds light on the high level of patient interest in screening for SMA carriers. Furthermore, the availability of prenatal diagnosis for high-risk patients can effectively prevent the birth of a child with SMA.

2 Materials and methods

2.1 Population samples and processing flow

This clinical study was performed at the Center of Genetics of Gansu provincial Maternity and Child-care Hospital between Jan 1, 2020, and Mar 31, 2023. A total of 39,647 women were accepted to SMA carrier screening, including 32,416 pregnancy participants (Supplementary Figure S1; Table 1) and 7,231 pre-pregnancy participants (Supplementary Figure S1; Table 2). Before the screening program, they were all received genetic counseling. Information on the participants is listed in Tables 1, 2. The ages of the participants during the pre-pregnancy and pregnancy screening mainly ranged from 25 to 35 years and the gestational weeks of the pregnancy screening participants mainly ranged from 12 to 14 weeks (Supplementary Figure S2). If a woman was a carrier of SMA, then her spouse needed to be screened. For couples who were SMA carriers, the fetus was carried out SMA prenatal diagnosis according to the wishes of both couples. The screening is limited to the deletion of *SMN1* (exon7/exon8), and other genes are not in the detection range. This study was approved by the ethics committee of Gansu provincial Maternity and Child-care Hospital. All participants signed written informed consent.

2.2 Genomic DNA

A total of 2 ~ 3 mL of peripheral blood was collected in vials containing ethylenediamine tetraacetate acid from every participant, and DNA was extracted using a Blood Genomic DNA Extraction Kit (Xiamen Kaiso Biotech Co., Ltd., RC1001). The extracted DNA was assessed for purity (absorbance ratio of 260/280 nm between 1.8 and 2.0), and concentration using a UV spectrophotometer. After genetic

10.3389/fneur.2024.1357476

TABLE 1 Details of the 32,416 pregnant women in different time periods.

Screening Date	2020.3–2020.12			2021.1–2021.6			2021.7–2021.12			2022.1–2022.6			2022.7–2022.12			2023.1–2023.4		
Total Number	4,200			4,474			6,658			5,657			6,352			5,075		
Ages (Years)	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI
<25	471	11.21	8.36–14.06	523	11.69	8.94–14.44	804	12.08	9.82–14.33	605	10.69	8.23–13.16	580	9.13	6.79–11.48	488	9.62	7–12.23
26–35	3,290	78.33	76.93–79.74	3,622	80.96	79.68–82.24	5,399	81.09	80.05–82.13	4,666	82.48	81.39–83.57	5,288	83.25	82.24–84.26	4,128	81.34	80.15–82.53
>35	439	10.45	7.59–13.31	329	7.35	4.53–10.17	455	6.83	4.52–9.15	386	6.82	4.31–9.34	484	7.62	5.26–9.98	459	9.04	6.42–11.67
Gestational age (Weeks)																		
<15	3,218	76.62	75.16–78.08	3,726	81.96	80.72–83.21	5,501	82.62	81.62–83.62	4,722	83.47	82.41–84.53	5,203	81.91	80.87–82.96	4,072	80.24	79.01–81.46
16–21	853	20.31	17.61–23.01	688	15.38	12.68–18.07	1,022	15.35	13.14–17.56	802	14.18	11.76–16.59	976	15.37	13.1–17.63	767	15.11	12.58–17.65
>21	129	3.07	0.09–6.05	119	2.66	−5.78	135	2.03	−4.76	133	2.35	−5.15	173	2.72	0.3–5.15	236	4.65	1.96–7.34

counseling, pregnant women who were SMA carriers underwent interventional prenatal diagnosis and 10 mL amniotic fluid that was extracted at 18–24 weeks gestation was taken for detection. Genomic DNA was extracted using a Tissue Genome DNA Extraction Kit (Tiangen Biochemical Technology Co., Ltd., DP304, Peking), and the final DNA concentration was adjusted to between 20 and 40 ng/μL.

2.3 Quantitative real-time PCR

The detection reagent kit is provided by Shanghai Medical Research Co., Ltd. to detect the copy numbers of *SMN1* gene E7 and E8. The total volume of each reaction is 20 μL and there were five controls for each assay, including a blank control with no DNA, a positive control for *SMN1* E7 and E8 deletions, and three *SMN1* two-copy ladder controls. The E7 and E8 PCR primers of *SMN1* were designed based on the article reported by Smith M (20). Furthermore, the human RPP40 gene was used as the internal standard to enhance the effectiveness of the detection. The PCR amplification was performed according to this condition: 10 min at 95°C followed by 40 cycles of 95°C for 15 s and 58°C for 60 s. The fluorescence data were collected from the FAM and VIC channels, and the result of qPCR was calculated using the cycle threshold (Ct) value. In the E7 and E8 reaction, $^{\triangle}$Ct_c is the value of the difference between FAM and VIC channels obtained by diluting the control at different ratios (1:2:4), and $^{\triangle}$Ct_s is the difference between the target gene and the internal standard gene in the E7 and E8 reactions of the sample to be tested. The $^{\triangle\triangle}$Ct is calculated as follows:

$$^{\triangle\triangle}Ct = \frac{\sum_i \left({}^{\triangle}Ct\_c \right)}{3} - {}^{\triangle}Ct\_s, i = 1,2,4$$

The *i* indicates the dilution of the control. $^{\triangle\triangle}$Ct > 0.8 or is no amplification signal, and $^{\triangle\triangle}$Ct > 1.5 or a lack of amplification signal signifies the presence of a homozygous deletion in both Exon7 and Exon8 regions of the *SMN1* gene. If $-0.45 < {}^{\triangle\triangle}Ct \leq 0.45$ indicated a heterozygous deletion in both Exon7 and Exon8 regions of the *SMN1* gene and $^{\triangle\triangle}$Ct ≤ −0.55 indicated normal of Exon7 and Exon8 of *SMN1* gene.

2.4 Multiplex Ligation-dependent Probe Amplification (MLPA) assay

For the authenticity of the results, we verified the positive and critical results of qPCR using MLPA P060 kit. SALSA MLPA Kit (P060) produced by MRC-company of the Netherlands was used, which contains 21 probes with amplification products including two probes each for *SMN1* and *SMN2* and 17 reference probes. We strictly followed the standard procedure of the SMA MLPA kit to perform experiments. DNA samples were diluted to approximately equal concentrations (20–40 ng/μL). After subjecting the samples to denaturation, hybridization, ligation, and amplification, the resulting products were analyzed utilizing the ABI 3500 genetic analyzer from Thermo Fisher Scientific. The initial data obtained were then processed and analyzed using the Coffalyser.net.

TABLE 2 Details of the 7,231 pre-pregnancy women in different time periods.

Screening date	2020			2021			2022			2023		
Total number	619			2,859			2,662			1,084		
Ages (Years)	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI	*N*	%	95% CI
<25	81	13.09	5.74–20.43	335	11.72	8.27–15.16	240	9.02	5.39–12.64	105	9.69	4.03–15.34
26–35	479	77.38	73.64–81.13	2,248	78.63	76.93–80.32	2,158	81.07	79.41–82.72	848	78.23	75.45–81.01
>35	59	9.53	2.04–17.02	276	9.65	6.17–13.14	264	9.92	6.31–13.52	131	12.08	6.5–17.67
Number of carriers (*n*)	14			46			47			27		
Carrier rate (%)	2.26			1.61			1.76			2.49		
95% CI (%)	1.09–3.43			1.15–2.07			1.26–2.26			1.56–3.42		
Spouse (*n*)	13			40			42			25		
Recall rate (%)	92.86			86.95			89.36			92.59		
95% CI (%)	79.37–106.35			77.22–96.68			80.54–98.18			82.71–102.47		
Number of carrier couples	1			1			1			0		

2.5 Statistical analyses

We performed statistical analysis using R (V4.2.1). The data was presented in the form of percentages and their 95% confidence intervals were calculated. All values were retained to two decimal places. Statistical significance was indicated by a p value of less than 0.05. To compare the prevalence of SMA carriers among various regions, we looked at previously published studies conducted in China within the past few years.

3 Results

3.1 The result of screening

A total of 39,647 blood samples of women were successfully tested, including 7,231 pre-pregnancy participants and 32,416 pregnancy participants. Among the 39,647 participants performed by qPCR, 726 asymptomatic SMA carriers were identified, including 134 pre-pregnancy carriers and 592 pregnancy carriers, with a carrier rate of 1.83% (95% confidence interval: 0.86–2.8%). After analysis, among the 726 asymptomatic carriers, 676 carried a single copy of both E7 and E8 and 50 carried a single copy of E7 only.

3.2 MLPA further confirms the results of qPCR

When using qPCR for SMA carrier screening, it is necessary to further validate the positive results of qPCR by MLPA methods (21). Therefore, we simultaneously performed MLPA testing on these 726 asymptomatic carriers. After MLPA validation, 726 asymptomatic SMA carriers were confirmed, while some variants in *SMN2* E7 and E8 were detected (Supplementary Figure S3). There were 41 cases of *SMN1* duplication, including 28 E7 single copy and 13 E8 single and double copy, and 157 cases of *SMN2* duplication, including 23 only E7 duplication, 83 E7 and E8 duplication, and only 51 E8 duplication (Supplementary Figure S4; Supplementary Table S1).

3.3 Prenatal diagnosis

After undergoing screening, a total of 592 pregnancy carriers were provided with genetic counseling, which included information on the etiology, genetic pattern, clinical characteristics, reproductive risk, and treatment options for SMA. Out of these carriers, 503 of their spouses (84.97, 95% confidence interval: 82.09–87.85%) voluntarily underwent SMA screening, which resulted in the identification of thirteen couples who were both SMA carriers. As a result, amniocentesis was performed on the high-risk fetuses of these thirteen couples. The findings revealed that two fetuses had a homozygous deletion of E7 and E8 of *SMN1* and two fetuses with compound heterozygosity for E7 homozygous deletion and E8 heterozygous deletion of *SMN1*, and six fetuses were carriers (Table 3). After receiving adequate genetic counseling and according to the wishes of pregnant women and couples, the parents of those high-risk fetus decided to terminate the pregnancy. On the other hand, the remaining six fetuses had a heterozygous deletion of E7 and E8 of *SMN1*, which indicated that they were SMA carriers. Despite this, the parents of these fetuses chose to continue their pregnancy.

4 Discussion

SMA, a serious and high-incidence autosomal recessive neuromuscular disease, has a wide variability in age of onset and may

TABLE 3 Results of the 32,416 pregnant women SMA carrier screening.

Screening date	2020.03–2020.12	2021.01–2021.06	2021.07–2021.12	2022.01–2022.06	2022.07–2022.12	2023.01–2022.04
Screened women (*n*)	4,200	4,474	6,658	5,657	6,352	5,075
Number of carriers	83	71	109	114	113	102
Carrier rate (%)	1.98	1.59	1.64	2.02	1.78	2.01
95% CI (%)	1.56–2.40	1.22–1.95	1.33–1.94	1.65–2.38	1.45–2.10	1.62–2.40
Spouse (*n*)	51	53	98	105	108	88
Recall rate (%)	61.44	74.64	89.90	92.11	95.57	86.27
95% CI (%)	50.97–71.91	64.52–84.76	84.24–95.56	87.16–97.06	91.78–99.36	79.59–92.95
Number of carrier couples	2	2	2	3	2	2
Prenatal diagnoses (*n*)	2	2	2	3	2	2
Carriers (*n*)	2	0	1	1	1	1
Affected cases (*n*)	0	1	0	1	1	1
Pregnancies terminated (*n*)	0	1	0	1	1	1

develop in any ethnic group and age from birth to adulthood (22). The main manifestation is progressive muscle weakness mainly in the proximal extremities, and as the disease progresses, multi-system involvement such as respiratory, digestive, and skeletal systems may occur. Fortunately, there were many ways to screen for SMA to prevent the birth of a child with SMA (23–25). If both spouses are SMA carriers, their offspring have a 25% probability of having SMA or the normal genotype, and a 50% probability of being carriers. Therefore, preconception screening is the only reliable, economical, and safe way to prevent SMA in offspring.

Recently, there has been a growing interest in SMA carrier screening, particularly in populations with a higher disease prevalence. The availability of new genetic testing technologies has made it easier to identify carriers of the *SMN1* gene mutation, which can help inform reproductive decisions and improve patient outcomes. In recent decades, pre-pregnancy and pregnant women accepted routine prenatal screening for chromosome abnormalities in China, which has effectively reduced birth defects. However, SMA carrier screening is not a routine prenatal examination program, but it may become a prevalent screening program in the future due to its high carrier rate and severe clinical phenotype as well as the increasing acceptance of the program by pregnant women. It is important to note that both ACOG and ACMG recommend that carrier screening for SMA should be offered to all women who are planning on becoming pregnant or who are currently pregnant. This testing can help identify carriers of the SMA gene and inform couples about their risk of having a child with the condition. Ultimately, carrier screening can help individuals make informed reproductive decisions and take appropriate steps to ensure the health of their future children (10, 26).

As of the current, SMA carriers screening is already open worldwide (14, 27–29), and even has been conducted in most areas of China (16, 17, 19, 30–34). In this study, we identified 726 SMA carriers from 39,647 participants who were screened for SMA in Lanzhou City, Gansu province. The carrier rate approximately was 1/55 (1.83%), which is higher than other regions of China (Table 4), such as Liuzhou, Zhaoqing, Guangdong, Guangxi, Hainan, Yunnan. Meanwhile, the SMA carrier rate of our report was consistent with the frequency of 1/40–1/60 in the literature (20). Nevertheless, there was no significant variation in the carrier rate of SMA among different regions within China. One study that investigated 10,585 healthy couples from 34 ethnic groups in southern China with an NGS-based method, showed that there were no significant differences in SMA carrier rate among provinces, but there were differences in carrier rate among ethnic groups (16). In addition, the results of another screening study with a large pan-ethnic population showed a detection rate of 91.2% for SMA, and a carrier rate of SMA in the range of 1/47–1/68, which had no significant differences in those carrier rates (3). These studies indicate that there may be no geographical or racial differences in SMA carrier rate. In this study, race could not be summarized due to a lack of the relevant information of participants. However, our screening participants all belonged to the same area, so there was no geographic variability.

Since *SMN1* and *SMN2* exhibit such a high level of sequence identity, previous research efforts have not fully leveraged the vantage of Next Generation Sequencing (NGS) technology. SMA carrier screening in domestic areas of China is now basically based on RT-PCR testing of specific regions of the *SMN1* gene, which cannot comprehensively cover the *SMN1* gene, especially single-nucleotide variants (SNVs) and insertions/deletions (Indels). The recent development of NGS-based technology for SMA carrier screening is gradually being used in the clinical, making SMA testing part of a comprehensive NGS carrier testing platform. Previous studies compared and validated the performances of the sequencing based and MLPA carrier status detection technologies, which shows a strong association between them (39). NGS-based screening technology for SMA carriers is expected to provide comprehensive coverage of the *SMN1* and *SMN2* genes and more scientific and detailed explanations of the causes of different clinical phenotypes of SMA. The different clinical phenotypes of SMA were further explained by increasing the depth of sequencing and optimizing the algorithms of data analysis to accurately call copy number variants of *SMN1* and *SMN2*. In this study, SMA carrier screening was conducted in three stages. First,

TABLE 4 SMA carrier rate in the different areas of China and different countries.

Areas	Number of screening (*n*)	SMA carriers (*n*)	Carrier frequency (%)	References
Taiwan	107,611	2,262	1/48 (2.10)	(30)
Shanghai	4,719	90	1/55 (1.90)	(31)
Sichuan	427	9	1/47 (2.11)	(35)
Liuzhou	4,931	61	1/80 (1.20)	(32)
Yunnan	3,049	62	1/49 (2.03)	(33)
Hongkong	569	9	1/63 (1.60)	(36)
Zhaoqing	5,200	75	1/69 (1.44)	(19)
Warsaw	1,076	26	1/41 (2.44)	(37)
Poland	600	17	1/35 (2.86)	(38)
Saudi	4,090	108	1/38 (2.63)	(14)
Indian	606	16	1/38 (2.63)	(15)
Thailand	505	9	1/56 (1.78)	(27)
Guangdong	4,755	60	1/79 (1.30)	(16)
Guangxi	5,009	71	1/71 (1.40)	(16)
Hainan	2,778	45	1/62 (1.60)	(16)
Yunnan	4,049	66	1/61 (1.60)	(16)
Guizhou	4,292	41	1/104 (1.00)	(16)
Gansu	39,647*	726	1/55 (1.83)	This study

*Includes 32,416 pregnant women and 7,231 pre-pregnant women.

we used RT-PCR to identify the copy number of E7 and E8 of the *SMN1* and *SMN2* genes, and we used MLPA to validate the abnormal results obtained by RT-PCR in pregnant women. Second, if the pregnant woman was identified as a carrier, her spouse should be recommended to accept SMA carrier screening. Finally, we proposed genetic counseling and prenatal diagnosis if the couples were confirmed as carriers. It is important that prenatal counseling for individuals or couples planning to conceive should include information related to Spinal Muscular Atrophy (SMA). This should include guidance on the genetic causes and transmission mode of SMA, recurrence risk assessment, options for prenatal diagnosis or preimplantation genetic testing, and recommendations for carrier screening of family members. By providing this information, families can make informed decisions about their reproductive choices and better understand the potential risks and implications associated with SMA. Healthcare providers must work together with patients and their families to provide comprehensive prenatal counseling and support (13).

In this study, out of the 726 prepregnant women and pregnant women who were identified as carriers during screening, only the spouses of 623 of them were advised to undergo SMA screening. The recall rate for this advice was 85.81% (95% confidence interval: 83.27–88.35%). Except for the families who were not yet ready for screening due to low gestational weeks, about 30% of spouses who were not recalled may be due to poor economic conditions or less recognition of SMA. At the same time, we also analyzed the SMA carrier status of these spouses, and the result showed a carrier rate of 2.08% (95% confidence interval: 0.96–3.2%), which is higher than the combined carrier rate in many countries. This may be because some spouses were not recalled. After undergoing thorough genetic counseling, the couple was advised to undergo prenatal diagnosis for their fetuses. Among the three fetuses identified as being at high risk for SMA, two were found to carry a heterozygous deletion of *SMN1* E7 and E8 genes, while one had a homozygous deletion of the same genes, which would have resulted in SMA after birth. After additional counseling, the parents of the latter opted for pregnancy termination. For the 28 women who were SMA carriers but did not have their partners undergo screening, postnatal follow-up was provided. The follow-up results showed that some mothers chose to have their babies diagnosed with SMA after birth, while others were unwilling to be screened for SMA carriers. The study discovered that almost 30% of pregnant women's spouses did not undergo SMA carrier screening, indicating that some newborns may have missed an early diagnosis. With SMA treatment drugs now covered by medical insurance, early detection, and diagnosis through newborn screening and other methods are crucial for effective SMA treatment.

Overall, it is crucial to recognize the significance of SMA carrier screening as a means of identifying those who may be carriers of this disease and ensuring that they receive appropriate counseling and care. The alarming rate of carriers discovered in recent studies underscores the importance of raising awareness and increasing access to screening services. Additionally, continued research into the underlying genetic mechanisms and treatment options for SMA holds great promise for improving the lives of those affected by this condition and their loved ones. However, there are some limitations in this study, we only detected copy number variants in exon 7 and exon 8 of *SMN1* and SMN2, but SNVs or Indels of *SMN1* and *SMN2*

or other special types such as the 2 + 0 type are outside the scope of this study, which may have missed this group of carriers. With other innovations in technology, it may be possible to compensate for the limitations of this technique in the future. In summary, it is our collective responsibility to prioritize and support efforts aimed at combating SMA and other genetic disorders through comprehensive prevention, identification, and treatment strategies.

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 Institutional Review Boards of Gansu Provincial Maternity and Child-care Hospital. 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

B-bZ: Data curation, Visualization, Writing – original draft. XC: Methodology, Writing – review & editing. CZ: Investigation, Writing – review & editing. Y-pW: Validation, Writing – review & editing. P-pM: Resources, Writing – review & editing. S-jH: Conceptualization, Writing – review & editing. LH: Funding acquisition, Writing – review & editing. Y-fB: Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Gansu Provincial Science and Technology Program (21JR7RA680), and Major Research Project of Gansu Provincial Maternity and Child-Care Hospital (2021). The Natural Science Foundation of Gansu Provincial (2022JR5RA725). The Lanzhou Science and Technology Plan Project (2021-1-182). The Lanzhou Science and Technology Innovation Project for Young Talents (2023-NQ-199).

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.2024.1357476/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Mini Review
PUBLISHED 16 April 2024
DOI 10.3389/fneur.2024.1340845

OPEN ACCESS

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RECEIVED 19 November 2023
ACCEPTED 02 April 2024
PUBLISHED 16 April 2024

CITATION
Zhang X, Duan X and Liu X (2024) The role of kinases in peripheral nerve regeneration: mechanisms and implications.
Front. Neurol. 15:1340845.
doi: 10.3389/fneur.2024.1340845

The role of kinases in peripheral nerve regeneration: mechanisms and implications

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Peripheral nerve injury disease is a prevalent traumatic condition in current medical practice. Despite the present treatment approaches, encompassing surgical sutures, autologous nerve or allograft nerve transplantation, tissue engineering techniques, and others, an effective clinical treatment method still needs to be discovered. Exploring novel treatment methods to improve peripheral nerve regeneration requires more effort in investigating the cellular and molecular mechanisms involved. Many factors are associated with the regeneration of injured peripheral nerves, including the cross-sectional area of the injured nerve, the length of the nerve gap defect, and various cellular and molecular factors such as Schwann cells, inflammation factors, kinases, and growth factors. As crucial mediators of cellular communication, kinases exert regulatory control over numerous signaling cascades, thereby participating in various vital biological processes, including peripheral nerve regeneration after nerve injury. In this review, we examined diverse kinase classifications, distinct nerve injury types, and the intricate mechanisms involved in peripheral nerve regeneration. Then we stressed the significance of kinases in regulating autophagy, inflammatory response, apoptosis, cell cycle, oxidative processes, and other aspects in establishing conductive microenvironments for nerve tissue regeneration. Finally, we briefly discussed the functional roles of kinases in different types of cells involved in peripheral nerve regeneration.

KEYWORDS

peripheral nerve regeneration, peripheral nerve injury, kinase, molecular mechanism, microenvironment

1 Introduction

Peripheral nerves are defined as nerves that are not part of the brain or spinal cord but instead connect the central nervous system (CNS) to target organs for neural signal transduction. Peripheral nerve injury (PNI) is a prevalent disease condition resulting from either physical injury, including traumatic events and surgical procedures, or other disease conditions, such as diabetes, and autoimmune diseases like Guillain-Barre syndrome, systemic lupus erythematosus, and rheumatoid arthritis (1, 2). Iatrogenic injury, primarily caused by traction, cutting, surgery, and neuroma, is a common way to disrupt the continuity of axons and leads to sensory and motor dysfunction in the innervated region, significantly compromising patients' quality of life (3–5). In certain regions, the incidence

of PNI caused by traffic accidents or mechanical injuries within the body has steadily risen alongside economic development (6).

There are different treatment therapies for disease condition-induced PNI, which depends on the causal diseases. For example, glucose control is the predominant method to prevent diabetic neuropathy, along with medicines for pain management (7). Guillain-Barre Syndrome (GBS), an autoimmune disorder involving demyelination of peripheral nerves, is the most common cause of acute flaccid paralysis worldwide. Traditional treatments for GBS encompass corticosteroids, plasma exchange, and intravenous (IV) administration of immunoglobulins (IVIG). Several novel therapies, such as complement inhibitors and cerebrospinal fluid (CSF) filtration, have been developing recently (8). Some patients with systemic lupus erythematosus can also get peripheral neuropathy, who are typically treated with corticosteroids and immunosuppression (9). For Sjogren's syndrome, another common autoimmune disease, apart from the clinical usage of gabapentin and pregabalin for pain relief, immunomodulatory and immunosuppressive therapies have been tested in trials (10).

Unlike the CNS, peripheral nerves possess an inherent capacity for self-repair and regeneration following injury. The treatment methods for physical PNI have evolved from initial microsurgery to current approaches, including autologous/allogeneic nerve tissue transplantation and tissue engineering material transplantation (11). However, the efficacy of these methods is exceptionally constrained due to the intricate nature of peripheral nerve differentiation and the limited understanding of the regeneration mechanisms involved in injured peripheral nerves. Consequently, it is imperative to identify and elucidate additional determinants and mechanisms that influence the regeneration process of the peripheral nerve system (PNS).

To date, numerous factors and molecules, such as Schwann cells (SCs), inflammation factors, kinases, and growth factors, have been identified as crucial regulators of peripheral nerve regeneration (PNR) (11–13). Kinases, a type of biochemical molecules ubiquitously present in cellular organisms, can catalyze the transfer of high-energy phosphate groups from high-energy donors (e.g., ATP) to substrates, primarily facilitating the transduction of various biological signals within cells. Due to their pivotal involvement in signal transduction, malfunctioning kinases often have severe detrimental effects and are associated with a series of diseases (14, 15). Here, we will review the recent progress of research on the mechanisms of PNR from the perspective of kinases.

2 Classification of kinases

The currently recognized kinases encompass protein kinases (including serine/threonine kinases and tyrosine kinases), lipid kinases, glucokinase (such as hexokinase and fructokinase), and others, with protein kinases comprising the majority. Over 500 protein kinases have been identified in the human body, encoded by more than 900 genes, accounting for ~5% of the human genome (16, 17).

2.1 Protein kinase

Based on the presence of phosphorylated groups on the receptors, protein kinases are categorized into various types, such as serine/threonine kinases, tyrosine kinases, histidine/lysine/arginine kinase, and aspartate/glutamate kinase, among others (18–24). Furthermore, protein kinases can also be classified based on their roles in signaling pathways, including AGC (Protein kinase PKA, PKG, PKC), calmodulin kinases (CaMK), mitogen-activated protein kinase (MAPK), MAPKK kinase (Raf), protein kinase B (AKT), Cyclin-dependent kinases (CDKs), protein tyrosine kinases (PTK), and other kinase families (25–31). Protein kinases play significant roles in diverse biological processes by activating target proteins and regulating cellular signaling transduction. Mutations and dysfunctions in protein kinases have been closely linked to human diseases, particularly cancer and inflammation. Consequently, protein kinases have emerged as promising pharmaceutical targets in medical applications (32, 33).

2.1.1 Serine/threonine kinase and tyrosine kinase

The two primary types of protein kinases are serine/threonine kinases (STK) and tyrosine kinases (TK), which were among the earliest kinases to be identified (34). STKs catalyze the phosphorylation of serine/threonine hydroxyl groups on target proteins, while TKs facilitate the phosphorylation of tyrosine residues. These kinases are ubiquitously found in nearly all eukaryotic multicellular organisms and are crucial in mediating cellular signal transduction (35, 36). Based on the localization, these kinases can be categorized into transmembrane receptor kinases and cytoplasmic kinases. Functionally, the transmembrane kinases bind with extracellular ligands to transmit signals into the cells. In contrast, the cytoplasmic kinases are indispensable for transmitting intercellular signals, which subsequently regulate a wide range of cellular processes encompassing cell growth, metabolism, differentiation, proliferation, division, and apoptosis through the modulation of the gene expressions in the nucleus (37, 38).

Various STKs have been identified, including PKA, PKC, CaMK, pyruvate dehydrogenase kinase (PDK), and DNA-dependent protein kinase (DNA-PK). PKA, a typical protein kinase, is widely recognized for its crucial involvement in regulating various biological processes through the cAMP/PKA signaling pathway (39). TKs, based on their location and function, can be broadly categorized into receptor tyrosine kinases (RTKs), which are transmembrane receptor proteins, and non-receptor tyrosine kinases (NRTKs), which are found in the cytoplasm and nucleus. RTKs can be further classified into two groups, which are tyrosine kinase receptor (TKR) and tyrosine kinase associated receptor (TKAR) (40). Non-receptor kinases include PTK, TEC, and Janus kinase (JAK) family members (35, 41). Numerous tyrosine kinases identified thus far have been found to originate from proto-oncogenes. For instance, the initial two categories of NRTKs were identified as resulting from structural alterations of typical tyrosine kinases (35). Furthermore, these kinases also play a role in regulating inflammation and immune processes, as evidenced by the rapid tyrosine phosphorylation of diverse

proteins during the proliferation of both standard and malignant tumor cells, as well as the activation of T cells, B cells, and mast cells (42, 43).

2.1.2 Histidine/lysine/arginine kinase

Histidine protein kinases (HPK) are signaling enzymes that can phosphorylate conserved histidine residues. The phosphorylation of arginine and lysine residues follows processes similar to histidine due to their analogous basic groups. HPKs and their downstream target proteins form a two-component signal transduction system (44). A typical HPK is a transmembrane receptor containing an extracellular receptor region at the N-terminal end and an intracellular signal region at the C-terminal end. Despite the low similarity between HPK, STK, and TK, reports have suggested a potentially distant evolutionary relationship among them (45).

2.1.3 Cysteine-rich receptor-like kinase

A receptor-like kinase (RLK) is a widely present protein kinase in plants, playing a crucial role in regulating various biological processes, including development, stress adaptation, and plant defense (46). A cysteine-rich receptor-like kinase (CRK), DUF26 receptor kinase, is pivotal in numerous signaling pathways. Functioning as a plasma membrane receptor, it recognizes and receives external signals and mediates subsequent intracellular signal transmission via phosphorylation (47).

2.1.4 Aspartate/glutamate kinase

Aspartate kinase is the initial pivotal enzyme in the biosynthetic pathway of aspartate amino acids. It is widely distributed and exerts crucial roles in the metabolic pathways of plants and microorganisms. N-acetyl glutamate kinase, commonly known as NAGK, functions as the second rate-limiting enzyme in the biosynthesis of L-arginine, and it is also susceptible to feedback inhibition by the end product L-arginine (48).

2.2 Lipid kinase

Lipid kinases primarily encompass phosphoinositide lipid kinases (PIK), a class of proteins that facilitate the catalysis of phosphorylated variants of specific phosphatidylinositols. In mammals, the PIK family consists of three main categories: phosphatidylinositol 3 kinase (PI3K), phosphatidylinositol 4 kinase (PI4K), and phosphatidylinositol P (PIP) kinase (PIPK) (49). These PIK family members play crucial roles in signal transduction, generating second messengers that regulate cellular metabolism, promote overall wellbeing, and are indispensable for sustaining the energy necessary for cell growth and survival. Therefore, these lipid kinases are potential therapeutic targets for various diseases (50, 51).

2.3 Sugar kinase

Hexokinases and galactokinases are the most critical sugar kinases involved in sugar metabolism. Hexokinases typically phosphorylate glucose at the 6-position, while galactokinases catalyze the phosphorylation at the 1-position of galactose (52). Glucokinase (GK) is one of the isoenzymes of hexokinases. As a crucial glucose sensor in the human body, GK is primarily localized in pancreatic β cells and the liver, responsible for monitoring alterations in glucose concentration and activating the blood glucose regulation system to maintain blood glucose homeostasis (53).

3 Peripheral nerve injury

PNI is a prevalent affliction that primarily results in impaired nerve conduction in patients, ultimately leading to sensory and motor impairments and potentially lifelong disability (1). PNI can be mainly divided into mechanical injury and iatrogenic injury.

3.1 Mechanical injury

Mechanical injury pertains to nerve damage caused by external forces, such as traffic accidents, warfare, earthquakes, and industrial accidents. The injuries can be categorized into three types: crush injuries, transection injuries, and missing injuries. Crush injury is considered the least severe form of mechanical injury. In fundamental research, the sciatic nerve transection model is the most commonly utilized model for studying nerve damage (54). This model enables the investigation of various aspects, including the development, structure, and material transport within axons of peripheral nerves, such as chemical substances, signal molecules, and physical and chemical factors. Transection injury is a mechanical trauma that severs nerve tissue without inducing a defect. Transection injuries present greater challenges in terms of recovery compared to crush injuries, as they involve the breakage of nerve axons and endoneurium. Microsurgery, commonly employed as a treatment for transection, entails surgical sutures to restore the functionality of the injured nerve, typically improving functional recuperation (55). Missing injury, also known as nerve avulsion, is one of the most severe forms of mechanical injury, resulting in irreversible nerve damage. The treatment for missing injury depends on the gaps of the missing part. Autologous nerve transplantation or allogeneic nerve transplantation techniques are commonly employed in cases with small gaps. In contrast, larger gaps often require nerve conduits to facilitate regrowth and recovery (56–58).

3.2 Iatrogenic injury

Iatrogenic nerve lesions are nerve injuries that occur as a result of medical treatment or surgical procedures; for instance, the neurological dysfunction caused by abnormal nerve conduction due to ischemia-reperfusion (3–5).

3.3 The PNR process after PNI

Compared to the CNS, the peripheral nervous system possesses a degree of capacity for regeneration after injury (1). Waller degeneration usually occurs in the distal nerve after PNI. It mainly involves the degeneration and collapse of the local axon and myelin in the distal segment of the injured nerve, originating from the cell body, accompanied by various cytokines produced simultaneously (59).

The restoration of PNI typically entails three essential processes: eliminating incomplete myelin debris, generating new tissue, and recovering nerve impulse conduction function (13). The process of myelin debris removal commences with the degeneration and collapse of the impaired myelin sheath, prompting Schwann cells to phagocytose the myelin debris (60). Concurrently, these cells recruit a substantial quantity of inflammatory cells, including macrophages, neutrophils, and others, to expedite the clearance of the remnants (61, 62). Subsequently, ~28 days post-injury, T lymphocytes congregate at the distal end of the damaged nerve to elicit an immune response, thereby averting malignant inflammation at said location (63). Generating new tissue encompasses various events, such as the migration of neurons and elongation of axons, along with the proliferation and migration of Schwann cells around neurons. Additionally, it involves the regeneration and reconstruction of blood vessels and support systems surrounding nerve tissues (13, 64, 65). The restoration of nerve conduction function includes the proliferation of Schwann cells activated by cytokines and re-encloses nerve axons to form myelin sheaths. Ultimately, the ends of nerve axons establish correct connections with target organs and tissues, enabling proper functionality (66).

3.4 Peripheral nerve regeneration-associated genes

To date, an increasing number of Regeneration Associated Genes (RAGs) have been reported to play critical regulatory roles during peripheral nerve regeneration. These RAGs can be classified into several groups, including transcription factors, growth factors, miRNAs, and other non-coding RNAs (Figure 1).

3.4.1 Transcription factors

Transcription factors are the main regulatory factors for various cellular processes under physiological and pathological conditions. Many transcription factors that are differentially expressed after peripheral nerve injury play essential roles in nerve regeneration, including c-Myc, Sox11, STAT3, Atf3, c-Jun, Smad1, Sox2, Krox20, Sox10, and p53 (67). Sox11 is a protein with an HMG domain that can effectively promote peripheral nerve regeneration. It regulates multiple genes, including adhesion molecules, cytoskeletal elements, growth factors, cytokines, neuropeptides, and other molecules related to regeneration (68). Bcl11a is crucial for Schwann cell activation and peripheral nerve regeneration. It participates in regulating Schwann cell activity via regulating the expression of Nr2f2. Reduction of Bcl11a in damaged peripheral nerves leads to restricted axonal extension and myelin sheath wrapping, reduced Schwann cell proliferation and migration rates, and impaired ability of debris clearance, thereby causing recovery failure (69).

3.4.2 Growth factors

Growth factors (GFs) are neurotrophic factors known for regulating cellular proliferation, migration, and differentiation. In preclinical trials, exogenous application of GFs to the lesion site of peripheral nerves has demonstrated their high potential in repairing peripheral nerves by promoting myelin debris clearance, axonal sprouting, remyelination, neurogenesis, and neovascularization (70–72). These GFs, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin 3 (NT-3), have been shown to stimulate axonal regeneration both *in vitro* and *in vivo* (73, 74).

3.4.3 MicroRNAs

MicroRNAs (miRNAs) have been found to exhibit significant expression variation after peripheral nerve injury, reflecting their essential roles during this process. MiRNAs are prevalently involved in various aspects of peripheral nerve regeneration, encompassing inflammation, cell proliferation and migration, neurite outgrowth, and axon remyelination (75). MiRNA182 was found to be decreased in the initial stage of acute nerve injury, allowing for essential inflammatory reaction and increased SC migration by targeting fibroblast growth factor 9 (FGF9) and Neurotrimin (NTM) (76). Let-7 family can be upregulated after nerve lesion, resulting in the downregulation of Notch1 and higher levels of EGR2, consequently inducing remyelination (77, 78).

3.4.4 Other non-coding RNAs

Apart from miRNAs, other non-coding RNAs, including LncRNAs and Circ-RNAs, are also involved in PNR regulation. Silc1 is a lncRNA that is highly expressed in neuronal tissue. Previous studies have shown that Silc1 regulates nerve regeneration by cis-activating Sox 11 (79). Knockdown of lncRNA Bc088327 inhibits cell viability of SCs and induces apoptosis and cell cycle arrest in S-phase. This lncRNA may also interact with Hereglin-1β, which is involved in nerve regeneration (80). Circ-Spidr is enriched in the cytoplasm of dorsal root ganglion (DRG) neurons. It can regulate the PI3K-AKT pathway and inhibit axonal regeneration of DRG after sciatic nerve injury (81). Overexpression of Circ-Ankib1 was reported to affect SC proliferation and axonal regeneration after sciatic nerve injury by directly binding to miR-423-5 p, miR-485-5 p, and miR-666-3p and regulating Cyp26b1 expression (82).

4 Kinase and PNR

The microenvironment of PNS undergoes alterations following nerve injury, including cellular damage and subsequent release of cellular constituents, leading to significant changes in the surrounding microenvironment of the injured tissue. Then, diverse cytokines and kinases are induced and participate in

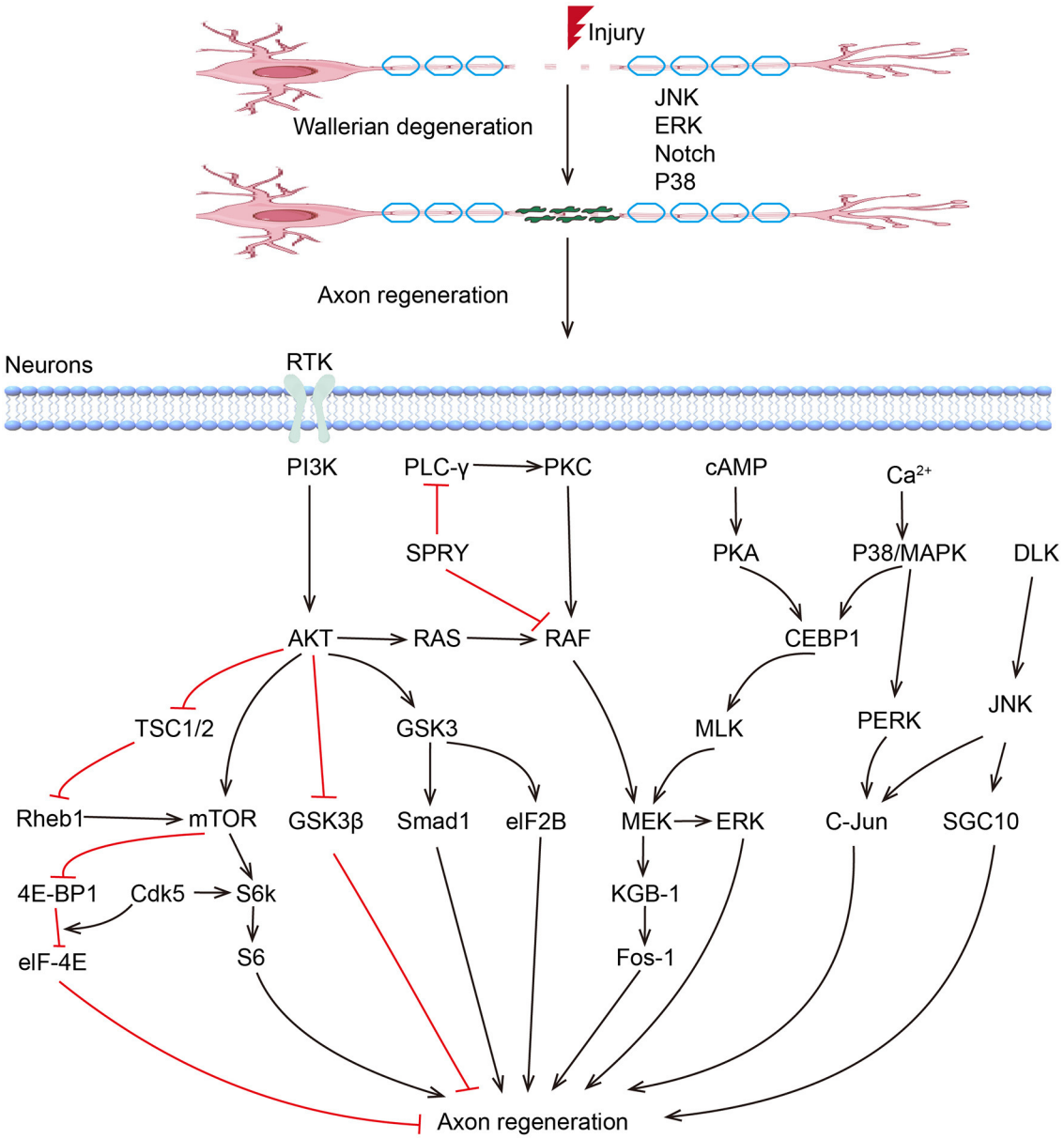

FIGURE 1
Kinase pathways regulate axon regeneration.

the clearance and regeneration process. Kinases, which regulate numerous signaling pathways and serve as crucial signaling molecules, are intricately associated with the regeneration of injured peripheral nerves, establishing the microenvironment necessary to regenerate injured nerve tissues (83, 84). It influences the repair pace for damaged peripheral nerves by modulating various processes, including autophagy, inflammatory response, cell apoptosis, cell cycle, and oxidative stress. Due to the involvement of multiple pathways, kinases have the potential to both facilitate and impede the regeneration process of injured peripheral nerves via regulating different biological processes.

4.1 Kinase affects the PNR by regulating the autophagy process

In the context of PNR, autophagy serves as a crucial regulatory factor. Studies have pointed out that the serine/threonine kinase, known as the mammalian target of rapamycin (mTOR), exerts significant regulatory influence on the autophagy process and neuronal protection (85). Suppression of mTOR activity in mice led to a substantial reduction in the phosphorylation level of downstream p70S6K protein and, concurrently, increased expression levels of autophagy genes *lc3* and *beclin1*, thereby facilitating autophagy and subsequently expediting the elimination

of myelin debris and the regeneration process (86, 87). DLK1, a conserved MAPKKK, is an essential injury sensor regulating regeneration in motor and mechanosensory neurons by activating autophagy through a MAP kinase cascade (88).

4.2 Kinase affects PNR by regulating the inflammatory response

Inflammation is closely associated with the regeneration of injured nerve tissue and assumes a dual role, either positive or negative, during this process. It is widely acknowledged that the prompt pro-inflammatory reaction following the PNI is an indispensable prerequisite for eliminating tissue debris and facilitating effective regeneration (59). Kinases are closely associated with the inflammation response of the injured nerves. Both inflammation and nerve injury recovery can be controlled by p38 MAPK, which plays an essential physiological role in nerve regeneration. It was found that after sciatic nerve injury, the elevation in p38-MAPK phosphorylation levels inhibited the synthesis of IL-1β and TNF-α and positively influenced the regeneration of impaired tissues (89). The activation of IKK kinase facilitates the upregulation of downstream NF-κB pathway factors, attenuating the inflammatory response during PNI and fostering nerve regeneration (90, 91). Kinase DLK (Map3k12) assumes a pivotal role in the initial phase of nerve damage, exerting control over various downstream signaling molecules, including immune factors Csf1, Sarm1, and JNK/c-Jun, thereby governing the process of damage repair (92–95).

4.3 Kinase affects PNR by regulating cell apoptosis

Enhancing anti-apoptosis effects is advantageous for facilitating the restoration of impaired nerves. Rat c-Jun N-terminal kinases (JNK) and extracellular signal-regulated protein kinase (ERK) have been demonstrated to effectively inhibit the PI3K/AKT/mTOR signaling pathway, thereby reducing the expression of apoptosis-related proteins such as Bax and cleaved-Caspase3 (96, 97). Inhibited PI3K/AKT/mTOR signaling pathway was found to hinder scar tissue formation in the sciatic nerve after injury, thereby creating ample room for nerve regeneration (98). Additionally, inhibiting the activity of mTORC1 may reduce the BCL-2 expression and stimulate apoptosis, thereby negatively regulating the development of diabetic peripheral neuropathy (99).

4.4 Kinases affect PNR by regulating the cell cycle

Alteration of the cell cycle of nerve cells is also one of the most important factors influencing the regeneration process of injured nerves. In the central nervous system, AKT kinase can enhance the expression of cyclin D1 by deactivating glycogen synthase kinase-3β (GSK-3β) and reducing protein 27 kinase inhibitor 1 (p27kip1), thereby modulating the cell cycle, influencing cell proliferation rate, and impacting myelin sheath regeneration (100–102). Suppression of AKT phosphorylation can easily result in the arrest of the G1 phase, leading to cell apoptosis and hindering the subsequent recovery of the injured nerves (103). Peripheral nerve extrusion and severance resulted in a notable increase in the expression of protein kinase SKP2 while simultaneously degrading the downstream p27kip1 protein, which had an impact on the cell cycle of cells involved in the regeneration process, ultimately leading to alterations in the progression of injured nerve regeneration (104). The elimination of cyclin-dependent kinase CDK in peripheral nerves typically prevented Schwann cells from initiating the cell cycle, resulting in a significant decrease in the proliferation rate of Schwann cells. Consequently, the reduction of the proliferative Schwann cells severely impeded the regeneration of the damaged nerve myelin sheaths, which in turn affected the recovery of nerve function in the later stage (105).

4.5 Kinase affects PNR by regulating oxidative stress

PNI induces neurotoxicity, and the involvement of the oxidative defense system in nerve tissue can significantly enhance the efficacy against neurotoxicity. It was found that decreased JNK by silymarin (SLM) upregulated the expression of cyclic adenylate response element binding protein CREB, augmented the activity of superoxide dismutase and catalase, reinforced the antioxidant defense system, and suppressed apoptosis and inflammation, thereby safeguarding peripheral nerves (106). Another study has demonstrated that FGF21 might inhibit excessive ERK activation, thereby reducing cellular oxidative stress and autophagy and consequently improving remyelination and nerve regeneration after PNI (107). In addition, the alteration in PI3K kinase activity is intricately associated with excessive oxidation and apoptosis of Schwann cells (108–110).

4.6 Roles of hexokinase in PNR

High glucose has been recognized as one of the most influential factors causing diabetic peripheral neuropathy (DPN) with significant peripheral nerve damage (59). High glucose concentration can induce Schwann cells' apoptosis by affecting various cellular aspects, including oxidative stress, inflammatory reactions, endoplasmic reticulum stress, autophagy, nitrification, and signaling pathways (110). Hexokinase is the first enzyme that catalyzes the phosphorylation of glucose in glycolysis. It has been found that blockade of the enzymatic activity or disruption of the location of hexokinase significantly inhibited the neurite outgrowth of the sensory neurons (111).

5 Kinase affects PNR by regulating the function of different cells in PNS

Kinases are intricate enzymes, the mechanism of which is multilayered, complex, and cell-dependent. Here, we will briefly

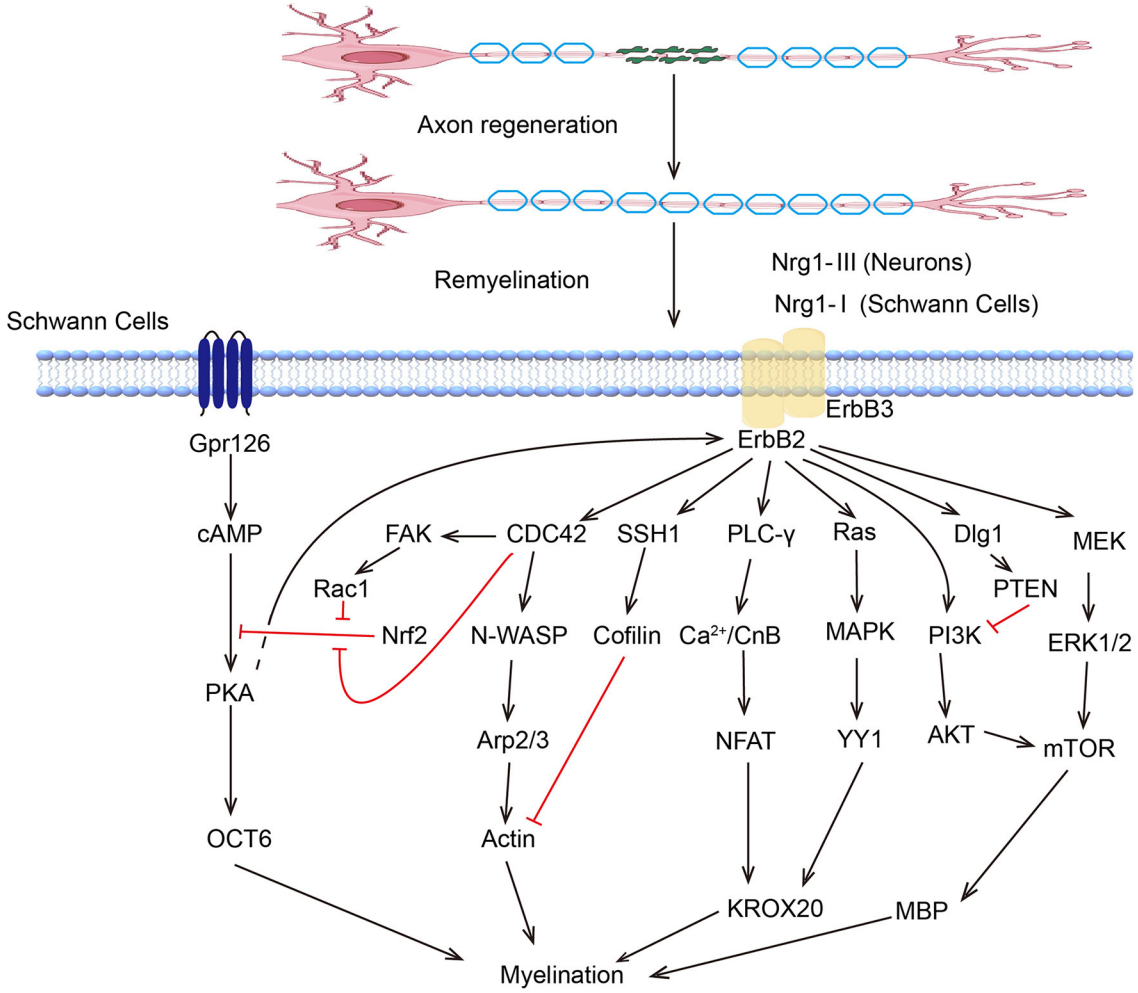

FIGURE 2
Kinase pathways regulate myelination of Schwann cells.

discuss the functional roles of kinases depending on the different cell types involved in PNR.

5.1 Kinase regulation of neurons

MAPKs play critical roles in peripheral nerve regeneration (Figure 1). Previous studies have demonstrated that P38 and JNK pathways are coordinated to regulate axon regeneration, which involves the participation of other kinases, including DLK1 and MLK1. MLK1/MEK-1/KGB-1 (JNK) MAPK Pathway is necessary for axon regeneration by facilitating the growth cone initiation and migration (112). ERK/MAPK and PI3K/AKT signal channels were found to be both activated in facial neurons after injury (113). The activation of ERK is necessary in proximal and distal nerve stumps, which promote neurite outgrowth and regeneration (114, 115). The Raf-ERK pathway was proved necessary for axon elongation in sensory neurons, while the PI3K-AKT pathway increases axon caliber and branching (116–118). Based on optogenetic systems, activated ERK and AKT successfully enhanced the axon regeneration in the peripheral nerve system in *Drosophila*, with an excellent ability to fine-tune and guide the axon regrowth, suggesting their application potential in treatments of peripheral nerve injuries (119). The role of GSK3 in PNR seems to be controversial (120). Although sustained GSK-3 without inhibition of PI3K/AKT was found to promote regeneration after sciatic nerve crush (121), blocking of GSK-3β enhanced axonal regeneration and remyelination in both CNS and PNS (122–124). In addition, Rho-kinase plays a negative role in neurite formation and maintenance in both CNS and PNS (125, 126). ROCK/ROCK pathway is involved in rearranging the cytoskeleton, and inhibition of the RhoA signal can counteract the inhibitory effects of other inhibitor molecules on axon growth, leading to increased axon sprouting and improved functional recovery (126, 127).

5.2 Kinase regulation of SCs

Peripheral nervous system SCs are renowned for their regenerative ability. Following the inflammatory response, the SCs

proliferate rapidly and reinnervate the targeted area with new myelin sheaths, which involve various kinase signaling pathways (Figure 2). The ERK/MAPK pathway is critical in SCs, particularly following nerve injury. ERK activation leads to the upregulation of genes associated with myelin breakdown and nerve repair. This kinase is essential for the proliferation and migration of SCs and their dedifferentiation and redifferentiation processes, which are essential for PNR (128). Studies have shown that melatonin can induce dedifferentiation and proliferation of SCs through the Ras/Raf/ERK, MAPK, and GDNF/PKC pathways, suggesting its potential therapeutic value in treating PNI (129). The PI3K/AKT pathway can promote cell survival and proliferation, enhancing the regenerative potential of SCs. Stab1 was found to activate PI3K/AKT activity, inhibit SCs apoptosis, and promote PNR (130). Sam68 also participates in SC proliferation and regulates regeneration after sciatic nerve compression by activating PI3K/AKT activity (131). The AKT/mTOR pathway in neurons is crucial for myelin sheath growth by supporting protein translation and myelin protein synthesis (132). Mek/ERK1/2-MAPK and PI3K/AKT/mTOR signaling were found to affect Schwann cells' differentiation, myelination, and dysmyelination in either synergetic or independent ways (133). JNK, another member of the MAPK family, regulates the dedifferentiation and apoptosis of SCs and the expression of RAGs (134).

5.3 Kinase regulation of macrophages

In macrophages, P38 MAPK serves as a pivotal kinase in regulating inflammatory cytokine production while also facilitating the transition of macrophages from a pro-inflammatory M1 state to a pro-regenerative M2 state at the site of nerve injury through the modulation of AKT activity. This phenotypic shift is essential for mitigating inflammation and establishing a milieu conducive to nerve regeneration (135, 136).

5.4 Kinase regulation of fibroblasts

Various tissues throughout the body contain fibroblasts, which are mesenchymal cells that synthesize extracellular matrix (ECM) and basement membrane (BL) (137). The wound-healing process in injured peripheral nerves is highly regulated and involves fibroblasts. Transforming growth factor beta-activated kinase 1 (TAK1) can be activated by TGF- β, thereby affecting fibroblast activity and regulating the production of extracellular matrix and scar tissue formation (138).

5.5 Kinase regulation of endothelial cells

TEK receptor tyrosine kinase (Tie-2) controls endothelial-pericyte adhesion to maintain vascular integrity. Tie2 kinases in endothelial cells play critical roles in angiogenesis during nerve regeneration. They facilitate the response to growth factors, such as VEGF, to stimulate the formation of new blood vessels, ensuring the delivery of essential nutrients and oxygen to regenerating nerves (139, 140).

6 Conclusion

PNI diseases are frequently encountered as accidental conditions. Despite the relatively well-understood mechanisms and enhanced precision in surgical interventions, a practical clinical treatment approach still needs to be discovered, leading to suboptimal functional recovery in the long term. PNI frequently induces alterations in kinase activity and tissue inflammation, influencing the subsequent reparative processes. However, the regeneration of peripheral nerve damage is influenced by numerous factors, including the extent of nerve severance, the length and depth of the nerve defect, the level of wound inflammation, the patient's age and physical condition, as well as the activity and expression of various kinases, transcription factor expression and regulation, and nutrient factor secretion. Considering the complexity of these factors, it is evident that more than one factor alone is needed to comprehensively and effectively address the problem. Hence, to overcome the challenges associated with the disease, the examination of kinase function and effectiveness within the framework of nerve injury restoration, alongside the simultaneous analysis of diverse contributing factors, will present a potential avenue for providing innovative perspectives and strategies in managing PNI conditions. In the future, the efficacy of clinical treatment could also be enhanced by identifying drugs that target the kinase enzyme activity.

Author contributions

XZ: Funding acquisition, Writing—original draft. XD: Writing—review & editing. XL: Conceptualization, Writing—review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Project of Wuxi Health Committee (Q202229) and the General Program of Maternal and Child Health Research of Wuxi Health Commission (FYKY202304) received by XZ.

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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frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 22 May 2024
DOI 10.3389/fneur.2024.1378689

OPEN ACCESS

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RECEIVED 30 January 2024
ACCEPTED 02 May 2024
PUBLISHED 22 May 2024

CITATION
Wang Y, Wang Y, Lv L, Li T, Wang Y and Pei F (2024) Visualization analysis of research frontiers and trends in the treatment of sciatic nerve injury.
Front. Neurol. 15:1378689.
doi: 10.3389/fneur.2024.1378689

Visualization analysis of research frontiers and trends in the treatment of sciatic nerve injury

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Objective: To visualize and analyze the literature related to sciatic nerve injury treatment from January 2019 to December 2023, and summarize the current status, hotspots, and development trends of research in this field.

Methods: Using CiteSpace and VOSviewer software, we searched the Web of Science database for literature related to the treatment of sciatic nerve injury. Then we analyzed and plotted visualization maps to show the number of publications, countries, institutions, authors, keywords, references, and journals.

Results: A total of 2,653 articles were included in the English database. The annual number of publications exceeded 230, and the citation frequency increased yearly. The United States and China were identified as high-influence nations in this field. Nantong University was the leading institution in terms of close cooperation among institutions. The authors Wang Yu had the highest number of publications and were highly influential in this field. Keyword analysis and reference Burst revealed a research focus on nerve regeneration and neuropathic pain, which involve regenerative medicine and neural tissue engineering. Chronic pain resulting from sciatic nerve injury often manifests alongside anxiety, depression, cognitive-behavioral disorders, and other issues. Interventions such as stem cells, electrical stimulation, electroacupuncture, total joint replacement, pharmacological interventions, gene therapy, nerve conduits, chitosan scaffolds, and exercise promote nerve repair and alleviate pain. Schwann cells have been the focus of much attention in nerve repair and regeneration. Improving the outcome of sciatic nerve injury is a current research challenge and focus in this field. Based on keyword Burst, nerve conduits and grafts may become a potential research hotspot in the treatment of sciatic nerve injury.

Conclusion: This visual analysis summarizes research trends and developments of sciatic nerve injury treatment and predicts potential research frontiers and hot directions.

KEYWORDS

sciatic nerve injury, nerve regeneration, nerve repair, neuroprotection, therapy, treatment, visual analysis, web of science

Introduction

The sciatic nerve is the longest and thickest nerve in the human body. It originates from the lumbosacral plexus and divides into two terminal branches: the tibial nerve and the common peroneal nerve, which innervate the motor and sensory functions of the lower limbs. Sciatic Nerve Injury (SNI), a common peripheral nerve injury, is often associated with hip dislocation, acetabular fracture, and other traumatic injuries (1, 2). Despite the availability of various supportive therapies, surgical and non-surgical interventions, the clinical manifestations of neurological dysfunction with intermittent chronic pain persist due to the slow recovery of sciatic nerve injury and the histological properties of neurons. However, the recovery of target organ function after sciatic nerve injury remains challenging. Inappropriate treatment not only fails to guarantee functional recovery, but may also result in irreversible neuronal atrophy, leading to limb paralysis and severe disability in patients (3, 4). Chronic neuropathic pain resulting from peripheral nerve injury is a challenging clinical issue. Existing treatments only provide partial relief of symptoms and are costly, placing a significant burden on patients and society. Additionally, patients often experience accompanying symptoms such as depression, anxiety, and insomnia, which can have a detrimental effect on their physical and mental health (5–7). The repair, regeneration, and pain relief associated with peripheral nerve injury remain essential topics for current research.

To date, only one study has been identified that utilizes CiteSpace software to visualize the repair and protection of sciatic nerve injuries, and it dates back a decade. Therefore, this paper utilizes CiteSpace 6.2R6 software and VOSviewer 1.6.20 to visualize and analyze the relevant literature in this field over the past 5 years. The aim is to summarize the development status, research hotspots, and shortcomings, providing a reference for current and future studies in sciatic nerve injury treatment.

Data and methods

Data source

Web of Science database was retrieved Web of Science core Collection, and the search period was set from January 2019 to December 2023 using the following search strategy. TS = ("Sciatic nerve injury" OR"Sciatic nerve") AND ("therapeutics" OR "therapy" OR "therapies" OR "treatment" OR "treatments" OR "repair" OR "regeneration" OR "protect").Document.

Types = "Article OR Review Article"; Time Span = "2019–2023"; Languages = "English," Index = "SCI-EXPANDED."The search for data was completed on December 23, 2023, and 2,658 documents were retrieved and exported.

Research methods

The English literature was downloaded and saved in the format of "full record with cited references" exported in "plain text," and named as "download_x-x.txt" CiteSpace 6.2.R6 was used to remove the weights, resulting in the inclusion of 2,653 documents. For the analysis, CiteSpace was set to the time period of 2019–2023 with a default time partition of 1. The data was converted into a recognizable format and visualized in terms of the number of publications, countries, institutions, authors, cited journals, and keywords. Additionally, VOSviewer 1.6.20 software was used to highlight the attention of relevant core institutions, and authors in the field. The analysis type includes co-authorship and co-occurrence, the analysis unit of analasis involves institutions, authors, and keywords. The calculation method selection is full counting. Each dot in the graph represents a node type, with larger dots indicating a higher frequency or number. The connecting lines represent the citation relationship between each dot, with more connecting lines indicating closer cooperation relationships. To obtain a visual mapping, run the software and then manually adjust the threshold, size, color of nodes and labels, and the clarity of the color of connecting lines to enhance the clarity and esthetics of the image.

Results

Publication outputs and citation trends

The literature included in this study was statistically analyzed in terms of the number of articles published and the frequency of citations based on the time of publication, as shown in Figure 1. A total of 2,653 articles were published in the past 5 years, with an upward trend in the number of publications from 2019 to 2021, reaching a peak in 2021. The overall annual number of publications remained above 490 from 2021 to 2023, although there was a slight decrease in the number of publications. The total citation frequency was 23,224, increasing annually, with the highest frequency of 8,001 in 2023. The average number of citations per item was 8.74, and the H-index was 49.

Countries and regions

A total of 2,653 documents were included in the English database from 2019 to 2023. Utilizing CiteSpace 6.2.R6 software to analyze literature from the Web of Science database, as shown in Figure 2, the data on countries and regions collaboration in the field reveals a network with 75 nodes, 207 connections, and a network density of 0.0746. Currently, 75 countries have published articles related to the treatment of sciatic nerve injuries, with relatively weak interconnections among them. Refer to Table 1, which shows that 8 countries have published more than 100 articles, with China having the largest number of publications in this field, accounting for 35.39% of the total number of publications and having a centrality score of 0.24. The United States follows in publication volume but has the highest centrality score of 0.3. China and the United States also rank in the top two in total citations, underscoring their significant contributions and influence in the field of sciatic nerve injury repair and applied research.

Institutions

A total of 288 institutions have published articles on the treatment of sciatic nerve injury, with universities being the primary contributors. As shown in Table 2, which lists the top 10.

institutions by publication volume, 7 of these are based in China. The top three institutions are Nantong University (125), Shanghai Jiao Tong University (72), and Sun Yat Sen University (8). Among them,

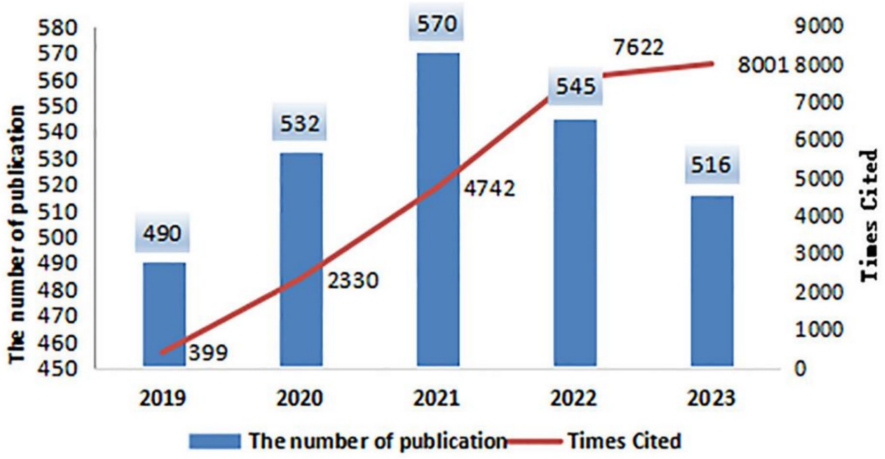

FIGURE 1
The number of annual publications and times cited.

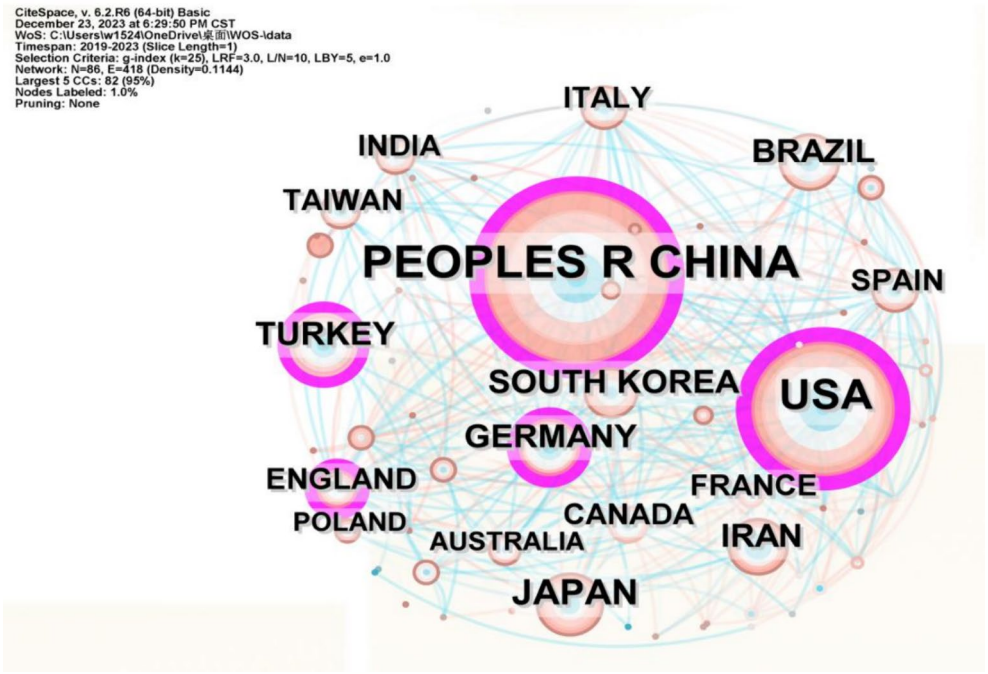

FIGURE 2
The figure shows the Country/regional cooperative network with relevant publications. The circles in the graph represent different countries, and the size of each circle is proportional to the number of articles published by that country. The size of the purple circle indicates the centrality of a country in the network, while the thickness of the connecting lines reflects the strength of collaboration between countries.

TABLE 1 The top 8 most productive countries and regions with publications.

Rank	Country/regions	Counts	Proportion (%)	Centrality	Citations
1	China	939	35.39	0.24	9,402
2	The United States	552	20.81	0.30	5,604
3	Japan	159	5.99	0.02	968
4	Brazil	139	5.23	0.07	944
5	SouthKorea	121	4.56	0.04	918
6	Turkey	118	4.45	0.16	573
7	Iran	108	4.07	0.07	1,526
8	Germany	108	4.07	0.18	1,063

TABLE 2 Ranking of organizations by number of publications and centrality

Institution	Country	Publications	Centrality
Nantong university	China	125	0.13
Shanghai Jiao Tong university	China	72	0.18
Sun Yat Sen university	China	48	0.01
Peking university	China	47	0.11
Universidade de Sao Paulo	Brizlin	44	0.16
University of California system	United States	41	0.36
Harvard university	United States	40	0.30
Sichuan university	China	39	0.08
Nanjing medical university	China	36	0.10
Jilin university	China	35	0.08

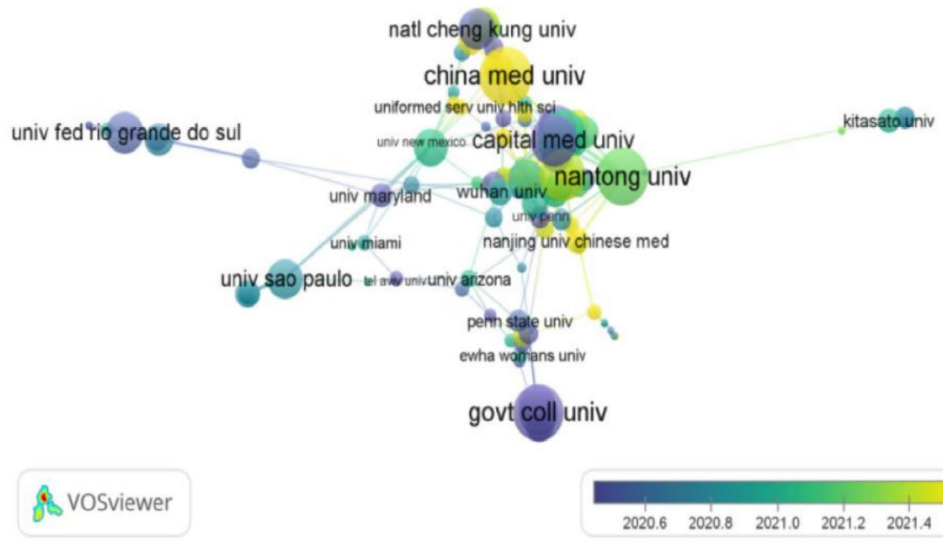

FIGURE 3
Institutional with co-occurrence relations shown as an overlay graph plotted. The circles represent keywords, and the size of the circles represents the frequency of keywords. The size of the circles is proportional to the frequency of keywords. Circles with the same color form a cluster group, and the connecting lines represent the connection between keywords.

two institutions are from the United States, the namely University of California System (9) and Harvard University (10). Although the number of publications of these two institutions is slightly less than that of some Chinese institutions, the centrality of these two institutions ranks the top two, respectively 0.36 and 0.30. All are high-impact institutions that are leading the way in this field of research. (refer to Figure 3). The co-occurrence time overlay Visualization of institutional publication volume is plotted using VOSviewer 1.6.20 (refer to Figure 3). The results indicate that domestic research institutions are more closely cooperating, with Nantong University having the most cooperation with other institutions. However, cooperation with foreign institutions is less frequent. Since April 2021, the Nanjing University of Chinese Medicine, Beijing University of Chinese Medicine, Southern Medical University, Shanghai University of Traditional Chinese Medicine, Dalian University of Traditional Chinese Medicine, and Guangzhou University of Traditional Chinese Medicine have demonstrated a growing interest in researching the treatment of sciatic nerve injuries. This indicates that major Chinese medicine institutes are focusing more on this field.

TABLE 3 The top 7 most productive author from 2019 to 2023.

Author	Publications	Citations
Wang, Yu	20	296
Yi, Sheng	18	190
Gu, Xiaosong	16	152
Hussain, Ghulam	13	156
Mika, Joanna	12	196
Navarro,Xavier	12	275
Peng, Jiang	10	196

Co-authorship and co-citation author

A total of 7,215 authors participated in 2653 documents. Table 3 shows that there were 7 authors with ≥10 publications, with Wang, Yu having the highest number of publications (11) and citation frequency (296). Price's law was used to calculate the number of publications of

core authors based on $M = 0.749 \times (Nmax)^{1/2} = 0.749 \times 20^{1/2} \approx 3.35$, which indicates that authors with 4 publications are the core authors in the field of sciatic nerve injury research, and there are a total of 483 core authors. A collaborative co-occurrence network mapping of authors was produced using VOSviewer 1.6.20 (Figure 4), which only displays authors of publications with a publication volume of ≥4. The research team consists of 16 core authors, including Wang, Yu, Yi, Sheng, Hussain, and Ghulam. Typically, the team is composed of researchers from the same university, affiliated hospitals, or region.

When using VOSviewer to create a density view of authors' co-authorship, it is recommended to set the weights to total link strength, as shown in Figure 5. This view can effectively display the collaboration and research density among high-impact authors in important fields. In conjunction with Table 4, this view highlights the top 7 authors, each having more than 60 links with others. It is evident that Hussain, Ghulam possesses the highest number of links (80) and the highest H-index (12), followed by Rasul, Azhar (75) and the H-index (11).

Keywords

Keywords co-occurrence

In bibliometrics, the frequency of keyword occurrences can reveal the hotspots and trends in a research field. In this study, 8 keywords directly related to the topic were excluded: sciatic nerve, injury, regeneration, repair, peripheral nerve injury, peripheral nerve, nerve regeneration, and peripheral nerve regeneration. The top 10 keywords are listed in Table 5, each appearing more than 160 times. Among them, neuropathic pain, expression, and Schwann cells are the most frequent, occurring 414, 396, and 357 times, respectively. With the highest centrality of 0.6, "expression" is considered a turning point or a key focus in the field.

By using VOSviewer 1.6.20 to create a keyword co-occurrence map (Figure 6), one can effectively visualize the research hotspot and direction of a particular field. To ensure accuracy, the minimum co-occurrence of keywords was set to 10, resulting in a total of 152 keyword co-occurrence maps. The keyword co-occurrence maps are categorized into five major groups. ① The green area represents research on neuropathic pain, which is often associated with oxidative stress, neuroinflammation, pain hypersensitivity, anxiety, depression, and cognitive-behavioral disorders. The treatment for nerve damage includes acupuncture, nerve catheters, and analgesic drugs such as nitric oxide, morphine, and cannabis. This treatment is mediated by cytokines, TNF-α, and NF-κB signaling. ② The red area represents research on nerve injury repair and regeneration, including Schwann cells, axonal regeneration, Wallerian degeneration, angiogenesis, and other mechanisms. It also covers therapeutic modalities such as 3D printing technology, drugs, electrical stimulation, nerve catheters, scaffolds, stem cells, and rehabilitation engineering. ③ The yellow area represents the animal experimental modeling approach, which involves establishing a rat model of sciatic nerve entrapment through surgical and pharmacological nerve block, as well as using total hip replacement surgery. ④ The blue area represents the treatment of muscle atrophy caused by sciatic nerve injury. Various methods are employed, including electrical stimulation, electroacupuncture, electrophysiology, exercise, magnetic resonance, mesenchymal stem cells, and exosomes. ⑤ The purple area represents the pathway of repairing sciatic nerve injury, which is studied from the perspective of proteomics, anti-inflammation, antioxidant, regulation of apoptosis, and autophagy. The map clearly shows that research on nerve regeneration and neuropathic pain forms a significant segment of the

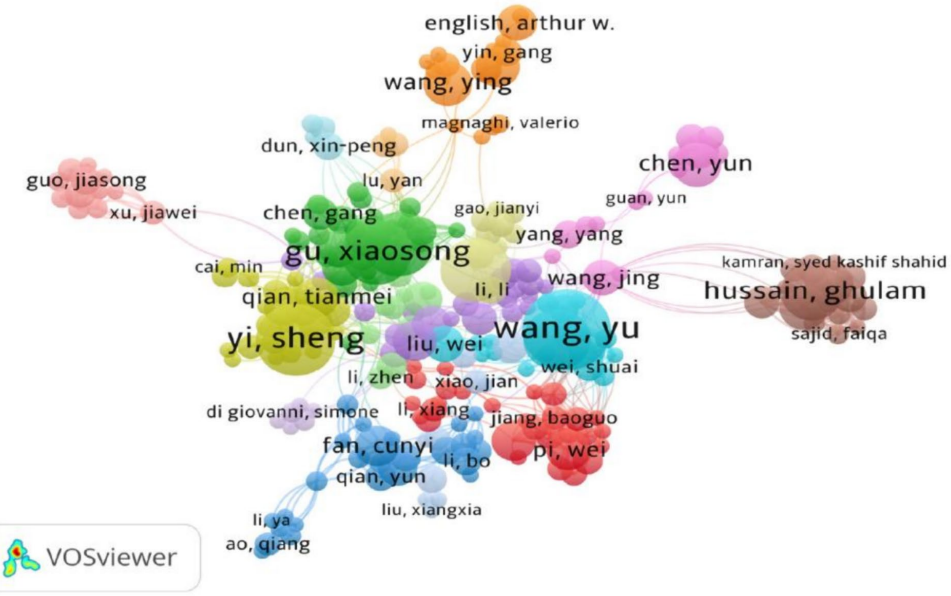

FIGURE 4
The shows the network diagram of Author Collaboration. In the map, each circle represents an author, which is proportional to the amount of papers published by the author. Circles of the same color represent the cooperative group formed between the authors, and the line represents the connection between each author, the thicker the line, the closer the co.

FIGURE 5
The shows a density mapping of author collaboration networks. In the atlas, areas with higher density of authors are closer to bright yellow, while those with lower density lean toward blue. The density is determined by the strength and significance of author connections in the surrounding area.

TABLE 4 The top7 Total link strength author from 2019 to 2023.

Author	Total link strength	H-index
Hussain, Ghulam	80	28
Rasul, Azhar	75	20
Anwar, Haseeb	72	15
Ikeguchi, Ryosuke	72	7
Matsuda, Shuichi	68	17
Aoyama, Tomoki	67	13
Takamatsu, Kiyohito	61	6

TABLE 5 Keyword frequency and centrality.

Rank	Count	Keywords	Centrality	Keywords
1	414	Neuropathic pain	0.06	Expression
2	396	Expression	0.05	Axonal regeneration
3	357	Schwann cells	0.05	Mesenchymal stem cells
4	224	Activation	0.05	Neuropathic pain
5	214	Functional recovery	0.04	Animal models
6	188	Model	0.04	Chronic pain
7	172	Spinal cord	0.04	Hyperalgesia
8	171	Oxidative stress	0.04	Involvement
9	166	Mechanisms	0.04	Microglia
10	163	Rat	0.04	Neurotrophic factor

field. It is important to note that these five research directions are interrelated and not independent.

Keywords cluster

The CiteSpace 6.2.R6 visualization software was used to perform keyword clustering network analysis. A keyword clustering map was generated using the log-likelihood ratio algorithm (LLS) after eliminating relevant subject words. 9 keyword clustering groups were obtained, as shown in Figure 7. It is generally accepted that a value of $S > 0.7$ indicates a convincing clustering, while $Q > 0.3$ indicates a significant cluster structure. The mapping shows a Mean Silhouette of 0.7673 and a Modularity Q of 0.4987, indicating good homogeneity among the keyword clusters and a satisfactory mapping effect. Table 6 displays the specific Silhouette value and Label (LLR). The research hotspot in this field in recent years is Neuropathic Pain, Nerve Catheterization, Peripheral Nerve Injury, and Stem Cells, which are the large research areas of the Keyword clustering. The

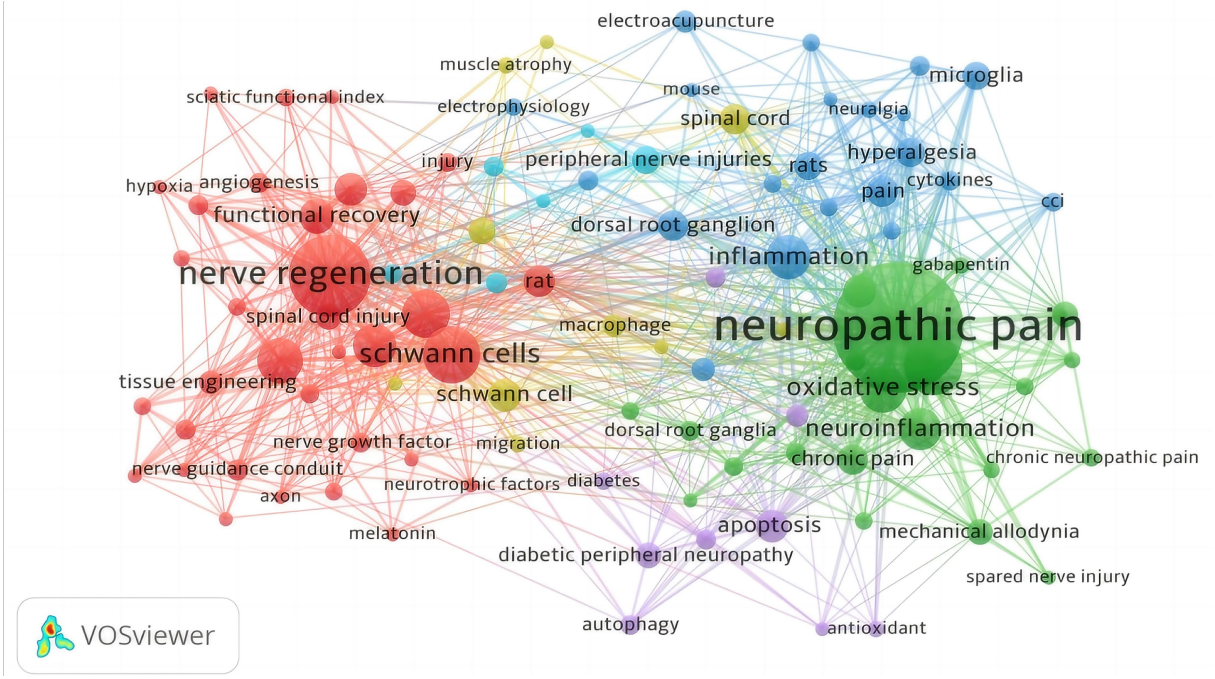

FIGURE 6
The shows the network diagram of Co-occurrence analysis of keywords. The circles represent keywords, and the size of the circles represents the frequency of keywords. The size of the circles is proportional to the frequency of keywords. Circles with the same color form a cluster group, and the connecting lines represent the connection between keywords.

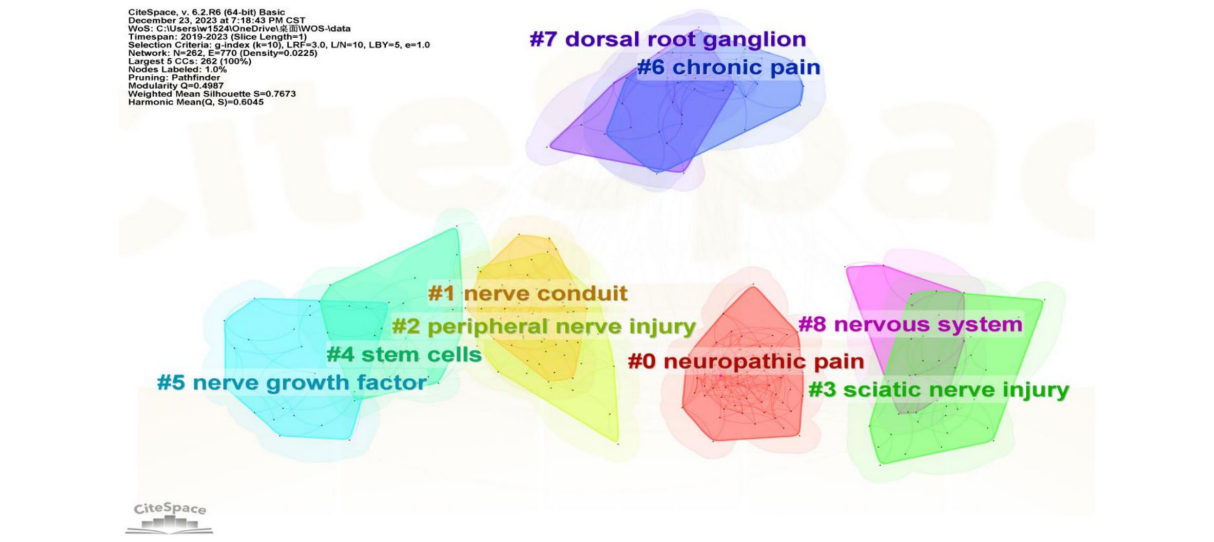

FIGURE 7
This diagram shows common citation clusters for research on sciatic nerve injury treatment from 2019 to 2023. Each color block represents a cluster group, with the cluster number being inversely proportional to the cluster size. For example, #0 represents the largest cluster.

English clustering labels can be classified into two categories. Category 1 pertains to sciatic nerve repair research (#2, #3, #5, #7, #8), which includes keywords such as nerve regeneration, schwann cells, functional recovery, nerve growth factor, neurotrophic factor, nerve conduit, pulsed radiofrequency, angioplasty, and dorsal root ganglion. Category 2 centers around sciatic analgesic treatment, including oxidative stress, nerve conduit, hyaluronic acid, chitosan nerve conduits, cannabidiol, tissue engineering, gene therapy, Schwann cell, and management. It has been found that chronic pain often causes emotional problems such as depression and anxiety and is associated with gender differences (11). Additionally, current research is increasingly focused on functional indices of nerve damage, tactile abnormalities related to pain, and other relevant indicators.

TABLE 6 Main clusters of keywords.

ClusterID	Size	Silhouette	Label (LLR, log-likelihood ratio)
#0	55	0.848	neuropathic pain (224.32, 1.0E-4); oxidative stress (83.93, 1.0E-4); nerve regeneration (59.27, 1.0E-4); chronic constriction injury (53.22, 1.0E-4);
#1	37	0.668	neuropathic pain (64.13, 1.0E-4); nerve conduit (40.69, 1.0E-4); nerve guidance conduit (31, 1.0E-4); hyaluronic acid (25.37, 1.0E-4); chitosan (21.96, 1.0E-4)
#2	36	0.853	peripheral nerve injury (93.49, 1.0E-4); schwann cells (44.63, 1.0E-4); nerve regeneration (40.25, 1.0E-4); functional recovery (39.62, 1.0E-4)
#3	35	0.736	sciatic nerve injury (52.22, 1.0E-4); system (20.08, 1.0E-4); sex differences (16.06, 1.0E-4); diagnosis (16.06, 1.0E-4); nerve guidance conduit (15.75, 1.0E-4)
#4	28	0.786	stem cells (46.22, 1.0E-4); neuropathic pain (41.08, 1.0E-4); mesenchymal stem cells (37.82, 1.0E-4); tissue engineering (27.2, 1.0E-4); transplantation (21.59, 1.0E-4)
#5	22	0.663	nerve growth factor (19.16, 1.0E-4); vascular endothelial growth factor (15.14, 1.0E-4); magnetic resonance imaging (11.08, 0.001); gene therapy (11.08, 0.001); angiogenesis (9.46, 0.005)
#6	22	0.701	chronic pain (38.2, 1.0E-4); management (32.84, 1.0E-4); cannabidiol (21.88, 1.0E-4); surgery (19.25, 1.0E-4); schwann cells (12.91, 0.001)
#7	18	0.733	dorsal root ganglion (36.71, 1.0E-4); neurotrophic factors (22.46, 1.0E-4); growth factor (18.2, 1.0E-4); pulsed radiofrequency (15.59, 1.0E-4); sensory neurons (14.25, 0.001)
#8	9	0.887	nervous system (22.14, 1.0E-4); spinal cord injury (19.24, 1.0E-4); angioplasty (14.26, 0.001); regional anesthesia (14.26, 0.001); schwann cells (10.36, 0.005)

Keywords burst

CiteSpace6.2.R6 software was utilized to analyze the selected literature for burst words. Burst words are words with a high-frequency change rate in the corresponding time and can reflect the development trend of a certain research field. Figure 8 displays the top 15 keywords with the strongest citation bursts in published articles on treatments related to sciatic nerve injury, the keyword bursts are divided into two distinct phases. The main burst words during the first phase (2019–2021) included complications, phosphorylation, pathway, femoral nerve, adipose-derived stem cells, and antioxidants. This phase aims to repair damaged nerves through the use of antioxidants, stem cell transplantation, and regulation of the phosphorylation level of related protein kinases and signaling pathways to promote nerve regeneration. The main keywords for Phase 2 (2021–2023) include peripheral neuropathy, surgery, chitosan, macrophage polarization, nerve conduit, nerve growth factor, and drug delivery. Research in this field is currently focused on using drugs and chitosan nerve conduits to induce macrophage polarization, promote neovascularization, and synaptic plasticity to repair sciatic nerve defects (9, 13, 14).

Journal

Cited journals

Based on the citation frequency of journals, one can determine the influence of a particular journal in the field of sciatic nerve injury repair. Data analysis reveals that between 2019 and 2023, publications related to this field were primarily featured in 118 different journals, with 11 of these journals receiving over 700 citations each, as detailed in Table 7. The *EXP NEUROL* has the highest citation frequency with 1,253 citations and the third-highest centrality ranking (0.24), following *BIOMATERIALS* (0.28) and *J NEUROSCI* (0.26). This journal has a significant impact in the field. The 11 top journals had an average impact factor of 6.02. *BIOMATERIALS* had the highest impact factor (IF = 14.0). All of the journals had more than 120 citations per year in sciatic nerve injury repair research, with a focus on bioengineering (15–18) and regenerative medicine (8, 10, 19).

Dual-map overlays showing the research directions of burst journals

The journal map overlay illustrates the position of sciatic nerve injury research within the broader academic field. Figure 9 shows that a total of 231 journals have published such research. The figure shows that the fields of Molecular Biology, Immunology (yellow trajectory $z = 9.14661$, $f = 14{,}098$), Medicine, Clinical Medicine (green trajectory $z = 1.9450856$, $f = 3{,}342$), Neurology, Kinesiology, and Ophthalmology (gray trajectory $z = 2.6876216$, $f = 4{,}455$) are influenced by Molecular Biology and Genetics. The authors primarily studied sciatic nerve repair from the perspective of Molecular Biology and Immunology.

References

Co-citation analysis of references

Literature citation frequency is commonly used to evaluate the influence of a researcher or publication in a particular field. Table 8 summarizes the top 10 cited literature based on citation analysis. The study with the highest citation frequency (76) and an impact factor of 81.5 is “Neuropathi

c Pain Literature” by Colloca L, published in *Nature Reviews Disease Primers*. The study reviews the neurologic mechanisms behind chronic neuropathic pain and potential treatments (20). Furthermore, Jessen KR’s article, having been published twice and cited a total of 125 times, demonstrates significant influence in this research field. Additionally, five out of the top 10 highly cited articles focus on Schwann cells, highlighting their crucial role in sciatic nerve repair.

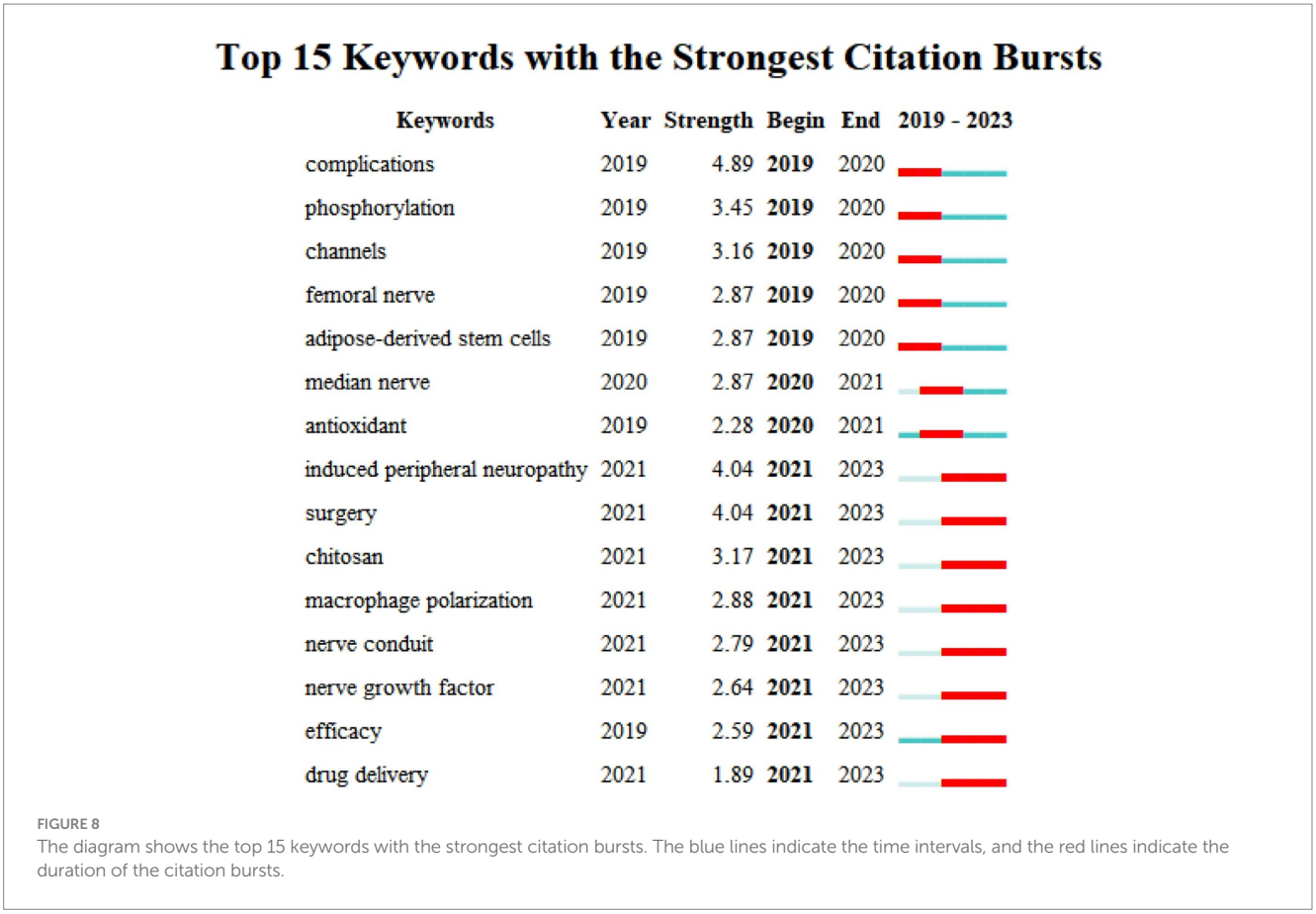

FIGURE 8
The diagram shows the top 15 keywords with the strongest citation bursts. The blue lines indicate the time intervals, and the red lines indicate the duration of the citation bursts.

TABLE 7 The top 11 cited journal.

Cited journals	Count	Centrality	2024-IF
EXP NEUROL	1,253	0.24	5.3
J NEUROSCI	1,201	0.26	5.3
PLOS ONE	1,164	0.05	3.7
PAIN	852	0.13	7.4
P NATL ACAD SCI USA	849	0.06	11.1
SCI REP-UK	849	0.02	4.6
NEURAL REGEN RES	833	0.07	6.1
BRAIN RES	804	0.1	2.9
NEUROSCIENCE	781	0.03	3.3
NEUROSCI LETT	758	0.02	2.5
BIOMATERIALS	729	0.28	14.0

Citation bursts analysis of reference

The CiteSpace 6.2.R6 software was used to analyze reference highlighting, with the node set to Reference. The top 24 references in terms of citations were identified. The document titled "Peripheral Nerve Reconstruction after Injury: a Review of Clinical and Experimental Therapies" by Grinsell et al. (21) published in *Biomed Res Int*, had the highest highlighting strength of 15. According to reference (8), surgery or nerve autograft can significantly improve the outcome of proximal nerve injury. Additionally, fascicular-level nerve reconstruction is a better option. The article emphasizes the importance of enhanced surgical care to promote axonal regeneration, improve distal motion through electrical stimulation, and delay or avoid Waller's degeneration to effectively resolve neurological deficits. Furthermore, Figure 10 illustrates that the majority of reference outbreaks have concluded by 2021 in terms of outbreak chronology. To date, 11 publications have been produced, focusing on the role and molecular mechanisms of Schwann cells, macrophages, and neurotrophic factors in reconstructing peripheral nerve fibers, promoting axon regeneration, and neurological recovery (22–26). Additionally, studies have focused on the mechanisms of neuropathic pain and potential therapies (20, 27, 28) discovered that cytosolic action plays a crucial role in nerve clearance, promoting an anti-inflammatory environment and regulating lesion-induced nerve repair. The literature, in which the subject term Schwann cell appeared several times, suggests that their involvement in regeneration and analgesia after sciatic nerve injury is a current research topic in this field.

Discussion

In this paper, we use CiteSpace and VOSviewer software to visualize the Web of Science database and present visual maps of the number of articles, countries, institutions, authors, journals, references, and keywords. We then analyze these maps to extract data. The study's findings indicate that scholars domestically and internationally are highly interested in the repair and regeneration of sciatic nerves following injury. Over the past 5 years, 2,653 articles have been published on this topic. Furthermore, the number of articles published has increased steadily from 2019 to 2021, peaking in 2021.

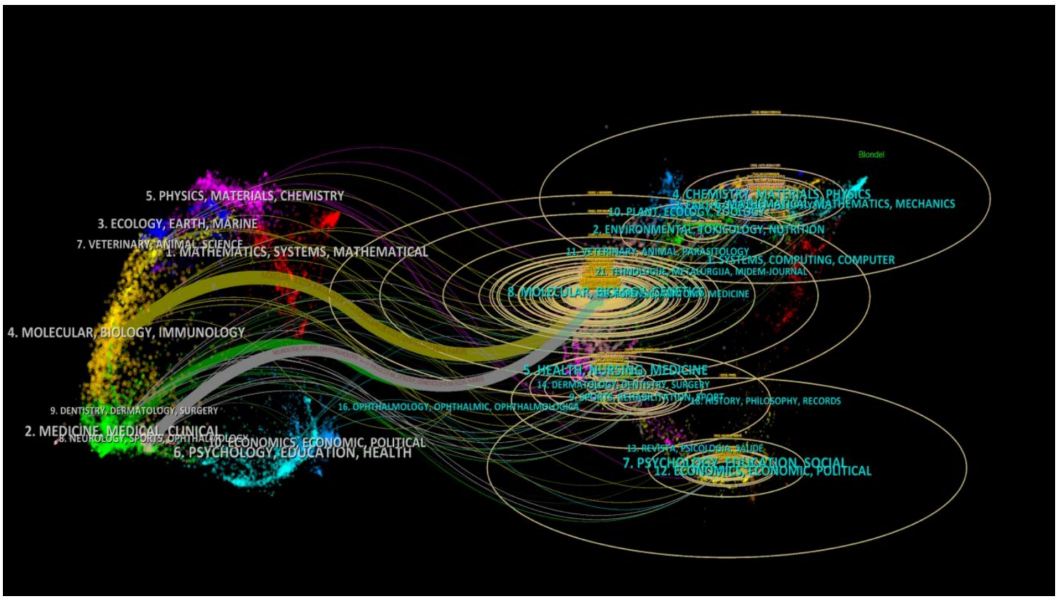

FIGURE 9
Dual-map overlays of cited/citing journals. Each point on the map represents a journal that has published research on therapeutic aspects related to sciatic nerve injury. The map is divided into two halves: the administering citation map on the left and the cited map on the right. The citation connectors provide interdisciplinary relationships between the fields. The z-Scores function highlights the smoother trajectories, with higher scores indicating thicker links. The ellipses represent the number of authors (length) and publications (width).

TABLE 8 The ten references with the highest citation frequency indexed.

Title	Frist author	Counts	Centrality	IF	Journal
Neuropathic pain	Colloca L	76	0.12	81.5	Nature Reviews Disease Primers
The repair Schwann cell and its function in regenerating nerves	Jessen KR	67	0.14	5.5	Journal of Physiology-london
Nerve guide conduits for peripheral nerve injury repair: A review on design, materials and fabrication methods	Vijayavenkataraman S	67	0.07	9.7	Acta Biomaterialia
Mechanisms of Schwann cell plasticity involved in peripheral nerve repair after injury	Nocera G	59	0.02	8.1	Cellular And Molecular Life Sciences
The Success and Failure of the Schwann Cell Response to Nerve Injury	Jessen KR,	58	0.1	5.3	Front Cell Neurosci
Macrophage biology in the peripheral nervous system after injury	Zigrnond RE	58	0.26	6.7	Progress in Neurobiology
Peripheral nerve regeneration and intraneural revascularization	Caillaud M	51	0.01	6.1	Neural Regen ResNeural Regeneration Research
Current status of therapeutic approaches against peripheral nerve injuries: a detailed story from injury to recovery	Hussain G	44	0.21	9.1	International Journal of Biological Sciences
The wound microenvironment reprograms schwann cells to invasive mesenchymal-like cells to drive peripheral nerve regeneration	Clements MP	43	0.11	16.2	Neuron
Macrophage-induced blood vessels guide schwann cell-mediated regeneration of peripheral nerves	Cattin AL	43	0.01	64.5	Cell

Although the number of articles published in 2021–2023 has decreased slightly, the overall number of articles issued in the year is more than 490. Additionally, the frequency of citations has increased substantially year by year. This suggests that research in this field will continue to be emphasized in the future. Moreover, a great majority of publications Document Typeswere articles, and only a few were reviews articles, according to the bibliometrics, suggesting that there is a continuing need for novel investigation at this stage. The most cited article is Repair-Schwann cell update: Adaptive reprogramming, EMT, and stemness in regenerating nerves, with 196 citations in the last 5 years and an impact factor of 6.2, which is significant in the field. The quality of the article is good. China and the United States are the countries with the highest number of publications, having published 939 and 552 documents, respectively, which accounts for 56.20% of the total number of publications in the past 5 years. The United States has a greater international impact, with a maximum centrality of 0.3, followed by China. Despite China having the highest number of publications, the overall quality is not sufficiently high. Therefore, Chinese researchers in this field should be encouraged to create high-quality articles to increase their international influence continuously.

Top 24 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2019 - 2023
Grinsell D, 2014, BIOMED RES INT, V2014, P0, DOI 10.1155/2014/698256, DOI	2014	15.48	2019	2019	
Cattin AL, 2015, CELL, V162, P1127, DOI 10.1016/j.cell.2015.07.021, DOI	2015	14.38	2019	2020	
Faroni A, 2015, ADV DRUG DELIVER REV, V82-83, P160, DOI 10.1016/j.addr.2014.11.010, DOI	2015	14.03	2019	2020	
Gu XS, 2014, BIOMATERIALS, V35, P6143, DOI 10.1016/j.biomaterials.2014.04.064, DOI	2014	13.83	2019	2019	
Chen PW, 2015, ACTA NEUROPATHOL, V130, P605, DOI 10.1007/s00401-015-1482-4, DOI	2015	11.93	2019	2020	
Jessen KR, 2015, CSH PERSPECT BIOL, V7, P0, DOI 10.1101/cshperspect.a020487, DOI	2015	9.19	2019	2020	
Jessen KR, 2016, J PHYSIOL-LONDON, V594, P3521, DOI 10.1113/JP270874, DOI	2016	8.66	2019	2021	
Navarro X, 2016, EUR J NEUROSCI, V43, P271, DOI 10.1111/ejn.13033, DOI	2016	6.83	2019	2020	
Clements MP, 2017, NEURON, V96, P98, DOI 10.1016/j.neuron.2017.09.008, DOI	2017	9.3	2020	2021	
Sarker MD, 2018, PROG NEUROBIOL, V171, P125, DOI 10.1016/j.pneurobio.2018.07.002, DOI	2018	6.55	2020	2020	
Panagopoulos GN, 2017, ORTHOPEDICS, V40, PE141, DOI 10.3928/01477447-20161019-01, DOI	2017	6.04	2020	2020	
Colloca L, 2017, NAT REV DIS PRIMERS, V3, P0, DOI 10.1038/nrdp.2017.2, DOI	2017	9.57	2021	2023	
Mahar M, 2018, NAT REV NEUROSCI, V19, P323, DOI 10.1038/s41583-018-0001-8, DOI	2018	7.07	2021	2021	
Arthur-Farraj PJ, 2017, CELL REP, V20, P2719, DOI 10.1016/j.celrep.2017.08.064, DOI	2017	6.56	2021	2021	
Stratton JA, 2018, CELL REP, V24, P2561, DOI 10.1016/j.celrep.2018.08.004, DOI	2018	9.04	2022	2023	
Vijayavenkataraman S, 2020, ACTA BIOMATER, V106, P54, DOI 10.1016/j.actbio.2020.02.003, DOI	2020	8.46	2022	2023	
Li R, 2020, THERANOSTICS, V10, P1649, DOI 10.7150/thno.40919, DOI	2020	8.27	2022	2023	
Wang ML, 2019, CONNECT TISSUE RES, V60, P3, DOI 10.1080/03008207.2018.1489381, DOI	2019	7.41	2022	2023	
Kornfeld T, 2019, WIEN MED WOCHENSCHR, V169, P240, DOI 10.1007/s10354-018-0675-6, DOI	2019	7.13	2022	2023	
Finnerup NB, 2021, PHYSIOL REV, V101, P259, DOI 10.1152/physrev.00045.2019, DOI	2021	7.13	2022	2023	
Gordon T, 2020, INT J MOL SCI, V21, P0, DOI 10.3390/ijms21228652, DOI	2020	7.13	2022	2023	
Nocera G, 2020, CELL MOL LIFE SCI, V77, P3977, DOI 10.1007/s00018-020-03516-9, DOI	2020	7.12	2022	2023	
Jessen KR, 2019, GLIA, V67, P421, DOI 10.1002/glia.23532, DOI	2019	6.49	2022	2023	
Kalinski AL, 2020, ELIFE, V9, P0, DOI 10.7554/eLife.60223, DOI	2020	5.98	2022	2023	

FIGURE 10
TOP 24 References with the strongest citation bursts.

Furthermore, an analysis of country and author co-occurrence revealed the formation of 16 collaborative teams. These teams were primarily composed of researchers from the same institution, affiliated hospitals, or region. Cross-province and cross-country studies are infrequent due to the lack of close connections between countries. Therefore, cooperation between countries in this field should be increased to establish a foundation for the treatment of clinical peripheral nerve injuries. Wang, Yu has the highest number of publications. His primary research is focused on neural tissue engineering. He uses self-assembled peptide nanofibers hydrogel combined with neurotrophic factors, as well as decellularized nerve catheters, nerve grafts, and Schwann cell grafts to promote peripheral nerve reconstruction and neovascularization (29–31). Yi Sheng's team investigated the mechanism of Schwann cells, proteins, growth factors, and cytokines in repairing sciatic nerve injuries (32–35). Hussain and Ghulam's third-ranked team published an article on modeling sciatic nerve injury through animal experiments in mice. The study found that certain plants and their derived compounds, such as the methanolic extract of *Foeniculum vulgare*, *Strychnos nux-vomica*, *Cannabis sativa* L., and *Moringa oleifera* Lam, possess anti-inflammatory, antioxidant, neuroprotective, and analgesic properties that promote the repair of peripheral nerves (4, 36, 37).

The study conducted by the issuing institutions revealed that the research advantage lies primarily with universities. Among the top 10 institutions, 7 are based in China, with Nantong University having the highest number of articles and a significant influence in the research field. Additionally, the study found that Chinese medicine universities have increasingly focused on the treatment of sciatic nerve injuries in recent years, indicating a growing interest in this field. Based on visual analysis of journals, *EXP NEUROL* has the largest number of document collections with a centrality of 0.21, indicating high influence and making it the mainstream journal in this field. Research in this field primarily focuses on Molecular Science, Biology, Immunology, Medicine, Clinical Medicine, Neurology, Kinesiology, and Ophthalmology.

Keyword co-occurrence and cluster can effectively summarize the main content of an article. An analysis of the keywords from the last 5 years reveals that neuropathic pain (414), expression (396), and Schwann cells (357) are the most frequently occurring hot keywords in this field. Neuropathic pain is a current research focus and a challenging field that significantly impacts patient's physical recovery and can lead to adverse emotions such as anxiety and depression (38). Various treatments have been used to alleviate this type of pain, including pharmacological interventions (39–42), electrical stimulation (43, 44), exercise (12), nerve catheterization (45), and electro-acupuncture (46, 47).

The cluster map primarily revolves around the research progress in nerve regeneration following sciatic nerve injury alleviation of

neuropathic pain muscle atrophy repair pathways and therapeutic mechanisms. Among these the most researched are Schwann cells which not only secrete signaling molecules to promote neuron survival and axonal regeneration but also activate local mesenchymal stem cells to migrate to the damaged tissue areas (48, 49).

The 15 keyword bursts were divided into two stages according to their mapping. In the first stage,(2019–2021), Complications had the highest burst strength of 4.89.Research indicates that diabetes mellitus is often complicated by sciatic nerve dysfunction and neuropathic pain (50–52) established a model of type I diabetes mellitus in rats by injecting streptozotocin into the intraperitoneal cavity. They found that exercise and insulin-like growth factor 1 treatment reduced the expression of vascular endothelial growth factor-A, platelet reactive protein-1, and nuclear factor-κB in the diabetic sciatic nerve, which promoted sciatic angiogenesis. In the second stage: From 2021 to the present, surgical treatments have exhibited the highest burst intensity, with a score of 4.04. These treatments mainly include nerve grafts (53, 54), fibrin glue (55–57), and nerve conduits (7, 58, 59, 60), indicating that surgical treatment is currently a popular research topic in the field of sciatic nerve repair and is predicted to continue to receive attention in the future.

Conclusion

This study conducted a comprehensive review of the research in the field of SNI over the past 5 years. The analysis of the research hotspots and keywords revealed that the repair of sciatic nerve injury and analgesia are the current research hotspots and challenges. Additionally, the study found that nerve transplantation, nerve catheterization, and cellular therapies are the current and future possible research focuses or significant breakthroughs in this field. Notably, stem cell therapy has made significant progress in the repair of SNI. Stem cells have the capacity to differentiate into neuronal and glial cells, which can facilitate nerve regeneration following sciatic nerve injury. This approach has the potential to revolutionize the treatment of sciatic nerve injury, offering new avenues for future therapeutic strategies. Secondly, the role of trophic factors in the repair of sciatic nerve injury has garnered significant interest. These factors can promote distal nerve regeneration after nerve injury, offering novel insights and avenues for future research and clinical practice. In the treatment of neuropathic pain, non-surgical aspects of the last 2 years have focused on the exploration of electrical stimulation, electroacupuncture, and medication. It is predicted that these will continue to be investigated in the future as well, with the aim of developing new analgesic treatments. Among them, electrical stimulation therapy has been shown to promote the increase of neurofactors for axonal growth and to improve the speed and effect of nerve repair. This provides a new tool for clinical practice. In conclusion, the results of the advances in sciatic nerve injury research provide useful information for future research and clinical practice. In the future, it is necessary to continue to explore new treatments and technologies in depth in order to provide better treatment options for patients with sciatic nerve injury. At the same time, it is important that policymakers pay attention to the development of this field and provide the necessary support and safeguards for related research and treatment.

However, autologous nerve grafting, despite being non-immunogenic effects and containing nerve regeneration promoting factors such as Schwann cells, adhesion molecules and neurotrophic factors, has limitations such as limited tissue availability, loss of neurological function, scarring, and formation of neuromas. On the other hand, allogeneic nerve grafts are easily available and have excellent recovery, but they are costly and have many side effects. Nerve conduits can serve as an alternative therapy to autologous nerve grafts and provide an ideal microenvironment for neuronal recovery. Biodegradable materials, such as collagen, polylactic acid, chitosan, and hydrogel, are currently the most commonly used. However, the biocompatibility of these materials is sometimes reduced due to their xenobiotic properties. In contrast, cell therapy and plant-derived compounds accelerate nerve regeneration, with Schwann cells being the most widely used. Future research should explore the use of more desirable and reliable materials for nerve conduits, as well as the discovery or design of potent compounds capable of restoring injured nerves. These treatments could be combined with rehabilitation or drug therapies to seek optimal results.

Limitations of the study

This study only selected literature from the Web of Science Core Collection Indexed Journal Database, which may introduce bias. To broaden the scope of the search and conduct more in-depth exploration in the future, strengthening talent exchange and regional cooperation is recommended for establishing a diversified research network. Additionally, this study's limitations in language, literature type, and time period may have led to the exclusion of relevant literature, resulting in potentially biased data. Therefore, further improvements in methodology are necessar.

Author contributions

YW (1st author): Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software. YahW: Writing – original draft, Data curation, Supervision. LL: Supervision, Writing – original draft, Data curation. TL: Supervision, Writing – original draft, Data curation. YW (5th author): Funding acquisition, Writing – review & editing, Project administration, Validation. FP: Investigation, Writing – review & editing, Formal analysis, Validation.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This research was supported by the National Natural Science Foundation of China (81973926, 82274623, and 81674077), the Natural Science Foundation of Heilongjiang Province (LH2021H090).

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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frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 23 May 2024
DOI 10.3389/fneur.2024.1381938

OPEN ACCESS

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RECEIVED 04 February 2024
ACCEPTED 06 May 2024
PUBLISHED 23 May 2024

CITATION
Zou X, Yi F, Zhou W, Dong Y, Alhaskawi A, Zhou H, Ezzi SHA, Kota VG, Abdulla MHAH, Alenikova O, Abdalbary SA, Lu H and Wang C (2024) Mechanisms and recent advances in the diagnosis and treatment of nitrous oxide-induced peripheral neuropathy: a narrative review.
Front. Neurol. 15:1381938.
doi: 10.3389/fneur.2024.1381938

Mechanisms and recent advances in the diagnosis and treatment of nitrous oxide-induced peripheral neuropathy: a narrative review

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Under standard conditions, nitrous oxide (N_2O) manifests as a colorless, odorless gas with a mildly sweet taste. The compound finds applications in various fields, including its use as an aerosol propellants, an accelerant in motor racing, and an anesthetic in surgical procedures and dentistry. Unfortunately, the recreational misuse of N_2O has become prevalent among young individuals due to its euphoric and hallucinogenic effects. Compounding this issue is the fact that nitrous oxide can be easily obtained from over-the-counter household items, facilitating its non-medical use. The global community has witnessed a surge in the recreational utilization of nitrous oxide gas in recent years. Despite the widespread non-medical abuse of N_2O, there remains inadequate understanding of the potential adverse effects resulting from exposure to it. This paper provides an overview of management findings, laboratory and electrodiagnostic characteristics, as well as clinical presentations associated with neurological disorders induced by nitrous oxide usage.

KEYWORDS

nitrous oxide – N_2O, peripheral neuropathy, abusive inhalation, neurological disorders, clinical characteristics

Introduction

N_2O is primarily utilized as an anesthetic agent. Distinguished from other inhalants, the inhalation of nitrous oxide induces a profound, transient, and pleasurable euphoria that is often described as mildly psychedelic and agreeable. It also subtly alters body image perception and can result in sensations of dissociation (1) along with its evanescent effects and rapid restoration of normal faculties, recreational users highly desire N_2O for brief intoxication

purposes, typically experiencing its effects within minutes. In recent years, the euphoric properties of N_2O have led to widespread recreational use in the Western world (2). For instance, data collected from drug users across more than 30 countries through the 2019 Global Drug Survey (GDS) revealed that at least once in their lifetime, 90% of respondents had used N_2O, positioning it as the tenth most popular substance in Western society after alcohol and tobacco.

The utilization patterns of N_2O are similar across these nations with a particular prevalence of 'whippets'—small canisters containing the gas. However, it is crucial to note that chronic exposure to elevated doses of N_2O can result in significant neurological damage including cobalamin (vitamin B_{12}) deficiency-induced neuropathy and even paralysis.

Therefore, it is imperative to understand and address the potential risks associated with prolonged inhalation of N_2O (3, 4). Additionally, the increasing incidence of individuals presenting at emergency departments with neurological impairments due to N_2O exposure highlights the concerning and serious nature of this trend (5).

Many of case reports have firmly established a clear correlation between the misuse of N_2O and a range of neurological and psychiatric disorders, including conditions such as subacute combined degeneration of the spinal cord, myelopathy, demyelinating polyneuropathy, peripheral neuropathy, and various mood and affective disturbances (6–8). Furthermore, fatalities resulting from N_2O inhalation have been documented (9). Currently, only a limited number of studies have focused on the peripheral neuropathy caused by abusive inhalation of nitrous oxide (10–12), highlighting a lack of awareness regarding the toxicity associated with N_2O abuse. Therefore, this study aims to comprehensively outline the clinical characteristics, mechanisms, and management strategies for N_2O-associated peripheral neuropathy.

The mechanisms of N_2O neurotoxicity

The manifestation of peripheral neuropathy can occur through various mechanisms, including distal axonopathy, myelinopathy, and neuronopathy. Each mechanism involves distinct pathological processes that result in the degeneration or dysfunction of nerve fibers, thereby impairing their ability to effectively transmit signals (13–15).

To date, Vitamin B_{12}, as called cobalamin, insufficiency has been extensively researched, while the exact mechanism of N_2O remains unclear. Although it has been observed that individuals who persistently use N_2O and experience neurological damage tend to have lower cobalamin levels, it is doubtful that a vitamin B_{12} shortage is the sole cause of such damage (11). Elevated serum levels of methylmalonate and homocysteine have proven to be more reliable biomarkers for brain injury following prolonged exposure to N_2O (16), promoting further investigation into the specific metabolic pathways underlying the toxicity associated with N_2O exposure.

Cobalamin, also known as Vitamin B_{12}, contains a cobalt ion at its core. Within the human body, it exists in two biologically active forms: methylcobalamin and adenosylcobalamin. Under specific conditions, N_2O can induce neurotoxic effects primarily through various biochemical mechanisms. One significant pathway of neurotoxicity involves interference with Vitamin B_{12} metabolism. N_2O oxidizes the cobalt ion from its functional +1 oxidation state to a non-functional +3 state (11). This oxidation renders cobalamin ineffective as a coenzyme for methionine synthase and methylmalonyl-CoA mutase (MMCoAM), thereby disrupting critical cellular processes such as DNA synthesis and energy production. The clinical implications of this disruption may include neurological dysfunction and hematological disorders due to impaired methionine synthesis and accumulation of homocysteine and methylmalonic acid (11). Furthermore, deficiency in MMCoAM enzymatic activity during lipid and carbohydrate biosynthesis leads to intracellular accumulation of methylmalonate acid (17, 18).

Another pathway involves methionine methyltransferase (MTR), a pivotal enzyme responsible for catalyzing the conversion of homocysteine and 5-methyltetrahydrofolate into tetrahydrofolate and methionine. Consequently, insufficient MTR enzymatic activity may result in an accumulation of homocysteine and 5-methyltetrahydrofolate, accompanied by reduced levels of methionine, tetrahydrofolate, and *S*-adenosylmethionine (19). Impairment in methionine and *S*-adenosylmethionine synthesis can disrupt the methylation process of myelin phospholipids, leading to various neurological consequences such as demyelination in the brain, spinal cord, and peripheral nervous system. Clinically, this disruption may manifest as megaloblastic anemia with potential progression to optic nerve atrophy (20, 21). Meanwhile, elevated levels of homocysteine can exert detrimental effects on physiological systems through distinct pathways: induction of oxidative stress resulting in reactive oxygen species (ROS) generation that triggers apoptotic cell death; activation of NMDA receptors (22). The activation of NMDA receptors has the potential to increase extracellular Ca^{2+} influx, cause mitochondrial Ca^{2+} overload and dysfunction along with ROS formation, potentially serving as the primary mechanism underlying homocysteine-mediated neurotoxicity (22).

Vitamin B_{12} depletion is not the only factor contributing to the neurotoxic effects observed after exposure to nitrous oxide (N_2O); other substantial mechanisms are also involved. Neonatal cerebral structures are especially vulnerable to N_2O-induced neurotoxicity, which occurs through antagonism of *N*-methyl-D-aspartate (NMDA) receptors (22). The activation dynamics of NMDA antagonists are widely recognized to produce divergent effects, ranging from neuroprotection to neurotoxicity (22). Short-term exposure to N_2O can cause reversible vacuolization in neuronal cells, while prolonged exposure is associated with neuronal apoptosis. Importantly, vacuolization involves significant swelling of mitochondrial structures (23).

It has been suggested that a change in cerebral blood flow is one of the underlying mechanisms responsible for the neurotoxic ramifications of N_2O, particularly in terms of cerebral damage (22). Furthermore, N_2O alone can inhibit the biosynthesis of xanthine and various monoamines, such as norepinephrine, dopamine, and serotonin. This inhibition may lead to neurotoxic outcomes, subsequently triggering a cascade of events including cytokine disequilibrium, cerebral hypoxia, and acidosis (Figure 1) (24).

Clinical features

The symptoms of peripheral neuropathy vary depending on the location and type of nerve damage. Common manifestations include

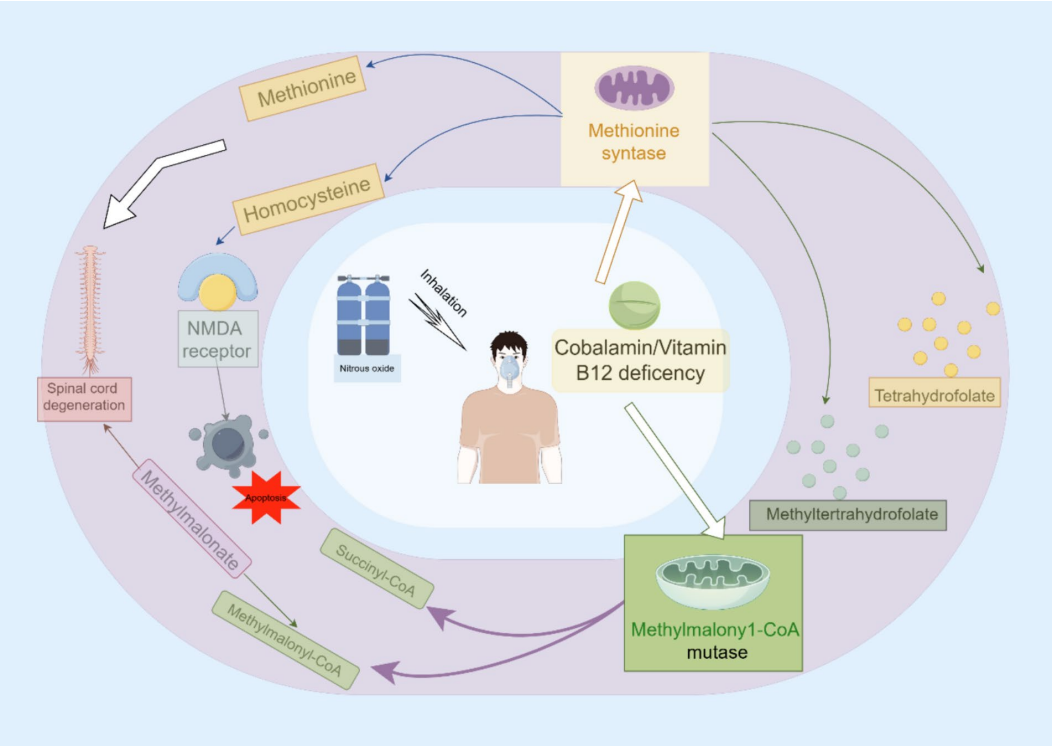

FIGURE 1
The main mechanisms involved in N_2O-induced neurotoxicity.

paresthesia in the hands and feet, muscle weakness or paralysis, impaired balance or coordination, as well as pain (25).

Abuse of N_2O can lead to peripheral neuropathy, a condition marked by symptoms such as weakness, numbness, and unsteady gait (26). Notably, the weakness is more pronounced in the lower limbs compared to the upper limbs. Studies of nerve function have consistently demonstrated that this nerve damage involves both motor and sensory fibers, with a considerable loss of motor nerve axons in the lower extremities (26). Further investigations, including sural nerve biopsies, have confirmed that ongoing axonal degeneration is the primary pathological change in nerves affected by this condition (26, 27).

A retrospective study (28) spanning was conducted between 2018 and 2020, involving 76 patients diagnosed with neuropathy attributable to N_2O misuse. The analysis of the collected data indicated that 36% of these patients exhibited an absence of response in nerve conduction assessments. Notably, the majority presented with reduced sensory and motor nerve conduction velocities, affecting 75 and 76% of the cohort, respectively. Additionally, diminished amplitudes in sensory nerve action potentials and compound muscle action potentials were observed in 57 and 59% of cases, respectively, along with prolonged distal motor latencies. The electrophysiological data (28) revealed diverse neuropathic presentations, with axonal neuropathy identified in 37 patients (49%), demyelinating peripheral neuropathy in 4 patients (5%), and mixed neuropathy in 12 patients (16%). The primary pathological features included predominant motor axonal damage in 67% of the upper and lower limb impairments, and sensory nerve demyelination accounting for 35% of the deficits. Furthermore, a subgroup analysis suggested a correlation between prolonged N_2O exposure, extended illness duration, and the severity of motor axonal damage in the lower extremities.

In our case series, the nerve conduction studies of a typical patient with peripheral neuropathy induced by N_2O revealed complaints of fatigue and numbness in the bilateral lower limbs (Tables 1, 2) (1, 2).

Diagnosis

In clinical practice, several diagnostic tests are available to identify the underlying etiology and assess the extent of peripheral nerve damage. Commonly employed techniques include nerve conduction studies (NCS), electromyography (EMG), imaging modalities, and nerve biopsy (29). When assessing patients, especially younger individuals, who exhibit symptoms indicative of peripheral neuropathy or myelopathy, clinicians should contemplate the potential for N_2O neurotoxicity. A detailed history of specific and prolonged N_2O use and exposure is essential for diagnostic confirmation. However, it is important to note that some patients may not disclose their N_2O usage during initial consultations, which can complicate the process of establishing a preliminary diagnosis. Moreover, Guillain-Barré syndrome (GBS) and N_2O-related peripheral neuropathy share several similarities (11), necessitating additional biochemical testing and nerve conduction testing to be conducted (30).

Biochemical testing for functional vitamin B_{12} insufficiency, such as accessing homocysteine and methylmalonic acid levels, can be used to confirm the diagnosis in cases where there are consistent clinical symptoms and a history of significant N_2O exposure (Table 1) (31). Furthermore, it is recommended to conduct nerve conduction studies

TABLE 1 Motor nerves conduction.

Nerve and site	Latency	Amplitude	Velocity
Peroneal. R			
Ankle	4.9 ms	0.8 mV	N/A
Fibula (head)	12.2 ms	0.1 mV	12.3 m/s
Tibial. L			
Fibula (head)	5.0 ms	2.5 mV	N/A
Popliteal fossa	14.3 ms	1.1 mV	41.3 m/s
Peroneal. L			
Ankle	6.4 ms	0.4 mV	N/A
Fibula (head)	14.3 ms	0.2 mV	40.5 m/s
Popliteal fossa	16.0 ms	0.1 mV	50.5 m/s
Tibial. R			
Fibula (head)	5.0 ms	0.7 mV	N/A
Popliteal fossa	14.7 ms	0.1 mV	40.2 m/s
Median. R			
Wrist	4.3 ms	3.6 mV	N/A
Below elbow	9.0 ms	2.7 mV	51.4 m/s
Ulnar. R			
Wrist	3.0 ms	7.6 mV	N/A
Below elbow	7.9 ms	5.3 mV	40.8 m/s
Above elbow	10.0 ms	7.2 mV	54.7 m/s
Axilla	11.2 ms	7.0 mV	60.0 m/s
Median. L			
Wrist	4.4 ms	4.0 mV	N/A
Below elbow	8.6 ms	2.6 mV	53.5 m/s
Ulnar. L			
Wrist	2.9 ms	10.7 mV	N/A
Below elbow	6.8 ms	10.7 mV	53.8 m/s
Above elbow	9.0 ms	10.7 mV	50.0 m/s
Axilla	10.3 ms	10.7 mV	53.8 m/s

*R means right side limb. L means left side limb.

TABLE 2 Sensory nerves conduction.

Nerve and site	Latency	Amplitude	Velocity
Sural. R			
Fibula (head)	2.3 ms	2.9 mV	41.3 m/s
Superficial peroneal. R			
Fibula (head)	2.2 ms	8.5 mV	43.1 m/s
Sural. L			
Fibula (head)	2.3 ms	4.6 mV	43.1 m/s
Superficial peroneal. L			
Fibula (head)	2.4 ms	3.4 mV	43.7 m/s
Superficial of ulnar. R			
Digit V	2.5 ms	8.1 μV	46.0 m/s
Superficial of ulnar. L			
Digit V	2.4 ms	9.4 μV	50.0 m/s

*R means right side limb. L means left side limb.

TABLE 3 Diagnostic examinations for individuals with suspected nitrous oxide poisoning (31).

Investigation type	Finding
Vitamin B_{12}	Patients with neurologic symptoms often have either low (50–75%) or normal (25–50%) levels.
Homocysteine	Increased
Methylmalonic acid	Increased
Nerve conduction studies	The majority of patients with symptoms exhibit abnormality. • Axonal degeneration, with or without demyelination, is a common occurrence. • Isolated demyelination without axonal degeneration is a rare phenomenon.

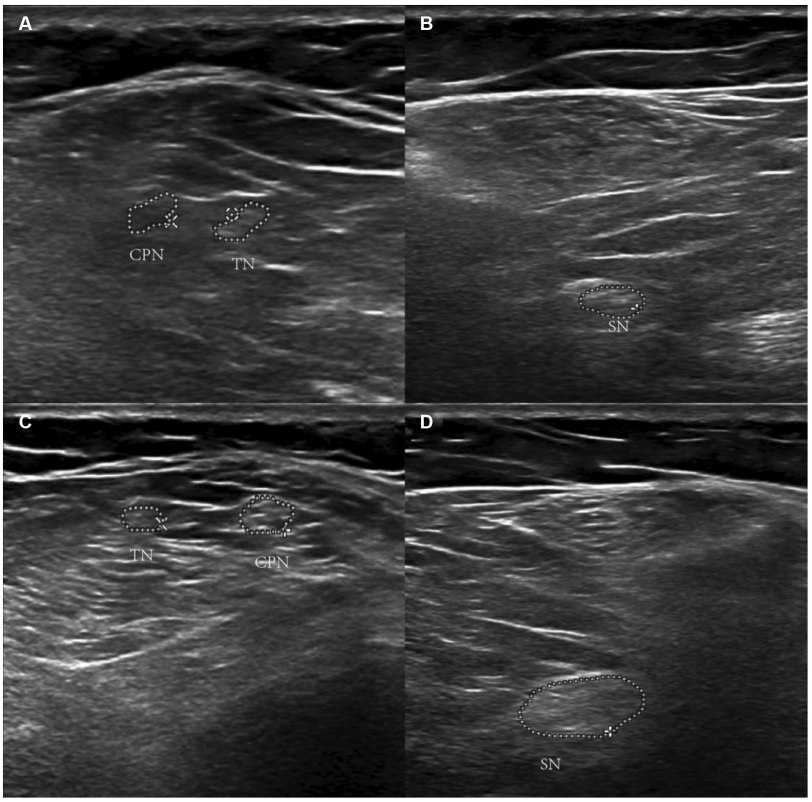

FIGURE 2
Ultrasonographic image of nitrous oxide-Induced peripheral neuropathy. Panels **(A,B)** show the echo enhancement around peripheral nerves in the left lower limb. Panels **(C,D)** are the right lower limb. *TN refers to the tibial nerve. CPN refers to common the peroneal nerve. SN refers to the sciatic nerve.

in order to further characterize the involvement of the peripheral nervous system (Table 3) (32, 33).

A low concentration of vitamin B_{12} is observed in 54–72% of patients experiencing neurological issues due to N_2O exposure (34, 35). This occurrence is more likely in individuals exhibiting symptoms after shorter doses, indicating increased susceptibility (35). Low concentrations of vitamin B_{12} in long-term users may be indicative of accelerated clearance (36, 37). This reduced enzymatic activity results in the accumulation of homocysteine and methylmalonic acid, with at least one of these being elevated in over 90% of patients (38). Consequently, these biomarkers are more sensitive indicators compared to vitamin B_{12} concentrations, as the latter can remain within the normal range in a significant proportion of users despite neurotoxicity. In an attempt to mitigate neurotoxicity and maintain normal levels of these biomarkers, some users supplement with additional vitamin B_{12}. However, although this practice may potentially mislead clinicians, it does not offer complete protection against the neurological side effects associated with nitrous oxide usage (39, 40).

The majority of patients exhibiting symptoms demonstrate atypical results in nerve conduction studies (33–35). While a minority of these individuals exhibit signs of isolated demyelination, the predominant irregularity observed is axonal degeneration, which may occur with or without accompanying demyelination. It is noteworthy that individuals who regularly use N_2O tend to experience more pronounced motor impairments compared to those with a deficiency of vitamin B_{12} not associated with nitrous oxide exposure (41).

In previous studies, MRI was used to diagnose lesions on the spinal cord and cerebral cortex (27). Based on our expertise, we recommend using ultrasonography to identify peripheral nerve impairments (42, 43). Echo enhancement around peripheral nerves can be observed with ultrasound (Figure 2).

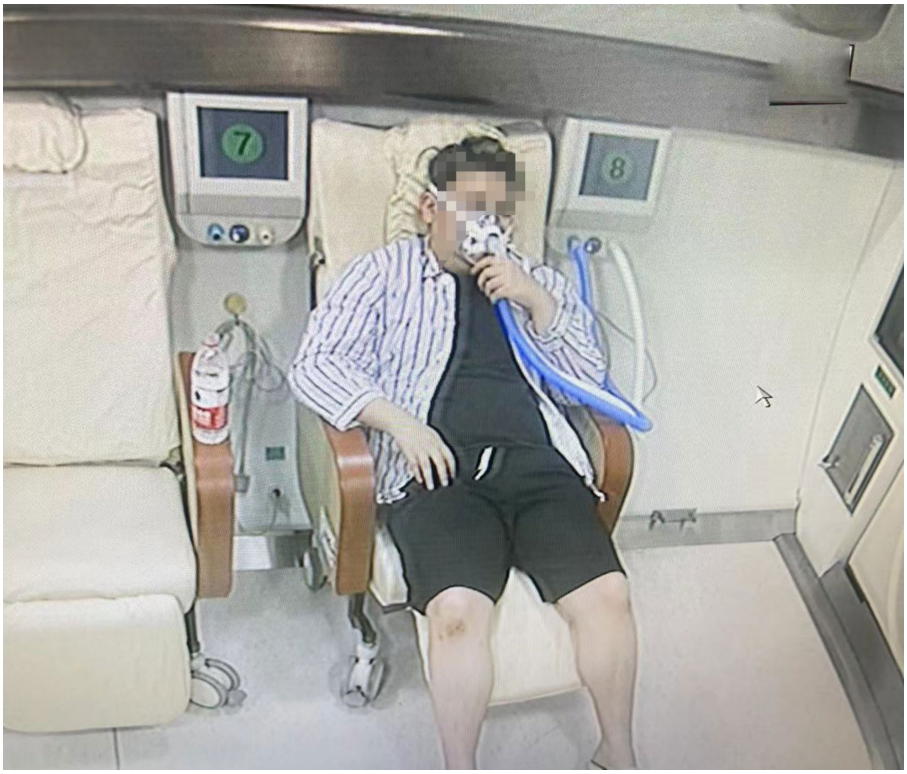

FIGURE 3
A patient with peripheral neuropathy caused by excessive inhalation of nitrous oxide is undergoing treatment with hyperbaric oxygen therapy.

In conclusion, when patients with a history of N_2O use present symptoms of peripheral neuropathy, physicians should consider the possibility of N_2O-induced peripheral neuropathy. Further nerve conduction studies (NCS) can confirm the presence of peripheral nerve damage. Additionally, a concurrent decrease in Vitamin B_{12} levels can aid in diagnosing N_2O-related peripheral neuropathy.

Treatment

Prior research has indicated that prolonged usage of N_2O heightens the likelihood of neurological impairments, and discontinuing exposure to the toxin is the foremost crucial initial measure for treatment (11, 12, 30). Supplementation with vitamin B_{12} is advised, and in some cases, it may be combined with methionine, despite the limited evidence underpinning its efficacy (31). We propose an administration of 1,000 µg of vitamin B_{12}, either subcutaneously or intramuscularly, on a daily basis for 1–2 weeks. Subsequently, either weekly injections administered by caregivers or daily oral doses of 2,000 µg should continue until symptomatic relief is achieved. This recommendation is based on the favorable safety profile of vitamin B_{12} (44, 45). Furthermore, we propose a secure and efficacious regimen of methionine supplementation, with an oral dosage of 1 g administered three times daily for a minimum of 4–6 weeks, or until significant symptomatic improvement is observed (46). Due to the potential for exacerbation of symptoms and prolonged recovery, initiating folate supplementation before the restoration of vitamin B_{12} levels is not recommended, as it is unlikely to benefit the patient (47, 48). In certain cases, integrating physical rehabilitation along with social and psychological support measures may be essential.

The beneficial effects of hyperbaric oxygen therapy (HBOT) in repairing peripheral nerve injuries have been well-documented in previous literature (49). A recent prospective study (50) assessed the efficacy of HBOT following primary nerve repair in patients with upper extremity nerve injuries. The study results shown that compared to the control group, the group treated with hyperbaric oxygen achieved a higher power score, exhibited a faster recovery rate, and demonstrated quicker impulse transmission. However, there is limited documentation regarding the use of HBOT for treating peripheral nerve injuries caused by N_2O. In our experience, we are investigating the potential use of HBOT as an adjunctive treatment for patients with peripheral neuropathy induced by the abusive inhalation of N_2O.

The prognosis for recovery varies among patients; however, the vast majority of patients (95–97%) exhibit some degree of improvement. It is important to note that despite months of therapeutic intervention, over one-third of hospitalized patients continue to manifest neurological symptoms (Figure 3 and Table 4) (34, 35).

Conclusion

Nitrous oxide, is known for its cost-effectiveness and ease of procurement. It is widely utilized as a recreational substance, particularly among the adolescent population. Its consumption is a frequently overlooked as a potential cause of neurological disorders, primarily myelopathy, peripheral neuropathy, and encephalopathy,

TABLE 4 Treatment for peripheral neuropathy caused by N_2O.

Methods	Description
Cessation of exposure	This represents the initial stage. Consideration should be given to specialized knowledge in addiction medicine, along with the provision of psychiatric, psychological, and social support.
B_{12} (cobalamin)	Administer 1,000 micrograms intramuscularly on a daily basis for a period of 1–2 weeks, then switch to a weekly dosage of 1,000 micrograms or a daily oral dosage of 2,000 micrograms until symptoms are resolved.
Methionine	1 g by mouth 3 times a day for at least 4–6 weeks, or until symptoms get a lot better.
Other	1. Rehabilitation. 2. Do not give folate before giving B_{12} supplements. 3. Hyperbaric oxygen therapy.

which may be accompanied by hematological abnormalities. Furthermore, it has the potential to induce functional vitamin B_{12} deficiency. Therefore, healthcare professionals are encouraged to consider and inquire about nitrous oxide use in patients presenting with unexplained clinical manifestations suggestive of vitamin B_{12} deficiency or other neurologic symptoms consistent with its usage.

In conclusion, a comprehensive understanding and recognition of the neurological implications associated with the utilization of N_2O is imperative for healthcare professionals. By considering the potential involvement of N_2O in patients presenting with inexplicable neurological symptoms or exhibiting signs of vitamin B_{12} deficiency, healthcare professionals can assume a pivotal role in early detection, diagnosis, and management of related conditions, thereby enhancing patient care and optimizing outcomes.

Author contributions

XZ: Writing – original draft, Writing - review & editing. FY: Writing – original draft, Writing – review & editing. WZ: Visualization, Writing – review & editing. YD: Investigation, Writing – review & editing. AA: Funding acquisition, Writing – review & editing. HZ: Methodology, Writing – review & editing. SE: Software, Writing – review & editing. VK: Supervision, Writing – review & editing. MA: Validation, Writing – review & editing. OA: Data curation, Formal analysis, Writing – review & editing. SA: Software, Writing – review & editing. HL: Conceptualization, Writing – review & editing. CW: Conceptualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 05 August 2024
DOI 10.3389/fneur.2024.1420402

OPEN ACCESS

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RECEIVED 20 April 2024
ACCEPTED 10 June 2024
PUBLISHED 05 August 2024

CITATION
Aisaiti A, Aierxiding S, Shoukeer K and Muheremu A (2024) Mesenchymal stem cells for peripheral nerve injury and regeneration: a bibliometric and visualization study.
Front. Neurol. 15:1420402.
doi: 10.3389/fneur.2024.1420402

Mesenchymal stem cells for peripheral nerve injury and regeneration: a bibliometric and visualization study

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Objective: To use bibliometric methods to analyze the research hotspots and future development trends regarding the application of mesenchymal stem cells in peripheral nerve injury and regeneration.

Methods: Articles published from January 1, 2013, to December 31, 2023, were meticulously screened using the MeSH terms: TS=("Mesenchymal stem cells" AND "Peripheral nerve injury") OR TS=("Mesenchymal stem cells" AND "Peripheral nerve regeneration") within the Web of Science database. The compiled data was then subjected to in-depth analysis with the aid of VOSviewer and Cite Space software, which facilitated the identification of the most productive countries, organizations, authors, and the predominant keywords prevalent within this research domain.

Results: An extensive search of the Web of Science database yielded 350 relevant publications. These scholarly works were authored by 2,049 collaborative researchers representing 41 countries and affiliated with 585 diverse academic and research institutions. The findings from this research were disseminated across 167 various journals, and the publications collectively cited 21,064 references from 3,339 distinct journals.

Conclusion: Over the past decade, there has been a consistent upward trajectory in the number of publications and citations pertaining to the use of mesenchymal stem cells in the realm of peripheral nerve injury and regeneration. The domain of stem cell therapy for nerve injury has emerged as a prime focus of research, with mesenchymal stem cell therapy taking center stage due to its considerable promise in the treatment of nerve injuries. This therapeutic approach holds the potential to significantly enhance treatment options and rehabilitation prospects for patients suffering from such injuries.

KEYWORDS

mesenchymal stem cells, neural regeneration, Schwann cells, bibliometrics, peripheral nerve injury

1 Introduction

Peripheral Nerve Injury (PNI) is a prevalent neurological condition encountered in clinical practice, frequently induced by a spectrum of physical traumas such as road traffic accidents, construction mishaps, natural disasters, combat injuries, athletic incidents, injectable drug-related trauma, and electrical injuries (1, 2). The global annual incidence of PNI is approximated

to fall within the range of 13 to 23 cases per 100,000 individuals (3–5). PNI is notorious for its challenging treatment landscape, unfavorable prognoses, high incidence of disability, and the considerable pain and psychological distress it inflicts on patients and their families (6, 7). While conventional treatment modalities encompass surgical intervention, physical therapy, and pharmacological treatments, these approaches often fall short of fully restoring functionality in many instances (8, 9). Consequently, the pursuit of novel therapeutic strategies to enhance the repair and regeneration of peripheral nerves assumes paramount significance (10, 11). Emerging from the horizon of regenerative medicine, the utilization of mesenchymal stem cells (MSCs) has demonstrated potential in differentiating into neural cells to treat PNI, thereby presenting novel avenues for augmenting patient treatment and rehabilitation (12, 13). This innovative approach has ignited optimism within the academic and medical communities, as well as among patients, regarding the potential for improved treatment outcomes and enhanced quality of life (14, 15).

MSCs are ubiquitously distributed within a plethora of tissues, including bone marrow, umbilical cord blood, the subendothelial layer of umbilical veins, adipose tissue, peripheral blood, and muscle (16, 17). As stem cells, MSCs possess a constellation of advantages, including their widespread availability, ease of accessibility, low immunogenicity, potential for osteogenic differentiation, and their capacity for robust proliferation and self-renewal (18, 19). Consequently, they are esteemed as the quintessential "seed cells" within the domain of tissue engineering (20, 21). In recent times, MSCs have garnered significant attention and support from researchers across various disciplines, including bone tissue engineering, peripheral nerve injury repair, and regeneration, with a particular emphasis on the latter (22–25). This therapeutic approach holds immense promise due to MSCs' potential to differentiate into nerve cells, thereby bolstering neural regeneration, enhancing the prognosis for patients with peripheral nerve injuries, reducing disability rates, alleviating pain, and diminishing the burden on patients and their families (26–28). However, the effectiveness and safety of this treatment method require further validation through rigorous research and clinical trials. In this study, a bibliometric approach was adopted, leveraging the Web of Science database to compile and select pertinent literature on MSCs within the context of peripheral nerve injury and regeneration, spanning from January 2013 to December 2023. Through a multifaceted visualization analysis of the aggregated literature, encompassing an examination of contributing countries, authors, institutions, journals, articles, and keywords (29), the objective is to offer insights into the prevailing research foci and emerging development trends in this domain. The purpose of current study was to chart new pathways for the treatment of PNI with the aim of maximizing benefits, and to furnish the scientific community with empirical data, and theoretical underpinnings to inform future research endeavors."

2 Materials and methods

2.1 Data collection and retrieval

A total of 360 articles related to MSCs and PNI were extracted from the Web of Science database, which provided a core collection of relevant literature. These publications were thoroughly reviewed according to unified standards, resulting in the confirmation of 350 valid articles and reviews. These publications were utilized for co-authorship, co-journal, co-institution, and co-country network analysis, along with citation analysis. To mitigate errors arising from database updates and to minimize the subjectivity of different screeners' selections, a single researcher completed the screening and collection of all the articles on December 31st, 2023. This approach established a robust data foundation for subsequent research analysis, thereby elucidating the cooperative networks and cutting-edge research trends within the domains of MSCs and PNI.

2.1.1 Retrieval method and search terms

In the advanced search function of the Web of Science database, we delineated our search within the Core Collection, targeting the specific topics of "Mesenchymal stem cells" and "Peripheral nerve injury" or "Mesenchymal stem cells" and "Peripheral nerve regeneration." The search query was constructed as Topic = ("Mesenchymal stem cells" AND "Peripheral nerve injury") OR Topic = ("Mesenchymal stem cells" AND "Peripheral nerve regeneration"). Following a meticulous screening of the retrieved literature, we compiled a comprehensive plain text file that encapsulated the complete bibliographic records and references. Subsequently, this data was processed through the visualization software Cite Space 6.4.2R for a detailed analysis. Furthermore, supplementary research analysis was conducted utilizing both Cite Space and VOSviewer. The literature search began on January 1, 2013, and ended on December 31, 2023, covering the "article" and "review" categories. This section offers a comprehensive narrative of the search methodology and the specific search terms employed, thereby aiding other researchers in comprehending the research approach and facilitating further studies within related disciplines.

#1 subject term: Mesenchymal stem cells
#2 free word: Peripheral nerve injury OR Peripheral nerve disease;
#3 #2 AND #1
#4 subject term: Peripheral nerve regeneration;
#5 subject term: treatment;
#6 #3 AND #4 AND #5

2.1.2 Inclusion and exclusion criteria

The inclusion criteria for this study were confined to article and review pertinent to the application of MSCs in the treatment and regeneration of peripheral nerves, sourced from the Web of Science database between January 1st, 2013, and December 31st, 2023. The exclusion criteria were meticulously defined to include: (1) duplicate literature, (2) non-original content such as notifications, comments, translations, conference papers, abstracts, newspaper articles, patents, news reports, lectures, autobiographies, and graduate theses. The establishment of these stringent criteria was instrumental in ensuring the consistency and quality of the literature selection process, thereby enhancing the reliability of the resulting corpus.

2.1.3 Data analysis

The Web of Science database was used to analyze data, extracting key information such as publication year, country/region, author, and other relevant factors from the selected literature. Visualization analysis tools such as Cite Space, VOSviewer, and Microsoft Excel

2019 were then employed for data visualization. Cite Space is a powerful bibliometric tool capable of analyzing citation networks, keyword networks, and author collaboration networks, among others, providing a deeper understanding of frontiers, hotspots, and trends in the research field. On the other hand, VOSviewer specializes in visualizing bibliometric networks, grouping related nodes and using different colors to distinguish clusters, thereby helping researchers discover patterns and relationships in large-scale bibliographic data. These two software programs have been widely used in bibliometric research to aid in better understanding bibliographic data visually. In this study, we used them to analyze various aspects of literature, such as annual distribution, country/region distribution, author cooperation networks, and keyword networks, to generate knowledge maps, keyword clustering maps, and other visual charts in order to comprehensively study and analyze the development trends and key nodes in the research field. This will help reveal cutting-edge research directions and provide valuable insights for researchers.

3 Results

We collected a total of 360 pieces of literature from the Web of Science database. After conducting a thorough review and eliminating some of the gathered literature, we ultimately chose 350 publications for inclusion in this study, as shown in Figure 1. These 350 publications were authored by 2049 individuals from 41 different countries and 585 institutions. They were published in 167 distinct journals and collectively referenced a total of 21,064 publications from 3,339 journals.

3.1 Global trend in article publications

The volume of literature publications serves as a critical metric for gauging the evolving trends and emerging focal points within a research domain. By examining the global literature output over the past decade in the field of MSC therapy for peripheral nerve injury and regeneration within the Web of Science database, we can discern shifts in research orientation and the developmental trajectory of this area. This analysis offers crucial insights into the research hotspots, thereby enriching our understanding of the field. Figure 2 encapsulates the publication status of literature in this domain over the past decade, detailing the retrieval of a total of 350 publications and an average annual output of approximately 32 literature. The Figure 2 reveal a consistent trend where the annual literature publication count has consistently exceeded 20 publications from 2013 to 2023. Notably, there were six years with a publication volume surpassing the average (31.8 literature), with 2018 and 2020 standing out as the pinnacles with 40 articles each. Despite annual fluctuations in publication counts, the overall pattern suggests a robust level of annual publications, with a minimum of 20 articles published annually in this field. It is noteworthy that, although the literature publication count for 2023 stands at 31, given the historical trend, it is highly probable that the total will surpass 31 by the year's end (Figure 2).

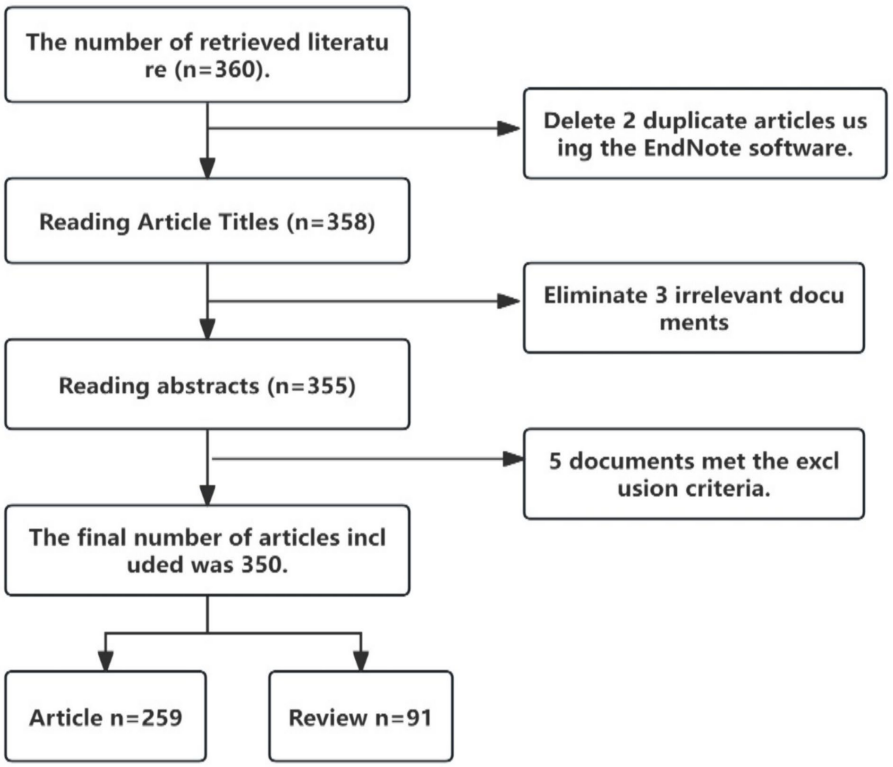

FIGURE 1
Flowchart of literature search and screening process.

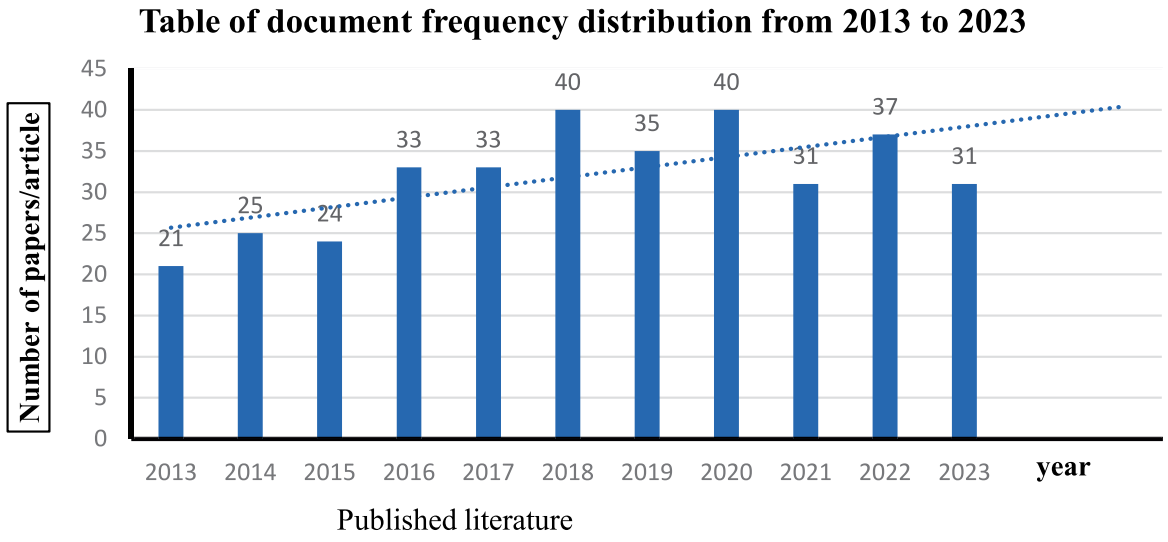

FIGURE 2
The annual distribution of publications in the Web of Science database.

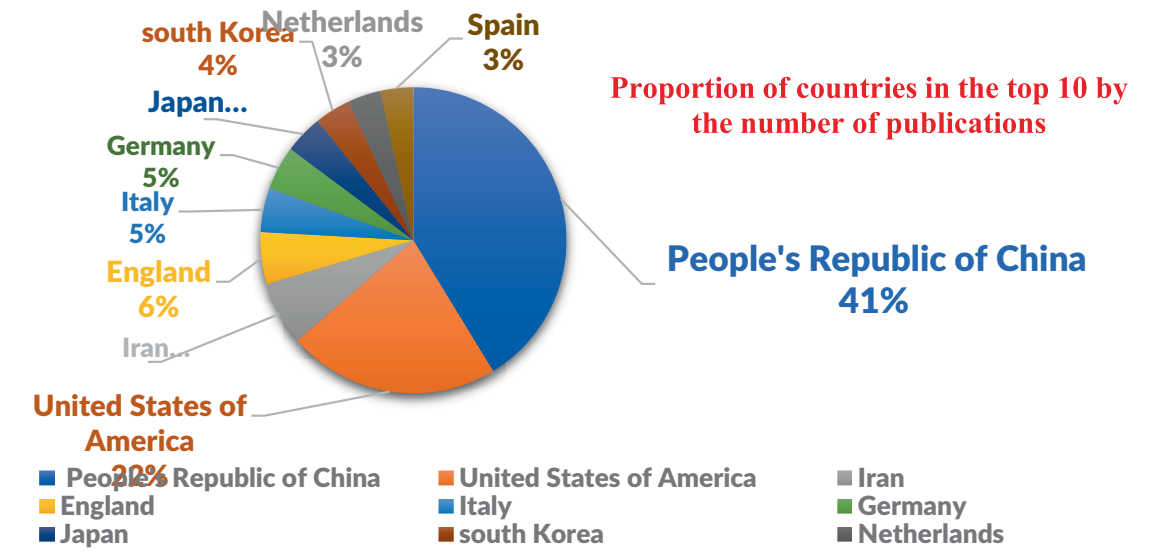

FIGURE 3
Proportion of the top 10 countries in the field of academic literature publications.

3.2 National distribution

Among the 40 distinct countries and regions represented, Figure 3 illustrates that China leads in terms of publication output, with a total of 142 papers, comprising 41.0% of the global total. The United States follows closely with 77 papers, accounting for 22.0% of the total. Collectively, these two nations account for 63.0% of the global publication output, underscoring their substantial influence in the field of mesenchymal stem cell therapy for peripheral nerve injury and regeneration (Figure 3). In the VOSviewer visualization (Figure 4), the size of each node corresponds to its frequency of occurrence, and the density between nodes indicates the level of association (Figure 5). Figure 6 demonstrates the geographical distribution of the top ten countries in terms of global publication output, suggesting a network of collaborative relationships among China, the United States, the United Kingdom, Germany, and other nations. This suggests that research in this domain has become a global academic endeavor. Cite Space visualization analysis reveals that the United States maintains the closest connections with other countries and holds a significant academic influence in this field (Figure 5).

3.3 Author distribution

Among the 350 publications within this domain, a total of 2049 authors contributed to their publication. From 2013 to 2023, authors

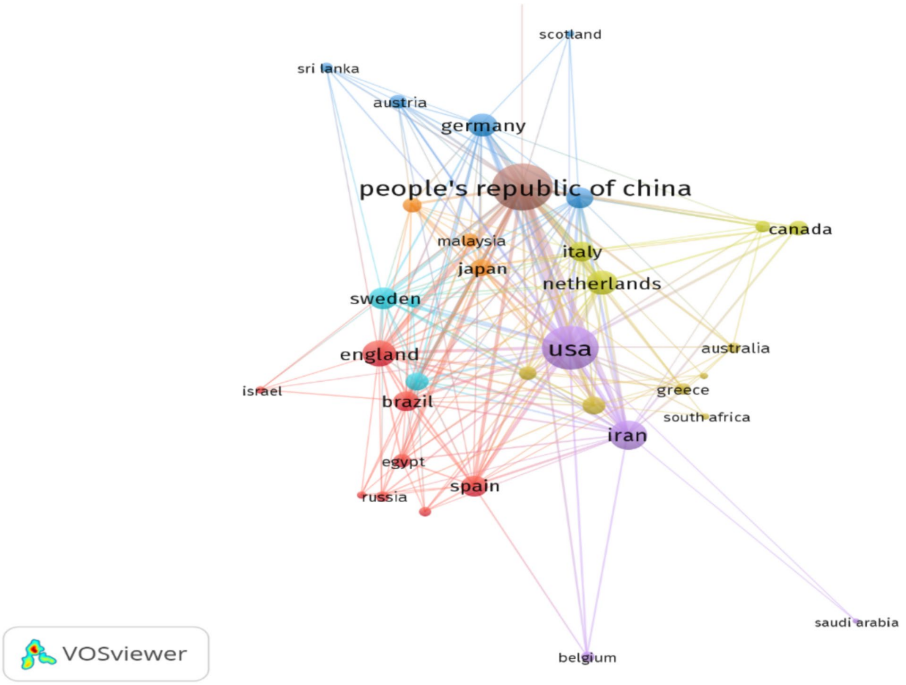

FIGURE 4
National collaborative analysis of studies related to using mesenchymal stem cells for the treatment of peripheral nerve injury and regeneration.

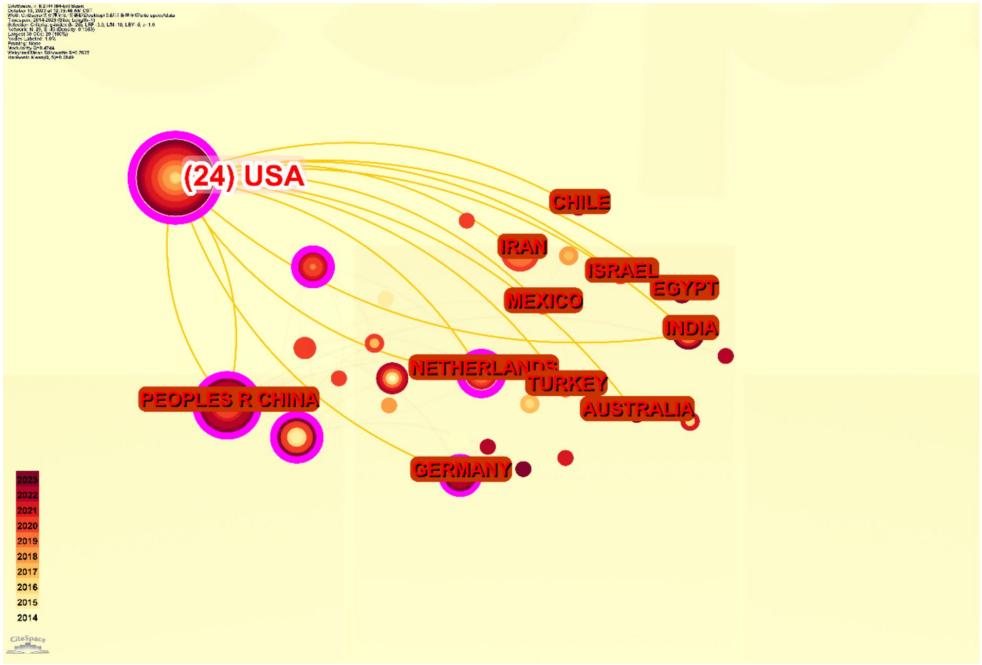

FIGURE 5
Chart of cooperative relations among various countries.

across the globe collaborated to produce 350 English-language literature on MSCs therapy for peripheral nerve injury and nerve regeneration. Table 1 details the top 10 authors, who collectively authored 62 articles, representing approximately 17.71% of the total. These authors hail from diverse nations including China, the United States, Sweden, Japan, and Portugal, and have collectively advanced the field with their substantial contributions. Dr. PENG J from Nantong University stands out with 10 publications, contributing 2.86% of the total and ranking first. Dr. WANG Y follows with 7 articles, representing 2.0% of the total and ranking second,

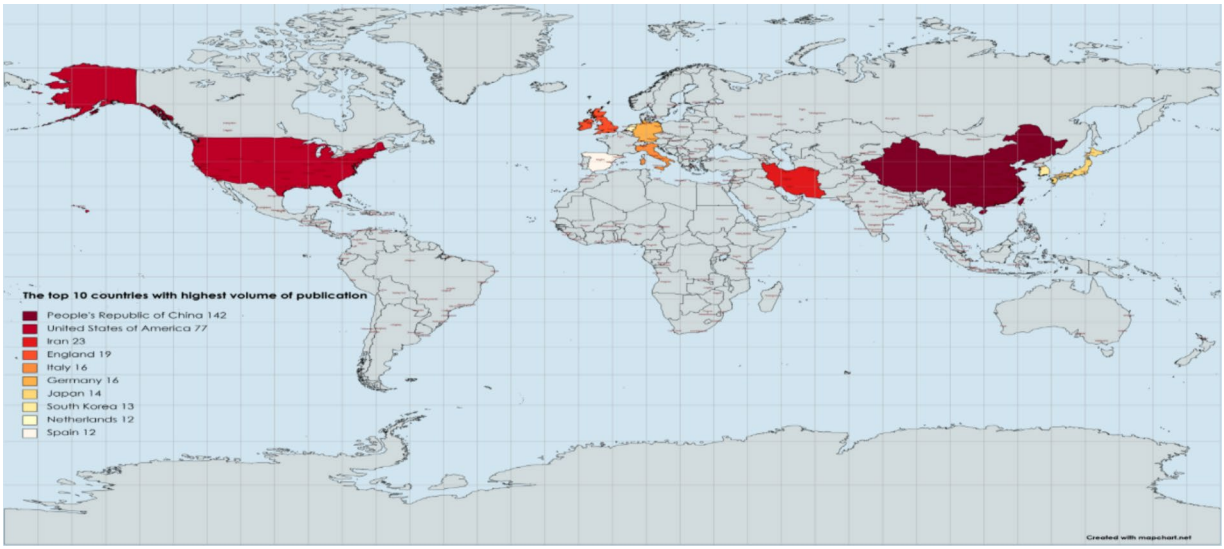

FIGURE 6
Global distribution of the top 10 countries in terms of published literature.

TABLE 1 Co-authorship analysis of the top 10 authors in terms of number of publications.

Author	Publication (NO)	Proportion (%)	Citations (times)	Country	Institution
Peng J	10	2.86	221	China	Nantong University
Wang Y	7	2.0	156	China	Nantong University
Sakaguchi	6	1.71	196	USA	Iowa State University
Gu XS	6	1.71	196	China	Nantong University
Yang YM	6	1.71	275	China	Nantong University
Kingham PJ	6	1.71	587	Sweden	University of Umea
Shin A	6	1.71	88	USA	Mayo School of Medicine
Malla PS	5	1.43	127	USA	Iowa State University
Ikeguchi R	5	1.43	139	Japan	Kyoto University
Mauricio AC	5	1.43	108	Portugal	University of Porto

underscoring the significant academic influence of Nantong University in this domain (Table 1).

3.4 Distribution of institutions

In the domain of MSCs therapy for peripheral nerve injury and regeneration, a total of 585 institutions and organizations worldwide are actively engaged, indicating a vibrant landscape of international collaboration and activity. Among these, 26 institutions/regions have published more than five articles. Figure 7 delineates the top 10 institutions/organizations in terms of publication volume. Nantong University in China leads the pack with 13 publications, closely followed by the Chinese PLA General Hospital and Sun Yat-sen University, each with 12 and 10 publications, respectively. This underscores the robust research activity in this field in China (Figure 7). Clustering analysis of these institutions conducted using VOSviewer software illuminates the collaborative relationships and research focal points among institutions/organizations (Figure 8). The size of the nodes in the figure corresponds to the number of articles published by each institution, with larger nodes indicating a greater number of publications. Additionally, the thickness of the lines connecting the nodes denotes the frequency of collaboration between the represented institutions. Consequently, from Figure 8, it is evident that there is a robust network of connectivity among various institutions/organizations within China, as well as between China and other global research institutions. This collaborative network fosters knowledge exchange and cooperation, contributing to the advancement of research on peripheral nerve injury and regeneration (Figure 8).

3.5 Journal analysis

Over the past decade, the top ten journals in the literature on mesenchymal stem cell therapy for peripheral nerve injury and regeneration research are listed in Table 2. The top three journals are Neural Regeneration Research, International Journal of Molecular

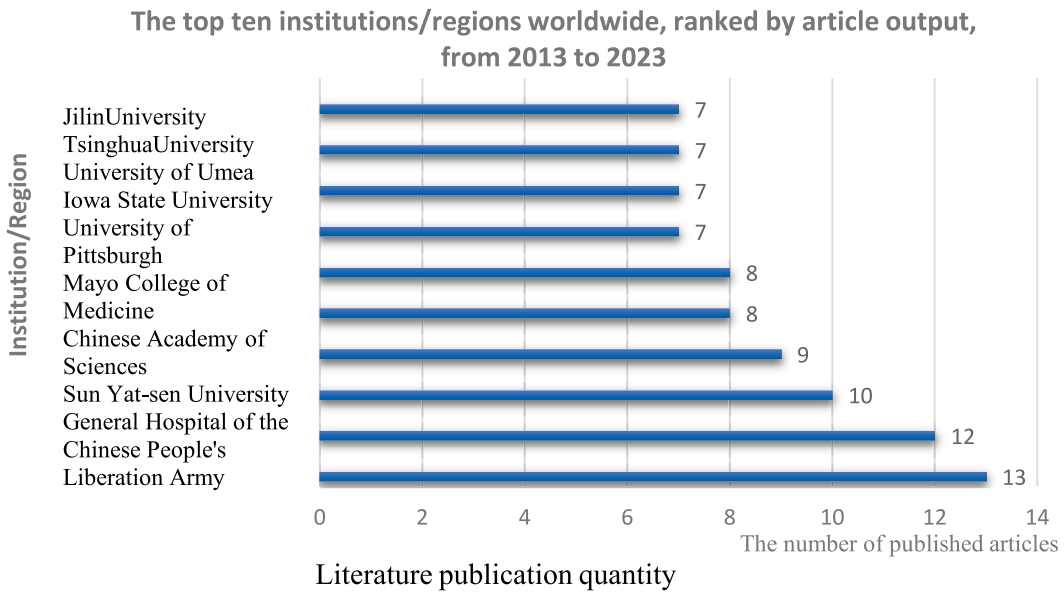

FIGURE 7
Top 10 institutions and regions ranked by the number of publications in the field.

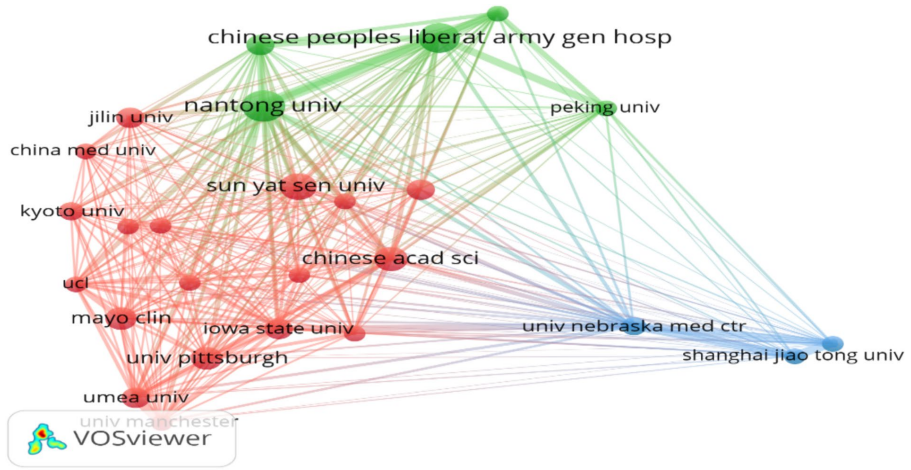

FIGURE 8
Co-authorship analysis of literature institutions.

Sciences, and Stem Cell Research Therapy, with 25, 8, and 8 publications, respectively. Notably, the impact factor of the Biomaterials journal reached 15.3 in 2022–2023, with an average citation of 96.57 times per article. Among the top ten journals, it consistently ranks first in both impact factor and average citation, signifying its preeminence in the field (Table 2). Figure 9 presents a visual analysis of the publication journals in this field from 2013 to 2023 using the publishing journal analysis feature of VOS viewer software. In the figure, a color-coded scale line is arranged from dark to light in the lower right corner. The closer the circle color is to the dark, the more likely authors are to submit and publish their work in earlier academic journals. Conversely, the closer it is to light, the more likely it is to represent current research hotspots (Figure 9).

3.6 Analysis of cited references and citations

Among the 21,064 cited references included in the study, a screening criterion was established for documents that had been cited at least 20 times. As a result, 34 references were selected for inclusion, as depicted in Figure 10. In the figure, each circle symbolizes a distinct cluster, with the number of circles indicating the number of references analyzed. The size of each circle represents the number of citations each reference has received. Two interconnected dots indicate that two references were cited by the same paper. The length of the connecting lines between the dots indicates the level of correlation between the cited references – the shorter the line, the stronger the correlation (Figure 10).

TABLE 2 The ranking of the top 10 journals in terms of the global publication output in the field.

Rank	Journal	Publication (NO)	Citations (times)	Average citations (times)	IF (2022)
1	Neural Regeneration Research	25	504	20.16	6.0
2	International Journal of Molecular Sciences	8	172	21.5	6.2
3	Stem Cell Research Therapy	8	362	45.25	8.0
4	Journal of Tissue Engineering and Regenerative Medicine	8	312	39.0	4.3
5	Frontiers in Cellular Neuroscience	8	138	17.25	6.1
6	Biomaterials	7	676	96.57	15.3
7	Frontiers in Bioengineering and Biotechnology	7	325	46.42	5.7
8	Plos One	6	127	21.2	3.7
9	Acta Biomaterialia	5	205	41.0	9.7
10	Tissue Engineering Part A	5	84	16.8	4.0

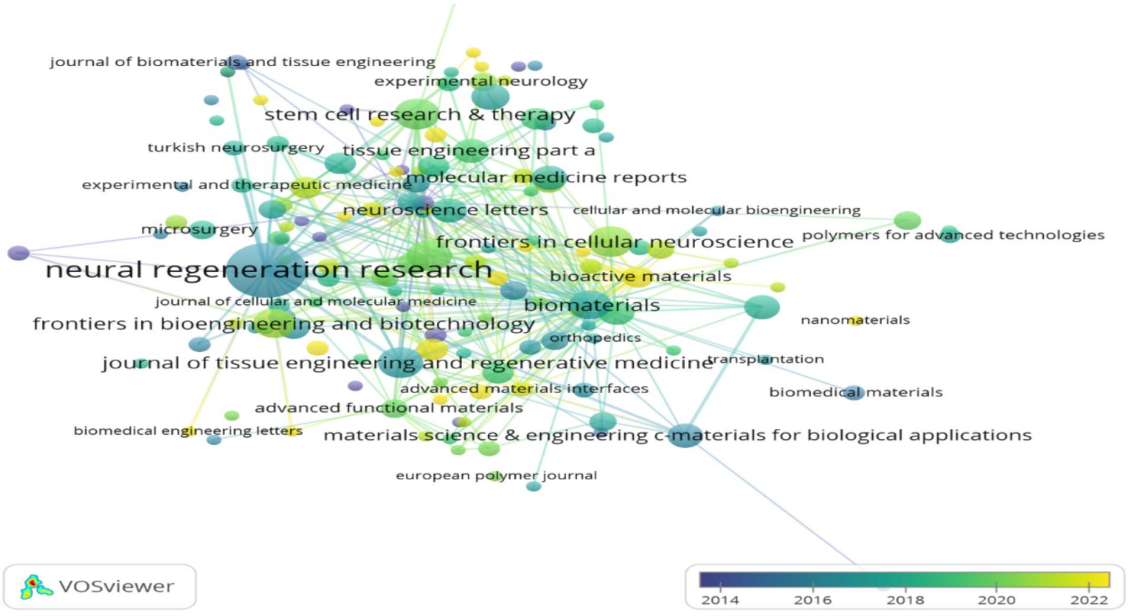

FIGURE 9
An analysis of publication time in the journal.

3.7 Literature analysis

Utilizing the VOSviewer software for citation analysis, we identified the most highly cited papers (Figure 11) and the top 10 most cited papers (Table 3) in the domain of mesenchymal stem cell therapy for peripheral nerve injury and regeneration research from 2013 to 2023. In Figure 11, the distinct colors of the circles represent different clusters, and the size of the circles denotes the number of times each paper has been cited. Larger circles signify a higher level of academic influence within the field (Figure 11). Table 3 reveals that the most cited paper is "Neural Tissue Engineering Options for Peripheral Nerve Regeneration" by the Chinese author "GU XS," published in the journal Biomaterials in 2014, and has been cited 422 times. The second most cited paper is "Peripheral Nerve Regeneration: Experimental Strategies and Future Perspectives" with "Faroni" as the first author, published in the journal Advanced Drug Delivery Reviews in 2015, and has been cited 372 times. The third most cited paper is "Agarose-based Biomaterials for Tissue Engineering" by "Zarrintaj" as the first author, published in the journal Carbohydrate Polymers in 2018, and has been cited 333 times (Table 3). The keywords of these highly cited papers are concentrated in the fields of "mesenchymal stem cells," "peripheral nerve injury," and "peripheral nerve regeneration."

3.8 Keyword analysis

By leveraging the VOSviewer software for keyword analysis, we compiled a total of 1,689 keywords from the literature on mesenchymal stem cell therapy for peripheral nerve regeneration research. Among these, 162 keywords appeared five times or more. "Mesenchymal stem cells" was the most frequently occurring keyword, appearing a total of 163 times, with an association strength of 1,197.

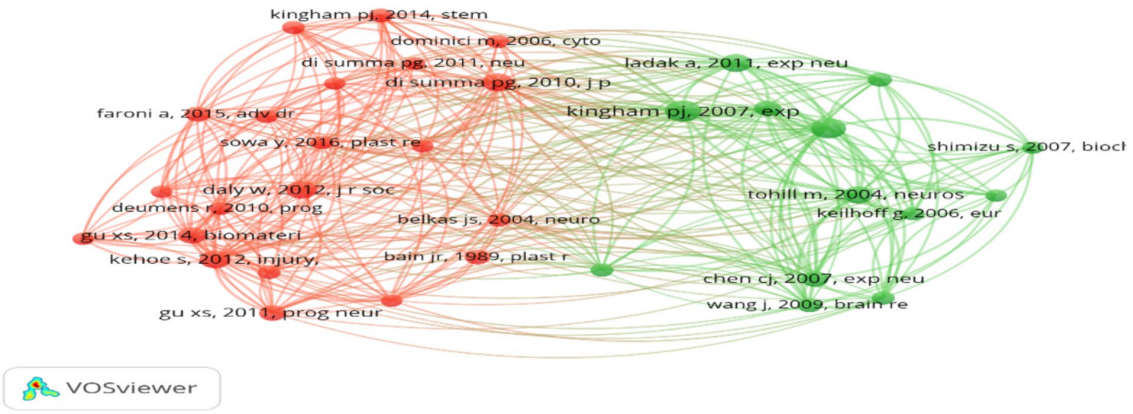

FIGURE 10
Analysis of cited reference.

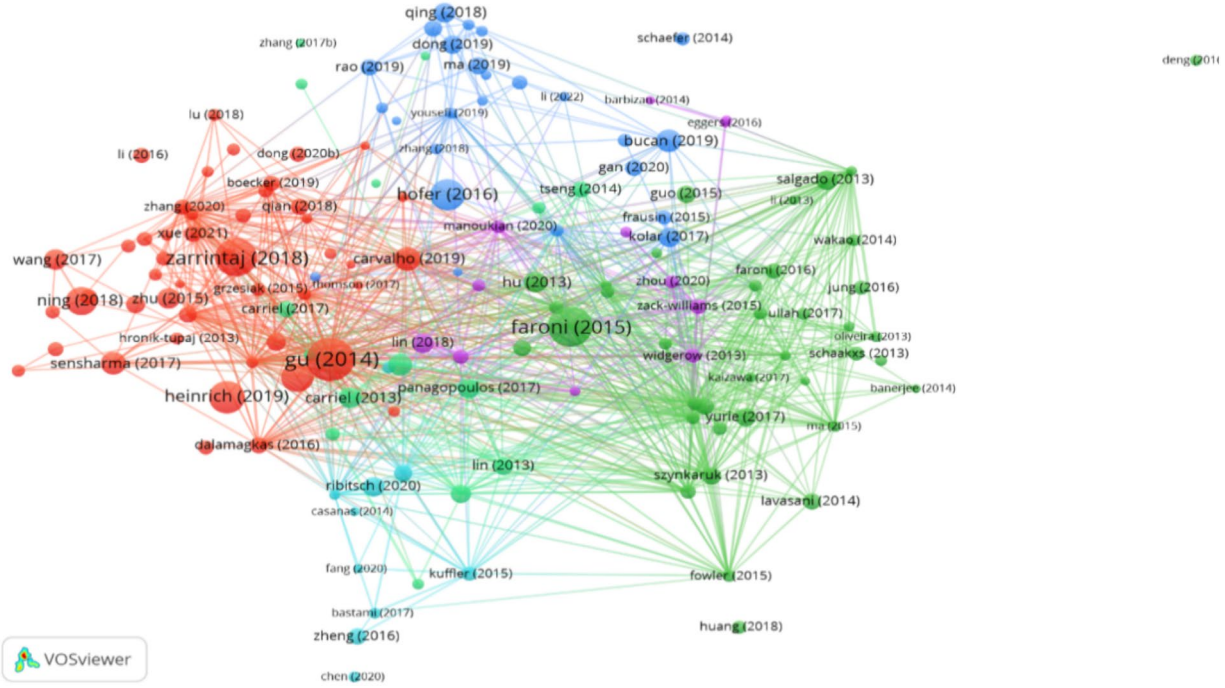

FIGURE 11
Distribution analysis of literature citations.

The second-ranked keyword was "regeneration," which appeared 87 times across all keywords, with an association strength of 696. The top five keywords also included "Schwann-Cells" (86 occurrences), "Repair" (85 occurrences), and "Peripheral-Nerve Regeneration" (84 occurrences). This underscores the centrality of these five keywords "Mesenchymal stem cells," "Regeneration," "Schwann-cells," "Repair," and "Peripheral-Nerve Regeneration"—in the conceptual landscape of this field (Table 4). Through VOSviewer analysis (Figure 12A), we categorized these 162 keywords with a frequency of 5 or more into four clusters. In the figure, each circle represents a keyword, and the size of the circle reflects the frequency of occurrence of that keyword. The larger the circle, the higher the frequency of occurrence of that keyword in the research field, signifying its greater importance within that domain of study (Figure 12A). The colors in Figures 12B,C reflect the frequency of the keywords. The keyword's appearance in Figure 12B is indicated by the darkness of the color, with darker colors representing earlier appearances and lighter colors indicating recent popularity. From these figures, it is evident that "Mesenchymal stem cells," "Regeneration," "Schwann-cells," "Repair," and other keywords have garnered significant attention in recent research and have emerged as research focal points (Figures 12B,C). Finally, we employed the timeline of these keywords to track their evolving popularity over time (Figure 13), which vividly illustrates the temporal relationship between keywords (Figure 13).

TABLE 3 Top 10 cited articles on mesenchymal stem cell therapy for peripheral nerve injury and regeneration research (2013–2023).

Rank	Title	Citations (times)	First author	Journal
1	Neural Tissue Engineering Options for Peripheral Nerve Regeneration	422	GU XS	Biomaterials
2	Peripheral Nerve Regeneration: Experimental Strategies and Future Perspectives	372	Faroni	Advanced Drug Delivery Reviews
3	Agarose-based Biomaterials for Tissue Engineering	333	Zarrintaj	Carbohydrate Polymers
4	3D Bioprinting: from Benches to Translational Applications	234	Heinrich	Small
5	Secreted Trophic Factors of Mesenchymal Stem Cells Support Neurovascular and Musculoskeletal Therapies	229	Hofer	Stem Cell Research Therapy
6	Collagen – Emerging Collagen-Based Therapies Hit the Patient	195	Abou NL	Advanced Drug Delivery Reviews
7	Electroactive Polymers for Tissue Regeneration: Developments and Perspectives	179	Ning	Progress in Polymer Science
8	Modern Trends for Peripheral Nerve Repair and Regeneration: Beyond the Hollow Nerve Guidance Consult	135	Carvalho	Frontiers in Bioengineering and Biotechnology
9	Biomaterials and Cells for Neural Tissue Engineering: Current Choices	124	Sensharma	Materials Science Engineering c-Materials for Biological Applications
10	Effect of Exosomes Trom Rat Adipose-Derived Mesenchyma Stem Celis on Neurite Outgrowth and Sciatic Nerve Regeneration Antercrush Injury	119	Bucan	Molecular Neurobiology

TABLE 4 Top ten keywords ranked by frequency of occurrence.

Rank	Keywords	Frequency (times)	Link strength (times)
1	Mesenchymal Stem-Cells	163	1,197
2	Regeneration	87	696
3	Schwann-cells	86	766
4	Repair	85	682
5	Peripheral-Nerve Regeneration	84	569
6	*In-vitro*	76	607
7	Differentiation	75	624
8	Peripheral Nerve Injury	70	580
9	Nerve Regeneration	64	542
10	Transplantation	63	533

3.9 Journal outbreak analysis

In Figure 14, we depict the top ten journals ranked based on a timeframe from 2013 to 2023, with a minimum outbreak intensity standard of 2.9. This ranking reflects a prevailing trend, with the journal "THERANOSTICS" emerging in 2021 and ascending in prominence until 2023, achieving an outbreak intensity of 4.84 and securing the top position. This ascent was sustained for two consecutive years. Trailing in second place is "TISSUE ENG PART B-RE," which emerged between 2015 and 2018, maintaining a continuous outbreak for a minimum of 3 years and registering an outbreak intensity of 3.68. This data suggests that these 10 journals are frequently chosen by researchers and are highly esteemed by the academic community (Figure 14).

4 Discussion

In this study, we employed bibliometric analysis to systematically examine the research trends in mesenchymal stem cell therapy for peripheral nerve injury and regeneration from 2013 to 2023. We delineated the developmental patterns over this period, encompassing the annual publication count, geographical distribution, the top 10 authors by publication volume, the top 10 cited articles, and the top 10 institutions by publication volume. Furthermore, we conducted a polynomial integration analysis on the cumulative publication volume per year. The Web of Science database, renowned for its high quality and reliability, served as our primary data source. Initially, a total of 360 publications were retrieved through extensive searches within the Web of Science database. Following meticulous screening and elimination, 350 publications were identified as pertinent to the research subject. These publications represent a broad spectrum of research disciplines, all dedicated to advancing the understanding and application of mesenchymal stem cell therapy for peripheral nerve injuries and regeneration.

Our study's findings revealed that China currently holds a preeminent position in both the quantity and quality of publications and practical applications within the domain of mesenchymal stem cell therapy for peripheral nerve injury and regeneration. This may be attributed to several factors, including its vast population and the substantial number of patients with peripheral nerve injuries annually due to diverse reasons. Additionally, China's robust research and development ecosystem provides a conducive platform for such studies. According to the analysis of the funding support from all over the world through the application of VOSviewer, the National Natural Science Foundation of China has significantly augmented its investment in research within this field, which has collectively bolstered China's research level and capabilities in mesenchymal stem cell therapy for peripheral nerve injury and regeneration.

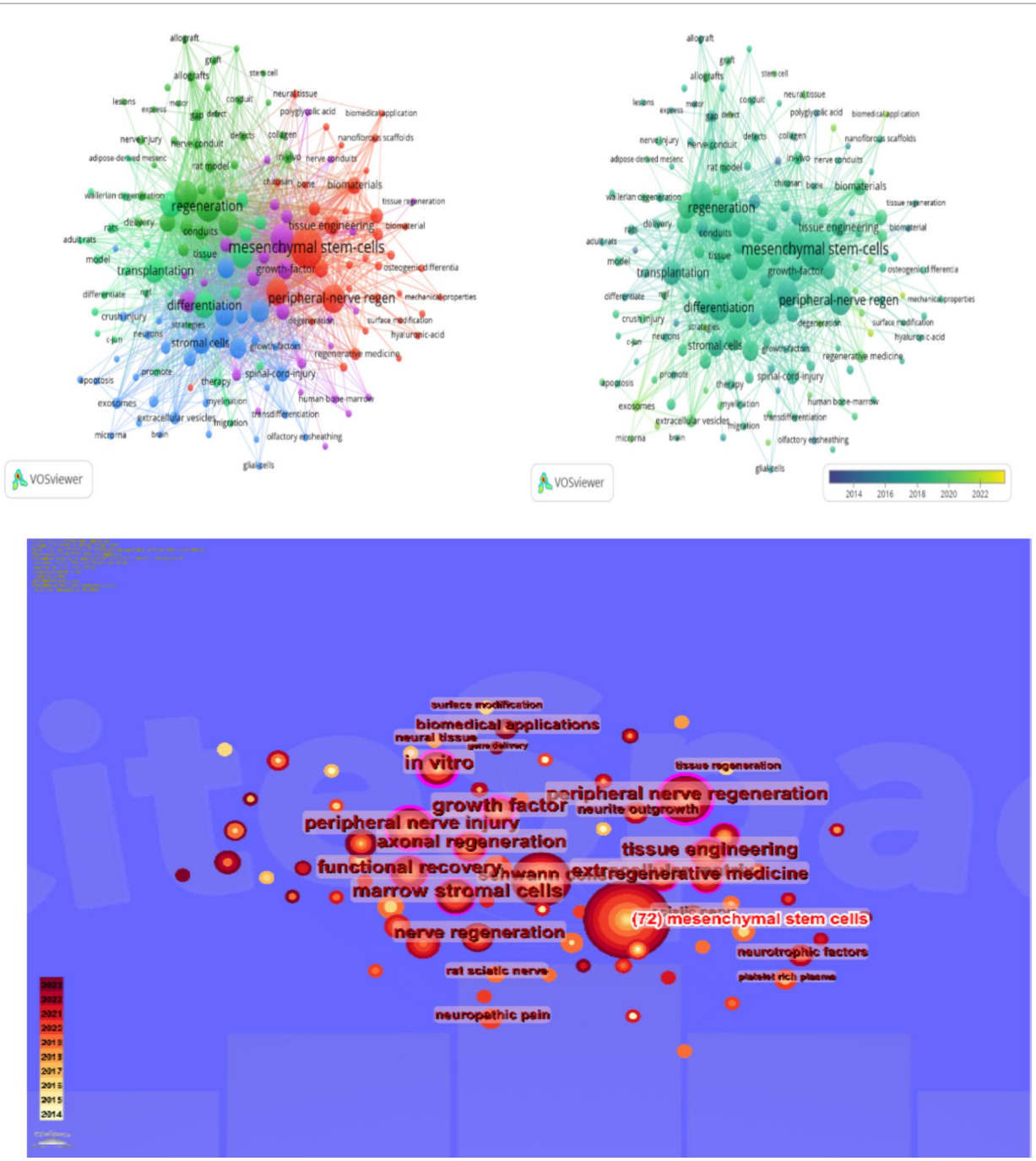

FIGURE 12
(A) Distribution analysis of keywords. **(B)** Time distribution analysis chart of keywords in the field. **(C)** Distribution of keywords in the field of mesenchymal stem cells for peripheral nerve injury and regeneration.

While there is close internal cooperation among Chinese scholars and institutions, United States is still the leading country in terms of international collaboration, with a relatively scattered network of collaboration. Studies have shown that strengthening international collaboration between authors, institutions, and countries helps to improve the impact of scientific research papers. Therefore, countries should continue to actively engage in international collaboration, and relevant institutions should provide more channels for collaboration, encourage researchers to actively participate in international research cooperation to share knowledge, leverage their respective strengths, and address shortcomings to make greater progress in this field to promote the research advancement in the field of mesenchymal stem cell-based treatment of peripheral nerve injury.

In this analysis, we employed two academic analysis tools, Cite Space and VOS viewer, to systematically review the research development trends of mesenchymal stem cell therapy for peripheral nerve injury and regeneration from January 2013 to December 2023 within the Web of Science database. Over the past decade, the global academic publication volume in this field has exhibited a relatively stable trend, with an annual output consistently exceeding 20 articles. This

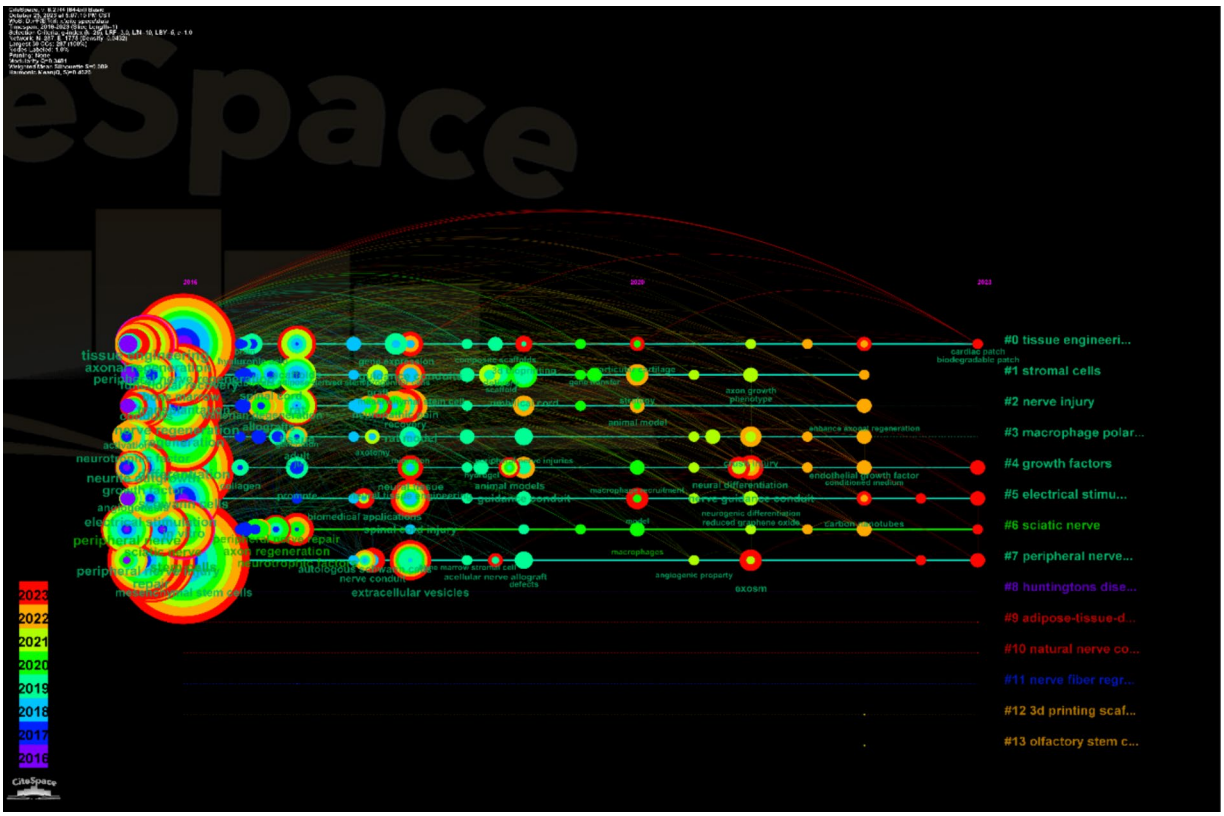

FIGURE 13
Distribution chart of the temporal analysis of keywords in this field.

Top 10 Cited Journals with the Strongest Citation Bursts

Cited Journals	Year	Strength	Begin	End	2014 - 2023
TISSUE ENG	2014	2.97	2014	2017	
TISSUE ENG PART B-RE	2015	3.68	2015	2018	
J ANAT	2017	2.88	2017	2019	
CRITICAL REVIEWS IN BIOMEDICAL ENGINEERING	2018	3.17	2018	2019	
MOL CELL NEUROSCI	2019	2.95	2019	2020	
J NEUROTRAUM	2020	3.52	2020	2021	
WOUND REPAIR REGEN	2020	3.17	2020	2021	
THERANOSTICS	2021	4.84	2021	2023	
BIOACT MATER	2021	3.55	2021	2023	
SCI ADV	2021	2.9	2021	2023	

FIGURE 14
Journal outbreak analysis of the main publications in this field.

sustained output reflects the growing interest from scholars in addressing the challenges of peripheral nerve injury and regeneration repair.

Peripheral nerve injury (PNI) is a prevalent clinical neurological condition, characterized by a high incidence rate and posing significant management challenges (30–32). The prognosis for PNI is typically poor, leading to a high incidence of disability. Patients and their families often endure prolonged physical and psychological suffering, accompanied by a considerable economic burden (33, 34). Worryingly, the incidence of PNI has been on the rise in recent years (35). Despite notable advancements in the field of peripheral nerve injury repair, such as the development of microsurgical techniques, surgical repair or nerve transplantation can address nerve defects or ruptures caused by external trauma in some patients (36, 37). However, due to the limited regenerative capacity of nerve cells, surgical interventions may exacerbate damage to already impaired nerves, resulting in suboptimal functional recovery (38, 39). Consequently, there is an urgent imperative to investigate safe and effective methods for PNI treatment, presenting a formidable challenge within the domain of regenerative medicine.

The common methods of PNI repair, the diverse cell types utilized, and the mechanisms by which cell therapy facilitates PNI repair necessitate further comprehensive research. Mesenchymal stem cells

(MSCs) are a type of multipotent progenitor cell that can be isolated from sources such as bone marrow, umbilical cord, and adipose tissue. These cells possess the capacity to differentiate into mesodermal and nerve cells (40, 41). MSCs are widely regarded as prime candidates for cell therapy and tissue engineering due to their unique ability to differentiate into various cell types, particularly nerve cells, both *in vitro* and *in vivo*. Currently, MSCs are being employed in clinical trials for a range of diseases (42–44). In the context of PNI repair and regeneration, MSCs have garnered extensive attention and support from researchers globally. This therapeutic approach holds broad promise because MSCs have the potential to differentiate into nerve cells and are anticipated to provide substantial support for nerve regeneration (45–47). Research in this domain has the potential to significantly improve outcomes for PNI patients, reduce disability rates, and alleviate the distress and economic burden on patients and their families (48, 49). However, more research and clinical trials are necessary to validate and refine the efficacy and safety of this treatment. Currently, research on the treatment and regeneration of peripheral nerve injuries using MSCs is in its early stages, and future studies will be pivotal in exploring the unknown related mechanisms (35, 50). Further investigation into the effects of MSCs on nerve injury repair and elucidating the mechanisms of action of MSCs will yield new insights into enhancing the repair of peripheral nerve injuries through stem cell transplantation.

Limitations of this Study include: (1) Language bias: This study only included English literature, which may lead to the exclusion of high-quality literature published in other languages. Therefore, the study results may not comprehensively cover all relevant literature in the field, which could introduce language bias. (2) Time constraints: The publication and citation frequency analysis of the literature were constrained by the time of Publication that we selected (2013–2023), which means that the papers published before 2013 and after 2024 may not be included in the analysis. This could result in relatively lower publication and citation frequency totals, affecting the comprehensiveness and accuracy of the study results. (3) Literature screening methods: Further clarification of the literature screening methods and exclusion criteria are needed to determine how to choose the criteria for literature inclusion. This can help clarify the credibility of the study and the transparency of the methods. (4) Data source selection: This study did not collect literature from multiple databases, so selection bias may exist in the data selection process. (5) Lack of in-depth analysis of publication content: Bibliometric analysis often focuses on the number and citations of publications rather than the depth and quality of literature content. This may ignore the actual contribution of the publications and the intrinsic value of the research. (6) Frequency of updates: The frequency of database updates may affect the timeliness and completeness of literature searches. If the database is not updated in real time, then the most recent research may be missed.

5 Conclusion

The current bibliometric analysis included 350 publications, which published by 2049 authors, distributed in 41 countries, and affiliated with 585 different institutions. This international and diverse representation reflects the complexity and attractiveness of this field. China and the Nantong University are currently the leading country and institution in this field. Although the basic research and clinical trials of MSCs based treatment of PNI have achieved remarkable results, challenges remain. Long-term follow-up and monitoring are indispensable in order to fully assess the long-term effects of MSCs in the treatment of PNI. With the continuous advancement of science and technology, we have reason to believe that these challenges will be effectively addressed, resulting in more effective MSC therapy for patients with PNI.

Data availability statement

The datasets presented in this article are not readily available because this article followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, R-AMSTAR guidelines, as well as the Cochrane Handbook for Systematic Reviews of Interventions. Requests to access the datasets should be directed to https://clarivate.com.cn/solutions/web-of-science.

Author contributions

AA: Data curation, Methodology, Writing – original draft, Writing – review & editing. SA: Conceptualization, Writing – original draft, Methodology. KS: Software, Writing – original draft. AM: Data curation, Formal analysis, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The current research was supported by the National Natural Scientific Foundation of China (No: 82260252, 82374487, 82074452, 81860235), Natural Scientific Foundation of Xinjiang Uyghur Autonomous Region (No: 2022D01C330, 2022D01C331, 2022D01C583, 2022D01C586), "Tian Chi Ying Cai" Young Doctors' Talent Introduction Program of Xinjiang Uyghur Autonomous Region, Open Research Program of the Key State Laboratory of Pathogenesis, Prevention, and Treatment of High Incidence Diseases in Central Asia (No: SKL-HIDCA-2022-16), Open Research Program of the Key Laboratory of High Incidence Disease Research in Xinjiang (Xinjiang Medical University) Ministry of Education (No: 2023A03).

Conflict of interest

AM was employed by Beijing Darwin Cell Biotechnology Co., Ltd.

The remaining 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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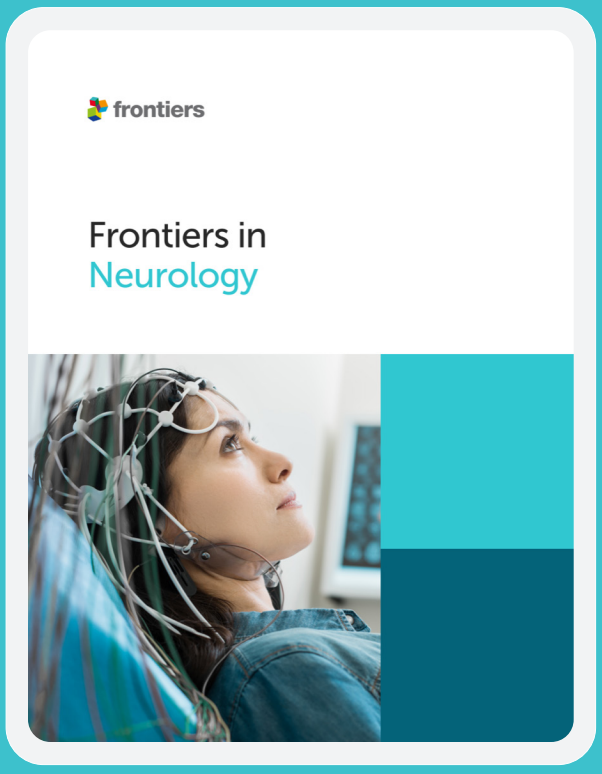

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