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New trends and approaches in perioperative pharmacotherapy, volume III

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Published in
Frontiers in Pharmacology

ISSN 1664-8714
ISBN 978-2-8325-5239-1
DOI 10.3389/978-2-8325-5239-1

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New trends and approaches in perioperative pharmacotherapy, volume III

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Citation

Soghomonyan, S., Bergese, S. D., Stoicea, N., eds. (2024). *New trends and approaches in perioperative pharmacotherapy, volume III*.

Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5239-1

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frontiers | Frontiers in Pharmacology

TYPE Editorial
PUBLISHED 19 July 2024
DOI 10.3389/fphar.2024.1453007

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 22 June 2024
ACCEPTED 11 July 2024
PUBLISHED 19 July 2024

CITATION
Soghomonyan S, Bergese SD and Stoicea N (2024), Editorial: New trends and approaches in perioperative pharmacotherapy, volume III. *Front. Pharmacol.* 15:1453007. doi: 10.3389/fphar.2024.1453007

Editorial: New trends and approaches in perioperative pharmacotherapy, volume III

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KEYWORDS

perioperative care, pharmacotherapy, anesthesia, surgical complications, postoperative recovery

Editorial on the Research Topic
New trends and approaches in perioperative pharmacotherapy, volume III

The perioperative period increases the existing stress for patients and healthcare providers and raises many problems for physicians preparing the patient for surgery. Preoperative patient stress may arise from a fear of the risks associated with surgery and anesthesia, an unfamiliar medical environment, cost of therapy, pain, and even death (Ji et al., 2022).

Responsibilities of the clinician include helping the patient to overcome the perioperative stress and anxiety, optimizing the drug therapy to keep the comorbid conditions under control, and taking all the necessary measures to decrease the risks of surgery. One of the important determinants of success remains the effective perioperative pain control based on opioid and non-opioid therapy, maintenance therapy, regional anesthesia, and enhanced recovery measures developed for specific surgical interventions (Hill and Lefkowits, 2021).

Nowadays, physicians encounter more patients with complex comorbidities requiring preparation in a short time to safely undergo surgery. Until recently, many of those cases would be considered inoperable requiring prolonged treatment prior to surgery. The safe and effective management of the perioperative period for such patients requires continuous update in medical knowledge, familiarity with recent advances in pharmacotherapy, and drug delivery methods. The perioperative clinician must consult various sources, from expert consensus statements to randomized studies, to make informed recommendations for preoperative medication management (Sahai et al., 2022).

Advances in surgery mandate corresponding adaptation of the perioperative treatment strategies to help the patients tolerate the procedure avoiding unnecessary risks and discomfort.

Our previously completed and published Research Topic and it's update on perioperative pharmacotherapy proved to be well accepted with over 95,000 views and downloads, and multiple citations. It became obvious that a new update is necessary to present the recent developments and trends in the field of perioperative pharmacotherapy.

With that in mind, our editorial team readily accepted an invitation from the journal to prepare a new update of the Research Topic. With a meticulous selection process, ten

manuscripts were included in the Research Topic covering various important aspects of perioperative care.

Wondesen Tsige et al. studied the appropriateness of stress ulcer prophylaxis (SUP) strategies in university hospital settings in Ethiopia. The authors found out inappropriate use of SUP in many surgical patients and concluded that this may be an important area for multidisciplinary research to develop standardized protocols for effective SUP.

Shelton et al. present two interesting cases and discuss the use of buprenorphine micro-dosing in surgical patients with opioid use disorder. The method suggested by the authors helps to avoid the risk of precipitated withdrawal and at the same time effectively manage the surgical pain in this complex patient group.

Echeverria-Villalobos et al. present an interesting review discussing the interconnection between the activation of glial and immune cells leading to creation of a neuroinflammatory state, which, in turn, promotes development of acute and chronic pain.

Mazzotta et al. present a mini review discussing the mechanisms of development, prophylaxis and treatment of the postoperative sore throat (POST). Being one of the most common post-anesthesia adverse events, POST is not well studied, and new approaches and treatment options are necessary for its effective management. The authors suggest a new intubation technique with rotation of the endotracheal tube prior to removal of the stylet, which may decrease the impact on the tracheal wall and decrease the incidence of POST.

Elias et al. discuss the role of dopamine receptor antagonist antiemetics, particularly Amisulpride, in management of postoperative nausea and vomiting (PONV). Given the widespread use of 5-HT3 antagonists for PONV prophylaxis and hypothesized side effects of the older dopamine receptor blockers, Amisulpride is suggested as an effective rescue antiemetic to treat persistent PONV.

Xu et al. present a meta-analysis of preclinical studies which studied the role of vagus nerve stimulation (VNS) in attenuating myocardial ischemia-reperfusion injury–a cascade of events undermining the protective benefits of revascularization, contributing to ventricular dysfunction, and increasing mortality. The authors conclude that VNS can effectively limit infarct expansion, ventricular remodeling, cardiac dysfunction, and improve the left ventricular ejection fraction.

Ginosyan et al. discuss the perioperative management strategies of patients with antiphospholipid and catastrophic antiphospholipid syndromes undergoing urgent neurosurgical procedures. The authors discuss the use of plasmapheresis, blood component and clotting factor transfusions in preparation of patients to surgery. They also discuss the potential risk of clotting complications in this extremely challenging group of patients.

Soghomonyan et al. present an interesting patient case of progressive portal, mesenteric, and splenic venous thrombosis. The authors highlight the necessity of timely establishment of diagnosis based on imaging studies and initiation of multi-component therapy with anticoagulants, anti-inflammatory drugs, and antibiotics. Such approach helps to stop thrombus progression, prevent irreversible intestinal ischemia, and allows for re-canalization of the occluded veins.

Liu et al. present the results of their clinical and *in vivo* experiments to find an association between the increased plasma renin concentration and activity caused by direct vasodilators, which promote progression of the abdominal aortic aneurysm. The authors present their interesting data indicating that directly acting antihypertensive drugs hydralazine and minoxidil increase the circulating renin concentration and activity, increase the aortic wall degeneration, and promote progression of abdominal aortic aneurysm.

Wang et al. conducted a network meta-analysis and reviewed the short-term antithrombotic strategies after left atrial appendage occlusion (LAAO). They compared dual antiplatelet therapy (DAPT), direct oral anticoagulants (DOACs), and vitamin K antagonist therapy (VKA) in patients who had experienced LAAO. Their study results indicate that there is no significant difference between DAPT, DOACs, and VKA in terms of stroke, device-related thrombosis (DRT), and major bleeding events after LAAO. DAPT was ranked the worst among all antithrombotic strategies due to the higher risk of stroke, DRT, and major bleeding events, while VKAs were ranked the preferred antithrombotic strategy. However, DOACs, according to authors, are worthy of consideration due to their advantage of convenience.

We believe the manuscripts included in the Research Topic will be interesting to the practitioners involved in perioperative patient care and will help them optimize their therapeutic plans suitable for their patient needs.

Author contributions

SS: Writing–original draft, Writing–review and editing. SB: Writing–original draft, Writing–review and editing. NS: Writing–review and 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

NS was employed by the Solid Biosciences Inc.

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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 13 June 2023
DOI 10.3389/fphar.2023.1174278

OPEN ACCESS

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RECEIVED 26 February 2023
ACCEPTED 22 May 2023
PUBLISHED 13 June 2023

CITATION
Liu Y, Liu S, Zhao J, Wu K, Xu B and Wang W (2023), Increased plasma renin by vasodilators promotes the progression of abdominal aortic aneurysm. *Front. Pharmacol.* 14:1174278. doi: 10.3389/fphar.2023.1174278

Increased plasma renin by vasodilators promotes the progression of abdominal aortic aneurysm

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Background: It is well-accepted that antihypertensive therapy is the cornerstone of treatment for abdominal aortic aneurysm (AAA) patients with hypertension. Direct-acting vasodilators were used in the treatment of hypertension by directly relaxing vascular smooth muscle but may have destructive effects on the aortic wall by activating the renin–angiotensin system axis. Their roles in AAA disease remain to be elucidated. In this study, we used hydralazine and minoxidil, two classical direct-acting vasodilators, to investigate their influence and potential mechanisms on AAA disease.

Methods and results: In this study, we investigated the plasma renin level and plasma renin activity in AAA patients. Simultaneously, age and gender ratio-matched patients diagnosed with peripheral artery disease and varicose veins were selected as the control group using a ratio of 1:1:1. Our regression analysis suggested both the plasma renin level and plasma renin activity are positively associated with AAA development. In view of the well-established relationship between direct-acting vasodilators and increased plasma renin concentration, we established a porcine pancreatic elastase-infused AAA mouse model, followed by oral administration of hydralazine (250 mg/L) and minoxidil (120 mg/L) to investigate effects of direct-acting vasodilators on AAA disease. Our results suggested both hydralazine and minoxidil promoted the progression of AAA with increased aortic degeneration. Mechanistically, the vasodilators aggravated aortic inflammation by increased leukocyte infiltration and inflammatory cytokine secretion.

Conclusion and relevance: The plasma renin level and plasma renin activity are positively associated with AAA development. Direct vasodilators aggravated experimental AAA progression, which raised cautionary concerns about their applications in AAA disease.

KEYWORDS

abdominal aortic aneurysm, hypertension, antihypertensive drugs, plasma renin level, plasma renin activity, vasodilator

Abbreviations: AAA, abdominal aortic aneurysm; PAD, peripheral artery disease; PPE, porcine pancreatic elastase; PRA, plasma renin activity; PRL, plasma renin level; VV, varicose vein.

Introduction

Abdominal aortic aneurysm (AAA) is the dilation of the abdominal aorta 1.5 times its original size, generally more than 3 cm, with structural disruptions of the aortic vasculature (Golledge, 2019). The incidence of AAAs increases significantly in men aged >55 years and women aged >70 years, posing a high risk to the elderly due to the high morbidity and mortality associated with aortic rupture (Bossone and Eagle, 2021). Although previous studies reported successful medical stabilization of growing AAAs in different animal models, the current management of AAA mainly relies on the prophylactic operative repair of larger aneurysms (Liao et al., 2001; Golledge et al., 2006; Sakalihasan et al., 2018). Currently, medical management during aneurysm surveillance warrants further studies.

Arterial hypertension is an important population-attributable risk factor for AAA, which is linked to an increased risk of cardiovascular events and adverse prognosis, following AAA (Kobeissi et al., 2019). Previous studies reported that for every 20-mmHg increase in systolic blood pressure and 10-mmHg increase in diastolic blood pressure, the relative risk for AAA increases by 14% and 28%, respectively (Kobeissi et al., 2019; Wanhainen et al., 2019). Although antihypertensive therapy has not been shown to inhibit aneurysm expansion, it could benefit patients by reducing the risks of cardiovascular events (Bicknell et al., 2016). Thus, guidelines encouraged AAA patients to seek appropriate medical management for hypertension (Chaikof et al., 2018; NICE guideline [NG156]). However, specific recommendations for the choice of antihypertensive medication remain poorly described, which is mainly referred to the local guidelines, as demonstrated in the ESVS and NICE guidelines (Wanhainen et al., 2019).

Direct-acting vasodilators are a heterogeneous group of drugs, which can directly dilate peripheral arterioles and lower blood pressure, and are generally used in systemic hypertension, especially in patients with refractory hypertension, stage III hypertension, or renal dysfunction (Cassis et al., 2009; Lu et al., 2012). Despite the decline in their use due to adverse effects, direct vasodilators are still valuable in clinical practice for these niche indications. Hydralazine and minoxidil are the most commonly prescribed direct vasodilators for hypertension (Laurent, 2017). However, it is reported that arterial vasodilation induced by direct vasodilators can activate the peripheral sympathetic nervous system via carotid and aortic baroreceptor reflexes, casing increased circulating renin levels and subsequent activation of the renin–angiotensin system, which eventually leads to tachycardia and fluid retention (Gottlieb et al., 1972; Campese et al., 1979; Sica and Gehr, 2001). As the only enzyme known to cleave angiotensinogen and the rate-limiting enzyme of the renin-angiotensin system, plasma renin can increase the synthesis of angiotensin II and aldosterone, which plays a critical role in cardiovascular disease (Ferrario and Strawn, 2006; Miyake et al., 2017). Considering the essential role of the renin–angiotensin system in the progression of AAA disease, it is worth investigating whether neurohumoral regulation by direct-acting vasodilators aggravates AAA disease.

In the study, we investigated the relationship between the plasma renin level (PRL) and plasma renin activity (PRA) with AAA in patients using a case–control design, which suggested PRL and PRA are positively associated with AAA development. Given that direct vasodilators may increase the PRL and PRA, we explored the effect of direct vasodilators on AAA disease using hydralazine and minoxidil. Our results suggested direct vasodilators aggravated experimental AAA progression, raising cautionary concerns about their applications on arterial disease and AAA disease.

Methods

Study subjects

Cases

Patients diagnosed with AAA were selected for pre-onset PRL and PRA determination according to the disease diagnosis code of the 10th edition of the International Classification of Diseases (ICD) as the case group. AAA is defined as 50% dilation of the abdominal aorta, generally more than 3 cm of normal (Golledge, 2019). At the same time, two investigators examined and determined the aortic angiography and computed tomography findings and classification of all cases to exclude false positives. Patients with connective tissue disease, Marfan syndrome, vasculitis, and traumatic aortic dissection were excluded. In addition, patients who had a definite diagnosis of secondary hypertension at the time of aldosterone testing (renal vascular hypertension, renal hypertension, and aldosterone-producing adenoma with adenoma larger than 1 cm, Cushing's syndrome, pheochromocytoma, and coarctation of the aorta) were excluded.

Control

Given the possibility of increased plasma renin levels in arterial disease (Marchesi et al., 2008), we included peripheral arterial disease (PAD) and varicose vein (VV) as controls using a case–control ratio of 1:1:1 matching age and sex with the same exclusion criteria. In addition, in order to explore the effects of AAA on the PRL and PRA, the PAD and VV groups were combined into the non-AAA group and compared with the AAA group.

Data collection

We obtained patient data from the hospital electronic medical database. The following general, clinical, and laboratory data were collected: general data (age, gender, and cigarette consumption), anthropometric data [body mass index, systolic blood pressure, diastolic blood pressure, pulse rate, and abdominal aorta diameter], biochemical measurements [total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, alanine aminotransferase, aspartate aminotransferase, serum creatinine, serum uric acid, serum potassium, serum sodium, plasma renin level (PRL), and plasma renin activity (PRA)], comorbidities [coronary heart disease diabetes, hypertension, chronic obstructive pulmonary diseases, and chronic kidney disease], and medication history (hypoglycemic medicine, lipid-lowering drugs, and antihypertensive drugs).

PRL and PRA measurements

After approval of Xiangya Hospital Institutes' Review Board and Ethics Committee of the Xiangya Hospital, Central South University, blood collection was carried out at dawn of the second day of patients' admission to ensure the measurements of recumbent position PRL and PRA are comparable. Then, the blood samples were transported to and evaluated at the clinical laboratory of Xiangya Hospital immediately.

Animals and animal care

Ten-week-old male C57BL/6J mice were purchased from the Xiangya School of Medicine, Central South University. Mice were given unique numbers after quarantine and then randomly divided into a vehicle group, hydralazine group, and minoxidil group, according to different administrations by stratified random sampling. The mice were housed under specific pathogen-free conditions in a 12-h light/dark cycle with *ad libitum* access to food and water. Calculation of the sample size was determined by power analysis, as previously reported (Festing and Altman, 2002). According to previous research on experimental AAA disease, n = 8–15 specimens per group are required. The sample size was calculated by referring to the previously published literature of our research group, and a total of 40 mice were used in this study (Liu et al., 2020). Each mouse constituted an experimental unit. The mice were divided into the vehicle group (n = 15), hydralazine group (n = 9), and minoxidil group (n = 13), and we declared no excluding animals. Hydralazine (250 mg/L) and minoxidil (120 mg/L) were administered via drinking water and were replaced every other day. The dosage, time points, and route of administration were chosen based on the prior literature (Tsoporis et al., 1998; Knutsen et al., 2018; Kobeissi et al., 2019).

Porcine pancreatic elastase (PPE)-induced AAA model in mice

AAAs were created via transient intra-infrarenal aortic infusion of PPE, based on the study conducted by Liu et al. (2022). Mice were randomly selected from each cage in turn, according to the stratified sampling results for the following steps. Briefly, the mice were anesthetized with inhaled isoflurane, and surgical procedures were performed under sterile conditions. The mouse was subjected to transient infusion of type I PPE (4.0 U/mL; E1250; Sigma-Aldrich) dissolved in saline at a pressure of 150 mmHg. The aortic diameters of pre-infusion and post-infusion were measured to ensure consistency and minimize potential confounders for each group (Liu et al., 2022). Following the closure of laparotomy, all mice were housed under specific pathogen-free conditions as the preoperative environment. At the end, mice were anesthetized using ketamine/xylazine (100 and 20 mg/kg i.p., respectively) and euthanized by exsanguination before aortic tissue collection on day 14. AAA was defined as more than 50% enlargement of the maximum abdominal aortic diameter. All processes were implemented under double-blind conditions.

Imaging AAA formation and progression

AAA was monitored via serial transabdominal high-frequency ultrasound (Vevo® 2100 Imaging System, VisualSonics, Toronto, ON, Canada) for determining the internal diameter or using a digital camera for the external diameter. Measurements of the aortic extra-diameter were performed before and after perfusion on day 0, and before euthanasia on day 14. Measurements of the aortic intro-diameter were performed on days 0 and 14 by investigators blinded to the group assignment.

Histological analyses

Mice were euthanized 14 days after PPE infusion. Aortae were harvested, fixed in 4% paraformaldehyde, embedded in paraffin, and horizontally cut into sections. For histological analyses, hematoxylin–eosin (H&E) staining, Masson, elastic Van Gieson (EVG) staining, and a two-step standard immunoperoxidase procedure for immunohistochemistry were conducted to identify $CD3^+$ T cells (ab16669; Abcam), $CD68^+$ macrophages (ab125212; Abcam), $CD31^+$ mural vessels (ab28364; Abcam), and MMP9 (ab38898; Abcam). The same concentration of rabbit control IgG (AC005, ABclonal) serves as the negative control.

Real-time polymerase chain reaction (PCR)

Mice were euthanized 14 days after PPE infusion. The total RNA of aortae was extracted using the TRIzol reagent (TaKaRa, Japan), according to the manufacturer's instruction. A measure of 500 nanograms of total RNA was used for reverse transcription using a PrimeScript RT Reagent Kit (TaKaRa). Quantitative RT-PCR on a real-time PCR system (Applied Biosystems) was performed using SYBR Premix Ex Taq qRT-PCR assays (TaKaRa). The Ct value of mRNA was normalized to GAPDH, and the fold change was calculated using the ΔΔCt method. The primer sequences for genes are listed as follows: ACTB, forward primer: *GTGCTATGT TGCTCTAGACTTCG* and reverse primer: *ATGCCACAGGATTCC ATACC*; NOS2, forward primer: *GTTCTCAGCCCAACAATACAA GA* and reverse primer: *GTGGACGGGTCGATGTCAC*; CCL2, forward primer: *TAAAAACCTGGATCGGAACCAAA* and reverse primer: *GCATTAGCTTCACATTTACGGGT*; IFN-γ, forward primer: *CAGCAACAGCAAGGCGAAAAAGG* and reverse primer: *TTTCCGCTTCCTGAGGCTGGAT*; IL-1β, forward primer: *GAA ATGCCACCTTTTGACAGTG* and reverse primer: *TGGATGCTC TCATCAGGACAG*.

Statistical analysis

Continuous variables are expressed as mean values ± standard deviation, unless otherwise stated. For the duration of hypertension, triglyceride, alanine aminotransferase, aspartate aminotransferase, serum creatinine, serum uric acid, PRL, and PRA, the medians in the 25th and 75th percentile ranges are provided because they do not satisfy the normal distribution. One- or Two-way ANOVA was used to compare the normal distribution of continuous variables including age, body mass index, systolic blood pressure, diastolic blood pressure, pulse rate, AAA diameter (for both humans and mice), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, serum K^+, and serum Na^+ among the three groups, and the independent sample t-test was used between two groups. If the data did not meet the normal distribution, the quantile-quantile graph was used to check its distribution. If the data were located near the diagonal, there was an approximate normal distribution between the groups (including total cholesterol and low-density lipoprotein cholesterol). Non-parametric tests (including Kruskal Wallis and Mann Whitney tests) were provided to compare the difference

TABLE 1 Baseline characteristics of the patients enrolled.

	VV (*n* = 20)	PAD (*n* = 20)	AAA (*n* = 20)	*p*-value	*p*-value with pairwise comparisons		
					AAA vs. VV	AAA vs. PAD	PAD vs. VV
Age (years)	67 ± 6.02	68.9 ± 6.83	67.6 ± 6.34	0.633			
Gender (women/men), *n* (%)	3/17 (15/85)	3/17 (15/85)	3/17 (15/85)	1.000			
BMI	24.75 ± 2.5	22.2 ± 3.19	22.99 ± 3.74	0.086			
Cigarette consumption (yes), *n* (%)	7 (35)	15 (75)	14 (70)	0.029	0.075	1.000	0.031
CAD, *n* (%)	4 (20)	12 (60)	11 (55)	0.025	0.082	1.000	0.035
Diabetes, *n* (%)	4 (20)	10 (50)	2 (10)	0.018	1.000	0.014	0.100
Hypertension, *n* (%)	12 (60)	17 (85)	14 (70)	0.250			
COPD, *n* (%)	0	4 (20)	5 (25)	0.062			
CKD, *n* (%)	2 (10)	4 (20)	4 (20)	0.749			
Duration of hypertension, y	0 (0~8.25)	9.00 (0~10.00)	5.00 (0~10.00)	0.104			
Systolic blood pressure, mm Hg	129.1 ± 15.41	144.5 ± 17.58	136.55 ± 17.51	0.020	0.503	0.425	0.026
Diastolic blood pressure, mm Hg	80.9 ± 10.11	83.6 ± 12.21	78.35 ± 15.89	0.445			
Pulse rate, beats per minute	75.45 ± 14.06	75.4 ± 10.92	75.45 ± 14.69	1.000			
Total cholesterol, mmol/L	4.75 ± 1.08	4.42 ± 0.93	4.83 ± 2.14	0.681			
Triglyceride, mmol/L	1.34 (1.02~2.42)	1.74 (1.03~2.40)	1.59 (0.98~1.99)	0.995			
LDL-C, mmol/L	3.07 ± 0.75	2.83 ± 0.74	3.03 ± 1.1	0.667			
HDL-C, mmol/L	1.1 ± 0.29	1.02 ± 0.26	1.05 ± 0.26	0.661			
ALT, U/L	18.40 (13.03~22.13)	15.50 (12.24~23.13)	14.65 (9.93~18.98)	0.314			
AST, U/L	22.10 (17.45~29.55)	20.25 (16.25~25.53)	20.20 (17.85~25.40)	0.557			
Serum creatinine, μmol/L	70.25 (58.75~82.75)	83.25 (69.00~93.20)	89.60 (67.95~103.08)	0.191			
Serum uric acid, μmol/L	367.75 (311.03~496.12)	344.40 (333.63~447.80)	437.15 (306.63~514.38)	0.627			
Serum potassium, mmol/L	4.04 ± 0.53	3.92 ± 0.4	3.97 ± 0.4	0.693			
Serum sodium, mmol/L	141.62 ± 1.87	140.86 ± 3.61	141.37 ± 3.4	0.728			
Abdominal aorta diameter, mm		17.89 ± 1.68	59.72 ± 17.33			<0.001	
Hypoglycemic medicine, *n* (%)	2 (10)	5 (25)	1 (5)	0.246			
Lipid-lowering drugs, *n* (%)	3 (15)	6 (30)	5 (25)	0.641			
Antihypertensive drugs							
CCB, *n* (%)	8 (40)	12 (60)	9 (45)	0.521			
ACEI/ARB, *n* (%)	4 (20)	2 (10)	6 (30)	0.416			
β-blocker, *n* (%)	4 (20)	3 (15)	6 (30)	0.630			
Diuretic, *n* (%)	2 (10)	3 (15)	2 (10)	1.000			

Note: Values represent means ± standard deviation or count and percentage where otherwise specified. Data satisfying normal distribution and homogeneity of variance were analyzed by single-factor ANOVA; if not, the non-parametric (K-W) test was applied. Pairwise comparison was applied for data with $p < 0.05$ in the multigroup comparison. The independent sample *t*-test was used for abdominal aorta diameter data (PAD vs. AAA). VV, varicose veins; PAD, peripheral artery disease; AAA, abdominal aortic aneurysm; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

among ranked data and continuous variables that do not satisfy normal distribution or homogeneity of variance (including the duration of hypertension, triglyceride, ALT, AST, serum creatinine, serum uric acid, PRL, PRA, EVG, and SMA score). We used the $\chi 2$ analysis ($\chi 2$ test) to compare categorical variables, frequencies, and proportions (including sex, cigarette

TABLE 2 Comparison of PRL and PRA among AAA, PAD, and VV groups.

	Groups			H-value (K-W test)	*p*-value
	VV (*n* = 20)	PAD (*n* = 20)	AAA (*n* = 20)		
PRL, μlU/ml	5.24 (3.28~7.55)	9.42 (4.35~13.21)	17.47 (11.48~65.86)	31.83	<0.001
PRA pg/ml	6.17 (4.21~9.24)	9.29 (8.42~20.16)	25.72 (9.89~37.64)	15.39	<0.001

Note: PRL, plasma renin level; PRA, plasma renin activity.

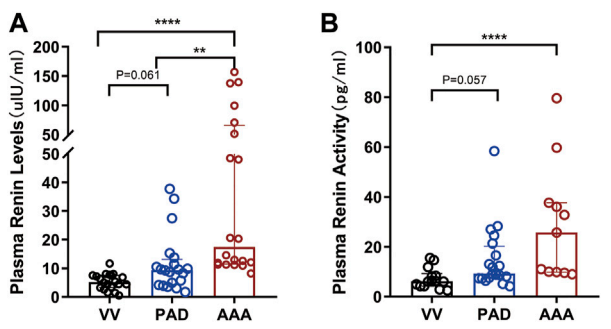

FIGURE 1
Comparison of PRL and PRA among AAA, PAD, and VV groups. Plasma renin levels and renin activity were measured in the included patients to evaluate the differences in plasma renin levels and activity among the AAA (*n* = 20), PAD (n = 20), and VV (*n* = 20) groups. **(A)** Plasma renin level (PRL) measurement (left). Data were expressed as the median with an interquartile range. **(B)** Plasma renin activity (PRA) measurement (right). Data were expressed as the median with an interquartile range. The K-W test and pairwise comparisons were applied. $^{**}p < 0.01$ and $^{****}p < 0.0001$.

consumption, coronary heart disease, diabetes, hypertension chronic obstructive, pulmonary diseases, chronic kidney disease, and medication history). Multivariate logistic regression analysis was used to evaluate the relationship between the PRL, PRA and AAA among the three groups, and binary logistic regression analysis was used for two groups. The multivariate linear regression analysis was used to test the collinearity between variables. Odds ratio and 95% CI were reported. A two-tailed *p*-value of 0.05 is considered significant. SPSS 26.0 version was used for data management and analysis.

Result

Baseline characteristics of patients enrolled

Finally, 20 patients diagnosed with AAA from 01/01/2022 to 01/11/2022 were enrolled in the case group. Meanwhile, 20 patients diagnosed with PAD and VV matched with age and sex were included, respectively. The baseline characteristics of the 60 patients are given in Table 1. As is shown, cigarette consumption, coronary heart disease, the diabetes composition ratio, and systolic blood pressure revealed significant differences among the three groups (Table 1). Specifically, the diabetes composition ratio (10% versus 50%, AAA versus PAD, and p = 0.014) showed statistically significant differences between AAA and other two groups when compared in a pairwise manner (Table 1). Statistical differences in cigarette consumption (75% versus 35%, PAD versus VV, and p = 0.031), the coronary heart disease composition ratio (60% versus 20%, PAD versus VV, and p = 0.035), and systolic blood pressure (144.5 ± 17.58 mmHg versus 129.1 ± 15.41 mmHg, PAD versus VV, and p = 0.026) were observed when comparing the PAD group with the VV group (Table 1).

Considering the critical role of renin in vascular disease (Wu et al., 2018), the PAD and VV groups were roughly combined into the non-AAA group to exclude the bias of the plasma renin level and activity in arterial disease. Characteristics of AAA and non-AAA groups are given in Supplementary Table S1. The AAA group showed no significant differences compared to the non-AAA group.

PRL and PRA are increased in AAA disease

As shown in Table 2 and Figure 1, the AAA group showed a significantly higher PRL [17.47 (11.48~65.86) versus 9.42 (4.35~13.21) versus 5.24 (3.28~7.55), AAA versus PAD versus VV ulU/ml, and $p < 0.001$] and higher PRA [25.72 (9.89~37.64) versus 9.29 (8.42~20.16) versus 6.17 (4.21~9.24), AAA versus PAD versus VV pg/ml, and $p < 0.001$] than the PAD and VV groups. Similarly, compared to the non-AAA group, the AAA group also showed a higher PRL [17.47 (11.48~65.86) versus 7.02 (3.67~9.65) ulU/ml, and $p < 0.001$] and higher PRA [25.72 (9.89~37.64) versus 8.28 (6.05~13.45) pg/ml, and p = 0.001] (Supplementary Table S2; Supplementary Figure S1).

PRL and PRA are positively associated with AAA development

Multiple logistic regression analysis was conducted to identify whether the progression of abdominal aortic aneurysms could be attributed to increased plasma renin levels and activity. It is important to mention that a detailed collinearity analysis (SPSS collinearity tests) was performed between the PRL and PRA, with the piece of evidence that the Spearman correlation coefficient of the PRL and PRA is 0.883 (Supplementary Table S3). Therefore, we analyzed the two indicators separately. A univariate analysis was conducted to evaluate the relationship between the increased PRL, and PRA and AAA development. Our results showed higher PRL was significantly associated with AAA development with an unadjusted OR of 1.456 [(95% CI, 1.180–1.797), and $p < 0.001$]

TABLE 3 Multiple logistic regression analyses for the association between PRL/PRA and AAA.

		Unadjusted model		Model 1		Model 2	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
PRL, μlU/ml	AAA vs. VV	1.456 (1.180–1.797)	<0.001	1.665 (1.258–2.204)	<0.001	1.667 (1.256–2.213)	<0.001
	PAD vs. VV	1.368 (1.114–1.681)	0.003	1.561 (1.183–2.059)	0.002	1.574 (1.190–2.083)	0.001
	AAA vs. PAD	1.064 (1.002–1.130)	0.041	1.067 (1.006–1.132)	0.032	1.059 (0.995–1.127)	0.069
PRA, pg/ml	AAA vs. VV	1.280 (1.045–1.568)	0.017	1.359 (1.064–1.735)	0.014	1.388 (1.068–1.804)	0.014
	PAD vs. VV	1.219 (1.000–1.487)	0.050	1.286 (1.011–1.637)	0.040	1.303 (1.006–1.686)	0.045
	AAA vs. PAD	1.050 (0.998–1.105)	0.061	1.056 (1.000–1.115)	0.050	1.066 (0.999–1.137)	0.054

Note: Model 1 was adjusted for the hypertension and chronic kidney disease composition ratio. Model 2 was adjusted for the hypertension, chronic kidney disease and diabetes composition ratio.

compared with VV and 1.064 [(95% CI, 1.002–1.130), and $p = 0.041$] compared with PAD (Table 3). Similarly, higher PRA was also associated with AAA development with an unadjusted OR of 1.280 [(95% CI, 1.045–1.568), and $p = 0.017$] compared with VV (Table 3). Similar trends were observed after adjustment of hypertension and the chronic kidney disease composition ratio in model 1, although the difference was not significant in model 2 (Table 3). Surprisingly, we also found that increased PRL and PRA were correlated with a higher risk of PAD (unadjusted OR, 1.368 and 1.219, respectively) than the VV group (Table 3).

In addition, a binary logistic regression was conducted between AAA and non-AAA groups, which demonstrated that both high-level PRL and PRA were positively associated with AAA development with an unadjusted OR of 1.099 [(95% CI, 1.026–1.176), and $p = 0.007$] for the PRL and 1.070 [(95% CI, 1.013–1.129), and $p = 0.014$] for PRA, and adjusted OR of 1.100 [(1.028–1.176); $p = 0.005$] for PRL and 1.075 [(1.015–1.138); $p = 0.014$] for PRA in model 1 and 1.102 [(1.024–1.186); $p = 0.009$] for PRL and 1.088 [(1.019–1.162); $p = 0.012$] for PRA in model 2, respectively (Supplementary Table S4).

As PAD and AAA shared similar etiology and pathological mechanisms, the elevated risk of AAA was reported in PAD patients (Hicks et al., 2021; Cai et al., 2022). Thus, a correlation analysis was performed to determine the relationship between aortic diameters and PRL and PRA in AAA and PAD groups. Our results demonstrated a significant positive correlation between the aortic diameter and both PRL ($\gamma = 0.529$; $p < 0.001$) and PRA ($\gamma = 0.412$; $p = 0.021$) (Supplementary Table S5). However, the correlation was not significant in the AAA group ($\gamma = -0.025$; $p = 0.917$) and PRA ($\gamma = -0.335$; $p = 0.285$).

Influence of direct-acting vasodilators on PRL and PRA

Hydralazine and minoxidil, the most commonly prescribed direct-acting vasodilators in hypertension (Laurent, 2017), were selected as representatives of direct vasodilators in our study. Given the well-established relationship between the administration of direct-acting vasodilators and PRL and PRA, a review of the published literature showed that the administration of minoxidil and hydralazine increased the PRL and PRA in both clinical and animal experiments, as shown in Table 4.

Direct-acting vasodilators aggravated experimental AAA

Considering the critical role of renin in AAA disease, we then established a PPE-induced experimental AAA mouse model to verify whether direct-acting vasodilators aggravated AAA development and progression. Hydrazine, minoxidil, and vehicle treatment were administrated 3 days before PPE infusion until euthanasia, while blood pressure and aortic diameters were monitored (Figure 2A). Our results suggested hydralazine administration significantly decreased systolic blood pressure and diastolic blood pressure compared to the vehicle group on days 7 and 14, respectively (Figure 2B). Although minoxidil-treated mice displayed a significant decrease in blood pressure (106.3 ± 19.04 versus 130.41 ± 7.18 mmHg and $p < 0.001$ for systolic blood pressure 82.45 ± 22.17 versus 103.06 ± 10.45 mmHg and $p = 0.007$ for diastolic blood pressure) on day 7, this significant difference disappeared on day 14 (Figures 2B, C), supporting the notion that the neurohumoral changes induced by minoxidil can offset its benefits to arteriolar vasodilatation (Baer et al., 1980; Sica and Gehr, 2001).

Monitoring external diameters using a digital camera, our results suggested AAA diameters in the three groups were comparable after PPE infusion but increased more rapidly in hydrazine and minoxidil groups than those in the vehicle group (1.48 ± 0.12 mm versus 1.33 ± 0.17 mm, hydralazine versus vehicle, $p = 0.037$; 1.50 ± 0.15 mm versus 1.33 ± 0.17 mm, minoxidil versus vehicle, $p = 0.018$) (Figures 2D, E). These images of all aneurysms are given in Supplementary Figure S2A. Likewise, hydrazine and minoxidil aggravated AAA progression, which was observed by monitoring internal diameters by ultrasonography (1.04 ± 0.05 mm versus 0.97 ± 0.07 mm, hydralazine versus vehicle, and $p = 0.017$; 1.06 ± 0.07 mm versus 0.97 ± 0.07 mm, minoxidil versus vehicle, and $p < 0.001$).

TABLE 4 Influence of hydralazine and minoxidil on PRL and PRA in published studies.

Vasodilator	Species	Dose and route	Effect on PRL and PRA	Effect on blood pressure	Reference
Hydralazine	Human	Varies with individuals, Q6h, oral administration	Elevated PRL compared with premedication (14.5 vs. 35.9 mug/ml/hr)	Lower blood pressure than premedication (191/128 vs. 169/108 mmHg; $p < 0.01$)	Gottlieb et al. (1972)
	Human	150 mg, Qd, oral administration	Elevated PRL compared with premedication (19 ± 3 vs. 25 ± 4 mIU/L; $p = 0.067$)	Lower blood pressure than premedication, with the aim of 140/90 mmHg	Veldhuizen et al. (2021)
	Human	Not available	Elevated PRA	Lower arterial blood pressure than premedication (107.0 ± 2.0 vs. 124.2 ± 3.7 mmHg; $p < 0.01$)	Velasco and McNay (1977)
	Rat	Concentration gradient administration, 0.1, 0.3, 1.0, and 6.0 mg/kg, intraperitoneal injection	PRA increased with dose and peaked at 20 min	Not available	Pettinger et al. (1973)
	Mouse	15 mg/kg, infused by osmotic minipumps subcutaneously	Increased mouse kidney renin mRNA 2.4-fold (248% ± 62% of vehicle)	Lower arterial blood pressure than premedication (73 ± 1 vs. 100 ± 2 mmHg)	Keen and Sigmund (2001)
Minoxidil	Human	Varies with individuals, Q6h, oral administration	Elevated PRL, but lower than hydralazine administration (31.1 vs. 35.9 mug/ml/hr)	Minoxidil was more effective in lowering blood pressure than hydralazine (169/108 vs. 142/92 mmHg; $p < 0.05$)	Gottlieb et al. (1972)
	Human	Start with 5 mg, doubling the dose every 6 h, oral administration	Elevated PRA compared with premedication (8.58 ± 2.83 vs. 1.12 ± 0.28 ng/ml/hr; $p < 0.02$)	Lower mean arterial blood pressure than in the control group (110.6 ± 3.1 vs. 141.2 ± 4.3 mmHg; $p < 0.001$)	Velasco et al. (1974)
	Human	Start with 5 mg, and doubling the dose every 6 h, up to a maximum of 20 mg at a single dose, oral administration	Elevated PRA compared with premedication (7.29 ± 2.68 vs. 1.03 ± 0.26 ng/ml/hr; $p < 0.05$)	Lower mean arterial blood pressure than that of the control group (108.5 ± 3.0 vs. 140.1 ± 5.1 mmHg; $p < 0.001$)	O'Malley et al. (1975)
	Rat	Concentration gradient administration, 0.3, 1.0, 6.0, and 30.0 mg/kg, intraperitoneal injection	PRA increased with dose and peaked at 45 min	Not available	Pettinger et al. (1973)

Direct-acting vasodilators promoted aortic degeneration

Next, histological analyses demonstrated that both hydrazine and minoxidil promoted inflammatory cell infiltration and deposited collagen fibers compared to the vehicle group in H&E and Masson staining (Figure 3A). Furthermore, hydrazine and minoxidil aggravated vascular structure disorder, as evidenced by increased elastic destruction scores and vascular smooth muscle cell degeneration scores qualified by EVG and α-SMA staining (Figures 3A, B). These results histologically confirmed aortic degeneration was aggravated by hydrazine/minoxidil administration.

Direct-acting vasodilators aggravated aortic inflammation

As mural inflammation promoted aortic degeneration in AAA disease, immunohistological analysis was conducted to evaluate inflammatory cell infiltration in the study. Our results revealed that both hydrazine and minoxidil aggravated mural angiogenesis and accumulation of $CD3^+$ T cells, $CD68^+$ macrophages, and MMP9 (Figure 4A; Supplementary Figure S2B). Furthermore, the relative mRNA level of inflammatory factors of aortic aneurysm was examined by quantitative PCR, which suggested minoxidil significantly upregulated the expression levels of *IFN-γ*, *NOS2*, and *CCL2* (Figure 4B). Similar trends were observed in the hydralazine group, but the difference was not significant, which may be due to the small sample size.

Discussion

Antihypertensive medication is a cornerstone therapy among AAA patients with hypertension, which minimizes risks of cardiovascular events and AAA rupture. However, specific recommendations for the choice of antihypertensive medication in AAA patients remain poorly described. In the current study, we demonstrated that the PRL and PRA increased in patients with AAA compared to patients with PAD and VV, and were positively associated with AAA development after further analysis of clinical characteristics. Despite their potent blood pressure-lowering effect, direct-acting vasodilators, such as hydralazine and minoxidil, were reported to increase PRL and PRA and upregulated the renin-angiotensin system which implied an increased risk of AAA development and progression. Hence, animal experiments were performed and confirmed that administration of hydralazine and minoxidil aggravated PPE-induced experimental AAA progression with increased aortic degeneration and inflammatory infiltration. Our results

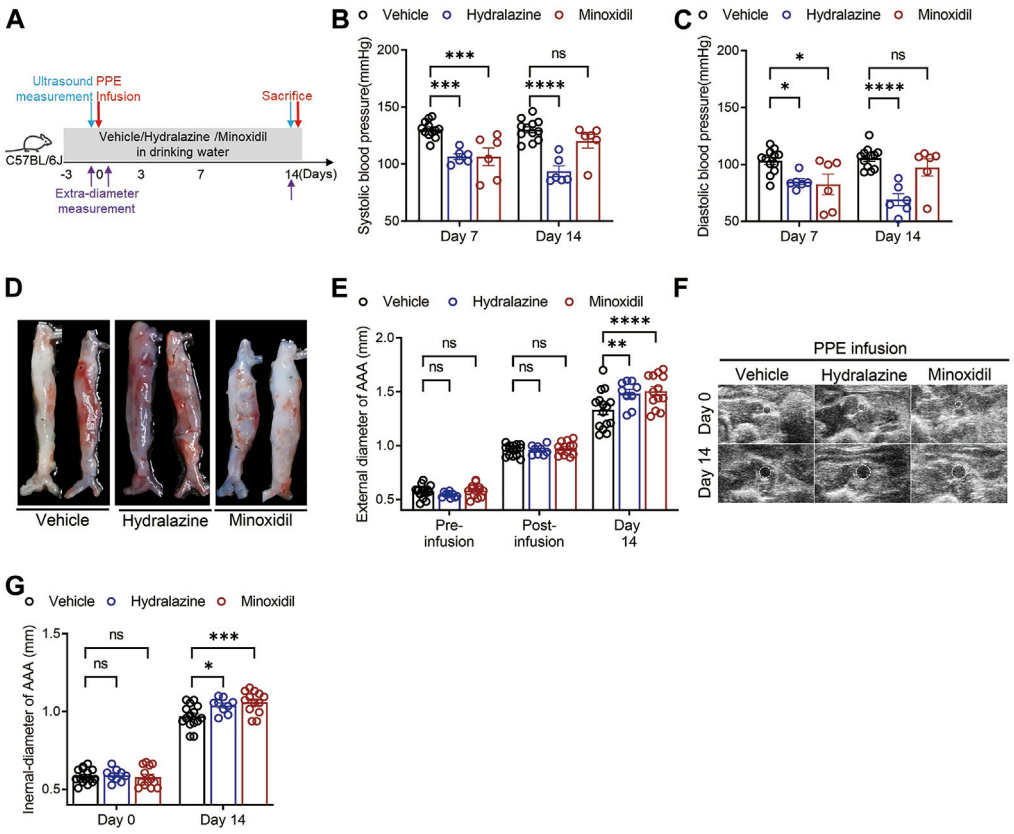

FIGURE 2
Hydrazine and minoxidil aggravated experimental AAA disease. **(A)** Scheme of the PPE-induced experimental AAA mouse model and monitoring of AAA diameters. **(B,C)** Effect of hydrazine and minoxidil on systolic blood pressure and diastolic blood pressure in experimental AAA. **(D,E)** Representative AAA images and quantitative analysis of aortic extra-diameters in the vehicle group (n = 15), hydrazine group (n = 9), and minoxidil group (n = 13). **(F,G)** Representative ultrasound AAA images and quantitative analysis of aortic intra-diameters and growth rate in the three groups. Data are presented as the mean ± SEM. Significance was analyzed using two-way ANOVA with the Bonferroni correction. *p < 0.05; **p < 0.01; and ***p < 0.001 vs. vehicle group.

highlighted the critical roles of renin in AAA disease, which raised cautionary concerns about the applications of direct vasodilators on AAA and other arterial diseases.

The involvement of the renin-angiotensin system in the pathophysiology of AAA disease has been well-established (Lu et al., 2012). Particularly secreted by juxtaglomerular cells of the kidney, renin is the rate-limiting enzyme of the renin-angiotensin system, and regulates blood pressure and cardiovascular functions. As renin catalyzes the first step in the renin-angiotensin system cascade, numerous studies have been conducted to investigate the link between PRL/PRA and the subsequent cardiovascular risk. Although the majority of these studies demonstrated a positive relationship between PRL and PRA, and cardiovascular morbidity and mortality, no definitive conclusions were obtained due to differences in the methodology among these trials (Volpe and Unger, 2013). In view of the critical role of the renin-angiotensin system in AAA disease, several previous studies demonstrated the potential role of plasma renin in AAA (Daugherty and Cassis, 2004; Steckelings and Bader, 2018). Early research addressed that excessive salt intake increased AAA incidence and rupture risk in hypertensive angiotensin and renin transgenic mice, which was protected by angiotensin converting enzyme inhibitor or angiotensin receptor blocker (Nishijo et al., 1998; Liao et al., 2001). The prorenin receptor, a specific receptor for renin and prorenin, aggravated Ang II-induced AAA on the Apoe$^{-/-}$ background, which was reversed by blocking the Ang II receptor using telmisartan (Ma et al., 2020). Furthermore, aliskiren, a direct renin inhibitor, was shown to limit atherosclerosis and AAA in an Ang II-infused mouse model by reducing prorenin receptor expression and Mitogen-activated protein kinases activity (Seto et al., 2014; Miyake et al., 2017). However, a recent case–control study reported plasma aldosterone concentrations increased in patients diagnosed with aortic dissection and aneurysms, accompanied by suppressed PRA in women rather than men (Zhu et al., 2022). In the study, we demonstrated that the PRL and PRA were increased in patients with AAA compared to those with PAD and VV, and considered risk factors for AAA, which indicated their potential role in arterial disease and AAA development. However, for patients with existing AAA, no significant correlation was found between PRL and PRA and AAA diameters. Considering the effect of Ang II on renin release through a negative feedback regulatory mechanism cannot be ignored, it suggested the roles of the renin-angiotensin system on AAA remain to be further clarified (Schweda et al., 2007).

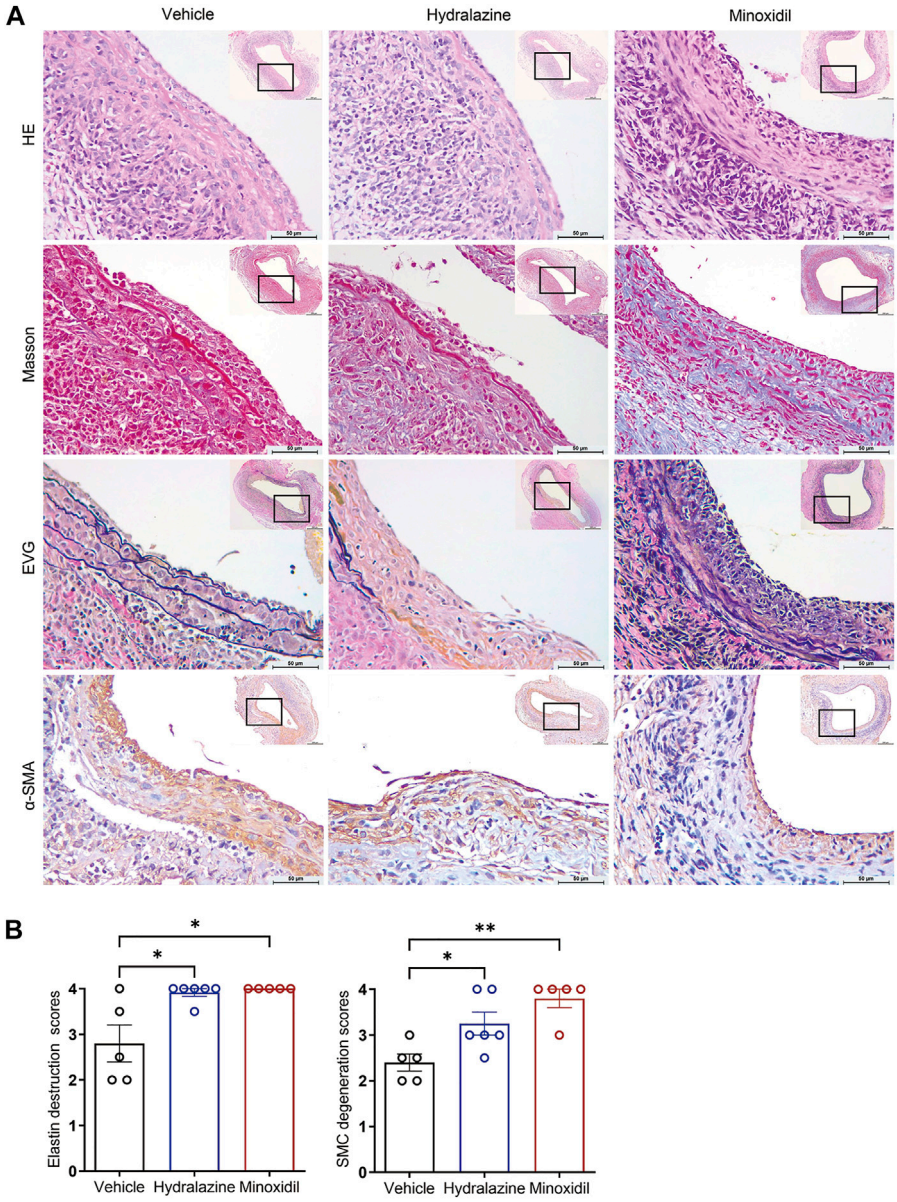

FIGURE 3
Hydrazine and minoxidil promoted aortic degeneration in experimental AAA. **(A)** Representative images of HE, Masson, EVG, and anti-SMC α-actin staining in the vehicle group (n = 5), hydrazine group (n = 6), and minoxidil group (n = 5). **(B)** Quantitative analysis of EVG and anti-SMC α-actin staining in the three groups. Data are presented as the mean ± SEM. Significance was analyzed using the Mann–Whitney test. *$p < 0.05$; **$p < 0.01$ vs. vehicle group.

Despite the lack of evidence that hypertension is linked to AAA progression and remains a potential risk factor for the development and prognosis of AAA (Rapsomaniki et al., 2014; Kobeissi et al., 2019; Li et al., 2019). Thus, it is encouraged to apply antihypertensive therapy in AAA patients with hypertension. Despite not being the first choice of antihypertensive agents, direct vasodilators, such as minoxidil and hydralazine, are still widely used in clinical therapeutics (Dormois et al., 1975; Mehta et al., 1975; Lu et al., 2012). Hydralazine, as a classical direct vasodilator, remains an option for the treatment of hypertension and systolic heart failure (Kandler et al., 2011). It is used as step 3 in the Hypertension Detection and Follow-up Program (HDFP) cooperative group trial and the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT) to reduce the incidence of hypertension and related complications (Five-year findings of the hypertension, 1979; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, 2002). It has been proposed to inhibit IP3-induced sarcoplasmic reticulum calcium release and to inhibit myosin phosphorylation in arterial smooth muscle cells, although its mechanism is not fully elucidated (McComb et al., 2016). Minoxidil, another direct vasodilator, was introduced in the early 1970s for treating refractory hypertension in cases where multidrug

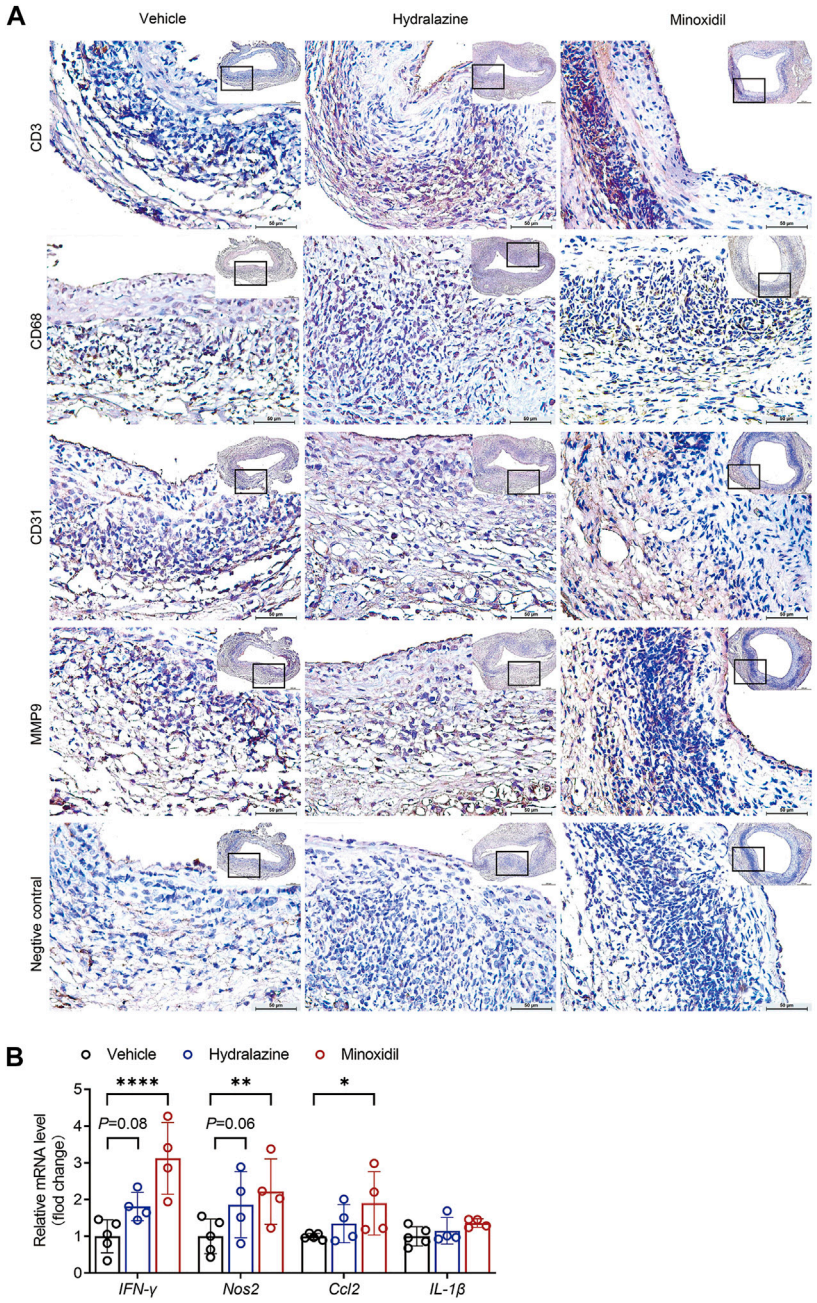

FIGURE 4
Hydrazine and minoxidil aggravated aortic inflammation in experimental AAA. **(A)** Representative immunohistological staining of $CD3^+$ T cells, $CD68^+$ macrophages, $CD31^+$ mural angiogenesis, and MMP9. Rabbit control IgG serves as the negative control. **(B)** IFN-γ, NOS2, CCL2, and Il-1β mRNA expression were normalized to GAPDH endogenous control mRNA expression by quantitative RT-PCR. Significance was analyzed using two-way ANOVA. $*p < 0.05$; $**p < 0.01$ vs. vehicle group.

regimens had failed. As an ATP-modulated potassium (K_{ATP}) channel-opening agent in the vascular smooth muscle cells, minoxidil allows potassium efflux and reduces calcium influx, which ultimately relaxes vascular smooth muscle cells, dilates the aortic lumen, and lowers blood pressure (McComb et al., 2016). In our current study, we found that administration of hydralazine and minoxidil increased AAA progression with increased infiltration of local inflammatory cells and arterial degeneration. Not coincidentally, this is not the first study to investigate the relationship between vasodilating-effect drugs and AAAs. It has been reported that hydralazine showed a trend toward aggravated AAA (1.59 ± 0.21 vs. 1.38 ± 0.03; hydralazine vs. vehicle) and atherosclerotic lesion areas (3.00 ± 0.40 vs. 1.74 ± 0.50 mm^2, hydralazine vs. vehicle, and $p = 0.06$) in Ang II-infused mice, although the differences were not significant (Cassis et al., 2009). In addition, sildenafil (Viagra), another vasodilator used to treat impotence and pulmonary hypertension, aggravated elastin degeneration and experimental AAA progression by

dysregulating cyclic guanosine monophosphate and contractile signaling in vascular smooth muscle cells (Zhang et al., 2022). Other direct-acting vasodilators, such as calcium channel blockers, were also proved to increase perioperative mortality in both acute and elective aortic aneurysm surgery (Wilmink et al., 2002; Kertai et al., 2008). Consistently, as one of the dihydropyridine calcium channel blocker, amlodipine has been demonstrated to significantly promote elastin degradation and enhance matrix metalloproteinase-9 activity in experimental porcine aneurysm (Boyle et al., 1998). However, studies reported that the calcium channel blocker protected from Ang II induced AAA by reducing inflammatory infiltration and preserving eNOS coupling (Kurobe et al., 2013; Miao et al., 2015). These completely opposite results may attribute to the differences in animal models, to be precise, that Ang II negative regulates renin levels (Schweda et al., 2007). Therefore, the risk of direct-acting vasodilators to AAA diseases should be considered.

It is worth mentioning that as a direct vasodilator, minoxidil has a direct antihypertensive effect when initially administered. However, long-term administration can weaken this hypotensive effect, which is attributed to the desensitization of K^+ channels in vascular smooth muscle cells in the aorta. This phenomenon was also observed in another ATP-dependent K^+ channel opener, levcromakalim, which attenuated vascular relaxation in NO-donors after 2 weeks of administration in rats (Trongvanichnam et al., 1996). Now, minoxidil is widely used to treat androgenetic alopecia mainly by topical application and oral administration at a low dose (Stoehr et al., 2019; Randolph and Tosti, 2021). Adverse cardiovascular events induced by topical minoxidil suggest that it can be systemically absorbed, implying its cardiovascular risks in AAA patients (Lu et al., 2012). Although there is no clinical research exploring the relationship between minoxidil and AAA, minoxidil should be used with caution in androgenetic alopecia patients with AAA or other arterial diseases.

The risk factors for AAA are mainly old age, male gender, hypertension, and hyperlipidemia, which are consistent with the risk factors for PAD (Morley et al., 2018; Golledge, 2019). A prospective analysis of 14,148-participants also indicated that symptomatic PAD had a higher hazard ratio of incident AAA [2.96 (95% CI 1.73–5.07)], as did asymptomatic PAD [1.52 (95% CI 1.00–2.30)] (Hicks et al., 2021). Moreover, our current study showed that PRL and PRA were correlated with a higher risk of PAD [odds ratio (OR), 1.368 and 1.219, respectively] than VV (Table 3), which was consistent with previous studies. To eliminate the selective bias of the current study, we included patients with PAD and VV together in the control group and compared them separately with patients with AAAs and matched them by age, sex, and history of hypertension to enhance comparability among the clinical data. In addition, patients with PAD also showed increased PRL and PRA compared to VV disease, which raised cautionary concerns about increased renin phenotypes and applications of direct vasodilators in PAD and other arterial diseases.

Nonetheless, this study has several limitations. First, a small sample size was a major drawback of the present study. A more comprehensive analysis is needed to determine the relationship between renin and AAA disease. Second, direct-acting vasodilators are a heterogeneous group of drugs. Although hydralazine and minoxidil are the most commonly prescribed direct vasodilators, they may not be representative of all vasodilators in the study. More retrospective studies are needed to assess their safety in vascular disease. Therefore, future studies with larger samples and longitudinal measurements of people taking vasodilators are warranted to overcome the limitations to our study and establish cause-and-effect relationships.

Conclusion

PRL and PRA are positively associated with AAA development. Hydralazine and minoxidil promote the progression of AAA in a mouse model, which might be associated with increased PRL and PRA. Direct-acting vasodilators should be used with caution in patients with AAA, as well as in those at high risk for AAA disease and other artery diseases.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Xiangya Hospital Institutes' Review Board and Ethics Committee of the Xiangya Hospital, Central South University. The patients/participants provided written informed consent to participate in this study. The animal study was reviewed and approved by the Animal Care and Use Committee of Ethics of the Xiangya Hospital, Central South University (NO. 201803481).

Author contributions

Conception and design: YL, SL, and WW. Analysis and interpretation: YL, SL, and JZ. Data collection: YL, SL, JZ, and KW. Writing the article: YL and SL. Critical revision of the article: YL, SL, and BX. Final approval of the article: YL, SL, and WW. Statistical analysis: YL and SL. Fund acquisition: WW. YL, and SL contributed equally to this article and share co-first authorship. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the National Natural Science Foundation of China (Nos 81873525 and 82070491).

Acknowledgments

The authors thank Yongping Bai at the Department of Cardiovascular Medicine, Xiangya Hospital, Central South University, for guidance during the experiments.

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/fphar.2023.1174278/full#supplementary-material

SUPPLEMENTARY TABLE S1
Characteristics of study participants stratified by AAA occurrence.

SUPPLEMENTARY TABLE S2
Comparison of PRL and PRA between AAA and non-AAA groups.

SUPPLEMENTARY TABLE S3
Multicollinearity analysis.

SUPPLEMENTARY TABLE S4
Logistic regression analysis for the association between PRL/PRA and AAA.

SUPPLEMENTARY TABLE S5
Relationship between PRL/PRA and AAA diameter.

SUPPLEMENTARY FIGURE S1
Comparison of PRL and PRA between AAA and non-AAA groups. Plasma renin levels and renin activity were measured in the included patients to evaluate the differences in plasma renin levels and activity among the AAA (n = 20) and non-AAA (n = 40) groups. **(A)** Plasma renin level (PRL) measurement (left). Data were expressed as the median with an interquartile range. **(B)** Plasma renin activity (PRA) measurement (right). Data were expressed as the median with an interquartile range. The M-W test was applied. $^{**}p < 0.01$ and $^{****}p < 0.0001$.

SUPPLEMENTARY FIGURE S2
All the images of PPE-induced aneurysms and statistical analysis of immunohistological staining in the three groups. **(A)** All the images of PPE-induced aneurysms in the vehicle group (n = 15), hydrazine group (n = 9), and minoxidil group (n = 11) are shown. **(B)** Quantitative analysis of $CD3^+$ T cells, $CD68^+$ macrophages, and $CD31^+$ mural angiogenesis staining in the three groups. Data are presented as the mean ± SEM. Significance was analyzed using one-way ANOVA. $^{*}p < 0.05$ vs. the vehicle group.

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frontiers | Frontiers in Pharmacology

TYPE Opinion
PUBLISHED 01 September 2023
DOI 10.3389/fphar.2023.1253655

OPEN ACCESS

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RECEIVED 05 July 2023
ACCEPTED 21 August 2023
PUBLISHED 01 September 2023

CITATION
Ginosyan K, Misakyan H and Zakaryan A (2023), Perioperative management of patients with antiphospholipid and catastrophic antiphospholipid syndrome undergoing urgent neurosurgery. *Front. Pharmacol.* 14:1253655. doi: 10.3389/fphar.2023.1253655

Perioperative management of patients with antiphospholipid and catastrophic antiphospholipid syndrome undergoing urgent neurosurgery

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KEYWORDS

urgent neurosurgery, antiphospholipid syndrome, catastrophic antiphospholipid syndrome, perioperative management, plasmapheresis

Acute neurosurgical conditions associated with brain compression, swelling, dislocation, and herniation require emergency surgery. These time-sensitive and life-saving procedures aim to reverse or stop further damage to the central nervous system, the success of which depends on immediate surgery. Despite this urgency, any co-morbidities, which may complicate the perioperative course, should be taken into account while developing a treatment plan. Patients with antiphospholipid syndrome (APS) and catastrophic antiphospholipid syndrome (CAPS) receiving anticoagulation therapy have an increased risk of perioperative thrombotic/bleeding complications. Perioperative management of such cases is a complex problem; moreover, these co-morbidities themselves may cause a neurosurgical emergency. Guidelines and studies for the perioperative management of pathologies with high thrombotic/bleeding risk recommend that patients undergoing a neurosurgical procedure should discontinue therapy with oral anticoagulants before surgery and continue therapy with heparin or low molecular weight heparin (LMWH) (Zakaryan, 2014; Douketis et al., 2022; Shah et al., 2023). However, such a scheme is applicable in cases with planned neurosurgical operations. In neurosurgical emergencies, additional strategies for managing the perioperative course are needed. This brief communication summarizes currently available approaches to perioperative management of patients with APS and CAPS undergoing urgent neurosurgical procedures.

APS is a systemic autoimmune disorder characterized by venous or arterial thrombosis in the presence of antiphospholipid antibodies: anticardiolipin antibodies IgG/IgM, anti-β2-glycoprotein-I antibodies IgG/IgM, lupus anticoagulant. APS may occur as a primary condition but also develop in the presence of systemic lupus erythematosus and other systemic autoimmune diseases (Tektonidou et al., 2019; Rodziewicz and D'Cruz, 2020). Patients with APS should receive long-term treatment with vitamin K antagonists along with low-dose aspirin when indicated. In case of recurrent thrombosis, the patients may need LMWH (Finazzi et al., 2005; Ruiz-Irastorza et al., 2011; Tektonidou et al., 2019). CAPS is a rare APS variant characterized by multiple small vessel thromboses, leading to multi-organ failure and insufficiency. Neurosurgical complications occur in one-third of CAPS patients (Drazin et al., 2014). In rare cases, CAPS emerges with cerebellar bleeding requiring urgent neurosurgery (Drazin et al., 2014). Several APS/CAPS-associated neurosurgical cases are described in the searchable literature (Inoue et al., 1994; Nagai et al., 1998; Miesbach et al., 2004; Cervera et al., 2005; Finis et al., 2005; Arinuma et al., 2011; Drazin et al., 2014; Arias

et al., 2019). Among these reported cases best outcomes were observed in patients managed with plasmapheresis perioperatively (Miesbach et al., 2004; Drazin et al., 2014; Arias et al., 2019). Miesbach et al. (2004) reported a case of CAPS-related bilateral subdural hematoma treated with plasmapheresis before neurosurgery (left frontal craniotomy, right frontal drill-hole trepanation with drainage tubes) with minimal postoperative neurological deficit and good outcome at discharge. Drazin et al. (2014) presented a unique case with CAPS-related cerebellar hematoma, idiopathic thrombocytopenic purpura, deep vein thrombosis, infarctions in the kidneys and spleen, adrenal hemorrhage, and altered mental status. The patient acutely deteriorated secondary to the development of a cerebellar subdural hematoma requiring an emergent decompression and excision of the hematoma. After recovery in the intensive care unit, the patient developed a new spontaneous epidural hematoma necessitating an additional surgical intervention. The patient received six courses of plasmapheresis which made it possible to decrease the level of antiphospholipid antibodies creating the possibility to conduct the neurosurgical procedure. Arias et al. (2019) reported two cases of APS when patients successfully received perioperative plasmapheresis for performing an extracranial-intracranial bypass (ECIC) to treat a left internal carotid artery aneurysm in one case and moyamoya disease in the second patient. Both cases were managed with perioperative plasmapheresis to avoid the need for anticoagulation during the perioperative period, and both patients underwent successful ECIC bypass procedures without perioperative ischemic or hemorrhagic complications.

Plasmapheresis or therapeutic plasma exchange is used to remove autoantibodies, immune complexes, cytokines, and pathologic inflammatory mediators from the circulation. It can be used in the perioperative period in autoimmune diseases (Roman et al., 2014; Prouvot et al., 2019; Rodriguez-Pinto et al., 2019). Fresh frozen plasma (FFP) is the most commonly used plasma product to correct clotting factor deficiencies, and its use could potentially reduce the bleeding risk in these patients. Along with FFP, cryoprecipitate, and recombinant factor concentrates are used as an option before neurosurgery in coagulopathic patients.

In conclusion, plasmapheresis and/or FFP along with cryoprecipitate and recombinant factor concentrates may be used for the management of APS and CAPS in urgent neurosurgical cases perioperatively. However, it is still unclear if their use could worsen the thrombotic storm of CAPS (Marson et al., 2008). It might be reserved for a subgroup of patients at higher risk of bleeding. Further multicenter trials are needed to estimate the safety, effectiveness, and limitations of this method in emergency neurosurgery.

Author contributions

KG: Conceptualization, Investigation, Writing–original draft, Writing–review and editing. HM: Conceptualization, Investigation, Writing–original draft, Writing–review and editing. AZ: Conceptualization, Investigation, Supervision, Writing–original draft, Writing–review and editing.

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 Pharmacology

TYPE Review
PUBLISHED 01 September 2023
DOI 10.3389/fphar.2023.1159857

OPEN ACCESS

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RECEIVED 06 February 2023
ACCEPTED 17 August 2023
PUBLISHED 01 September 2023

CITATION
Wang L-M, Chen Y, Xu L-L, Dai M-F, Ke Y-J, Wang B-Y, Zhou L, Zhang J-F, Wu Z-Q, Zhou Y-J, Gu Z-C and Xu H (2023), Short-term antithrombotic strategies after left atrial appendage occlusion: a systematic review and network meta-analysis.
Front. Pharmacol. 14:1159857.
doi: 10.3389/fphar.2023.1159857

Short-term antithrombotic strategies after left atrial appendage occlusion: a systematic review and network meta-analysis

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Background: Percutaneous left atrial appendage occlusion (LAAO) has emerged as a stroke prevention strategy in patients with nonvalvular atrial fibrillation (NVAF), and these patients were required to receive antithrombotic therapy post-procedure. However, the optimal antithrombotic strategy after LAAO remains controversial. This study explored the safety and efficacy of different antithrombotic strategies after LAAO through a network comparison method.

Methods: We systematically searched the MEDLINE, Embase, and Cochrane Library databases for studies that reported the interested efficacy and safety outcomes (stroke, device-related thrombus (DRT), and major bleeding) of different antithrombotic strategies [DAPT (dual antiplatelet therapy), DOACs (direct oral anticoagulants), and VKA (vitamin k antagonist)] in patients who had experienced LAAO. Pairwise comparisons and network meta-analysis were performed for the interested outcomes. Risk ratios (RRs) with their confidence intervals (CIs) were calculated using a random-effects model. The rank of the different strategies was calculated using the surface under the cumulative ranking curve (SUCRA).

Results: Finally, 10 observational studies involving 1,674 patients were included. There was no significant difference in stroke, DRT, and major bleeding among the different antithrombotic strategies (DAPT, DOACs, and VKA). Furthermore, DAPT ranked the worst in terms of stroke (SUCRA: 19.8%), DRT (SUCRA: 3.6%), and major bleeding (SUCRA: 6.6%). VKA appeared to be superior to DOACs in terms of stroke (SUCRA: 74.9% vs. 55.3%) and DRT (SUCRA: 82.3% vs. 64.1%) while being slightly inferior to DOACs in terms of major bleeding (SUCRA: 71.0% vs. 72.4%).

Conclusion: No significant difference was found among patients receiving DAPT, DOACs, and VKA in terms of stroke, DRT, and major bleeding events after LAAO. The SUCRA indicated that DAPT was ranked the worst among all antithrombotic strategies due to the higher risk of stroke, DRT, and major bleeding events, while

VKAs were ranked the preferred antithrombotic strategy. However, DOACs are worthy of consideration due to their advantage of convenience.

KEYWORDS

left atrial appendage occlusion, network meta-analysis, warfarin, dual antiplatelet therapy, direct oral anticoagulants

1 Introduction

Nonvalvular atrial fibrillation (NVAF) is the most common arrhythmia in the middle-aged and elderly and is associated with an increased risk of stroke and thromboembolic events. Studies showed that more than 90% of thromboembolic events originate from the left atrial appendage in patients with NVAF because of the influence of anatomical location and function (Gallinoro et al., 2019; Holmes et al., 2019). Percutaneous left atrial appendage occlusion (LAAO) has gradually emerged as an effective treatment strategy for patients with NVAF (Cimmino et al., 2021). However, despite the surgeon's experience and device technology having significant improvements, LAAO is still associated with the risks of potentially serious stroke, device-related thrombus (DRT), and major bleeding, which was the same as most implantation procedures (Yu et al., 2021). This is because when a foreign material is placed into the human system during the LAAO procedure, thrombosis may occur on the device surface contributing to thromboembolic events before adequate endothelialization (Price, 2019). Therefore, antithrombotic therapy is essential for patients undergoing LAAO (Mahajan et al., 2012). Although the U.S. Food and Drug Administration labeling for the WATCHMAN device recommended using 45 days of warfarin followed by 6 months of DAPT (Jalal et al., 2017; Saw et al., 2019), practitioners rarely used the approved treatment protocols when using the WATCHMAN device in clinical practice, while some prefer dual antiplatelet therapy or direct oral anticoagulants (Reddy et al., 2017; Boersma et al., 2019). In addition, DOACs are favored for stroke prevention because of better safety and convenience compared with warfarin (Connolly et al., 2009; Giugliano et al., 2013; Carnicelli et al., 2022), whereas some studies show that there seem to be similar risks of thromboembolism and bleeding between different antithrombotic strategies in patients after LAAO (Boersma et al., 2019; Osman et al., 2020). Currently, there are no published systematic reviews on randomized controlled trials or observational studies comparing all commonly used antithrombotic strategies. The optimal antithrombotic strategies for patients undergoing LAAO remain controversial and, hence, require further exploration. Therefore, we decided to conduct a network meta-analysis to systematically explore the safety and efficacy of different antithrombotic strategies after LAAO to provide credible evidence for clinical decision-making.

2 Methods

2.1 Search strategy

The study was conducted according to the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement PROSPERO registry with the registration number CRD42022304389 (Moher et al., 2015). The Cochrane Library, MEDLINE, and Embase databases were systematically searched for studies that directly compared different antithrombotic strategies (DAPT, DOACs, and VKA) after LAAO. All the English publications until October 2022 were searched. For the theme "Left Atrial Appendage Occlusion," the terms used were "Left Atrial Appendage Occlusion" OR "Left atrial appendage closure." For the theme "Platelet Aggregation Inhibitors," we included the following terms: "Aspirin" OR "Ticlopidine" OR "Clopidogrel" OR "Dipyridamole" OR "Thienopyridines." For the theme "Anticoagulants," we included the following terms: "Warfarin" OR "Non-vitamin K antagonist oral anticoagulants" OR "NOACs" OR "Direct oral anticoagulants" OR "DOACs" OR "Novel oral anticoagulants" OR "New oral anticoagulants" OR "Factor Xa inhibitors" OR "Rivaroxaban" OR "Xarelto" OR "Edoxaban" OR "Lixiana" OR "Savaysa" OR "Apixaban" OR "Eliquis" OR "Dabigatran" OR "Pradaxa." We used the Boolean operator "AND" to combine the three comprehensive search themes. To confirm articles that were missed in the early search, the reference list of each paper was filtered. In addition, unpublished data were obtained from the ClinicalTrials.gov website.

2.2 Inclusion criteria and exclusion criteria

The following were the inclusion criteria: 1) observational studies; 2) studies that enrolled patients who received LAAO device implantation (WATCHMAN, Amulet, or Amulet Cardiac Plug [ACP]); 3) studies that adopted specific antithrombotic regimens after LAAO; and 4) studies that explicitly reported the detailed information about the safety and efficacy outcomes of patients. The following studies were excluded: 1) studies with fewer than 10 subjects; 2) studies without follow-ups; 3) studies with duplicate or lost data; and 4) case reports, reviews, conference abstracts, and guidelines. We also excluded the subsequent studies or sub-studies based on similar study cohorts. In addition, for multiple publications based on the same patient pool, we only included the most recent published articles.

2.3 Study outcomes

The primary efficacy and safety outcomes were stroke, device-related thrombus (DRT), and major bleeding. The stroke events were defined as all-cause strokes (ischemic or hemorrhagic) following implantation. The DRT events were defined as thrombosis on the atrial surface of the device visible through transesophageal echocardiography (TEE) or CT scan (Korsholm et al., 2019). Furthermore, the major bleeding events included a

decrease in the hemoglobin level of 2 g/dL or greater within a 24-h period or leading to a transfusion of 2 or more units of packed red cells or requiring an additional endoscopy intervention, according to the International Society on Thrombosis and Hemostasis (ISTH) criteria (Mega et al., 2009).

2.4 Data extraction

We used a pre-customized form to extract and collect data from the included studies. The data extracted from each study included characteristics of the individual study (study name, year of publication, number of patients, antithrombotic strategy, duration of follow-up, and study design), the baseline characteristics of patients (age, sex, type of atrial fibrillation, heart failure, hypertension, diabetes mellitus, CHA_2DS_2-VASc score, and HAS-BLED score), and the information of the interested outcomes (stroke, DRT, and major bleeding).

2.5 Quality assessment

Quality assessment of the enrolled observational studies was performed via the Newcastle–Ottawa Scale (NOS) (GA Wells, 2021). This scale was divided into NOS evaluation criteria for cohort studies and for case–control studies. The scale consists of three major parts (evaluation of selection, comparability, and outcome), using a star system, with full marks of 13 stars for cohort studies and nine stars for case–control studies. We conducted this quality assessment using the evaluation criteria for cohort studies. Studies with at least six stars were included in the meta-analysis.

2.6 Statistical analysis

The extraction form of effects was events for dichotomous data and means or median for continuous data. These data were recorded directly according to the study data or computed according to the data provided in the study. To estimate the pooled relative risk (RR) with 95% confidence intervals (CIs), we first performed a pairwise meta-analysis using Stata 15.1. A value of I^2 ≥50% was considered substantial heterogeneity. When there was statistically significant heterogeneity, a random-effects model was used; otherwise, a fixed-effects model was used. In addition, we performed network meta-analysis and assessment of inconsistency using the command "mvmeta" of the Stata Statistical Software 15.1. Inconsistency of the indirect and direct evidence was assessed using the heterogeneity variance parameter (tau-squared, τ^2) in the loop-specific approach, which assesses the bias of effect sizes among the study participants. At least three treatment pairs are required to form an evidence loop. Probability values were shown as the surface under the cumulative ranking (SUCRA) curve and provided a rank of antithrombotic strategies; the SUCRA value becomes 0% when it is certain to be the worst and 100% when it would be the best. The robustness of treatment effects in different antithrombotic strategies was evaluated by meta-regression in direct comparative treatment subgroups using the proportion of the device type. Moreover, we used comparison-adjusted funnel plots to observe the potential publication bias among the studies that were included. *p*-values of less than 0.05 were considered statistically significant.

3 Results

3.1 Study selection

A total of 3,507 studies were initially retrieved. After excluding duplicate studies, 1,988 studies were screened for eligibility for further scanning. Then, a total of 226 studies were assessed for eligibility using the preordained selection criteria. Through reading the abstract and browsing the partial text of the articles, 216 studies were excluded according to the exclusion criteria. Finally, 10 studies that met the inclusion criteria were enrolled in this network meta-analysis (Figure 1).

3.2 Quality assessment

All 10 comparative studies were assessed for quality, with NOS scores ranging from 6 to 9, which indicated that the studies included were moderate to high-quality studies. The quality assessment results of all included studies are shown in Supplementary Table S1.

3.3 Characteristics of the studies

A total of 10 studies with 1,674 patients were enrolled in this meta-analysis (Bösche et al., 2015; Wiebe et al., 2015; Kim et al., 2016; Enomoto et al., 2017; Cohen et al., 2019; Duthoit et al., 2019; Cepas-Guillen et al., 2021; Chen et al., 2021; Faroux et al., 2021; Zhu and Xu, 2021). The patients were divided into three groups according to the antithrombotic strategies they received: DAPT (aspirin + clopidogrel/ticlopidine), DOACs (rivaroxaban/dabigatran), and VKA (warfarin). The incidence of stroke and major bleeding were both reported in nine studies and DRT in six studies. Of the 10 studies, five compared DOACs and DAPT, four compared DOACs and VKA, and only one compared DAPT and VKA (Supplementary Figure S1). This analysis mostly included elderly patients with hypertension as the main complication. The detailed baseline characteristics are presented in Table 1.

3.4 Pairwise comparison

The results of direct comparisons are shown in Supplementary Figure S2. Compared with DOACs, DAPT did not show an increased risk of stroke (RR 1.83; 95% CI, 0.44–7.63; p = 0.56), DRT (RR 4.07; 95% CI, 0.51–32.18; p = 0.94), and major bleeding (RR 1.54; 95% CI, 0.82–2.89; p = 0.45). Similarly, treatment with DAPT was not associated with a significantly increased risk of stroke, DRT, and major bleeding compared with VKA. Moreover, no statistically significant difference was found between DOACs and VKA regarding stroke, DRT, and major bleeding.

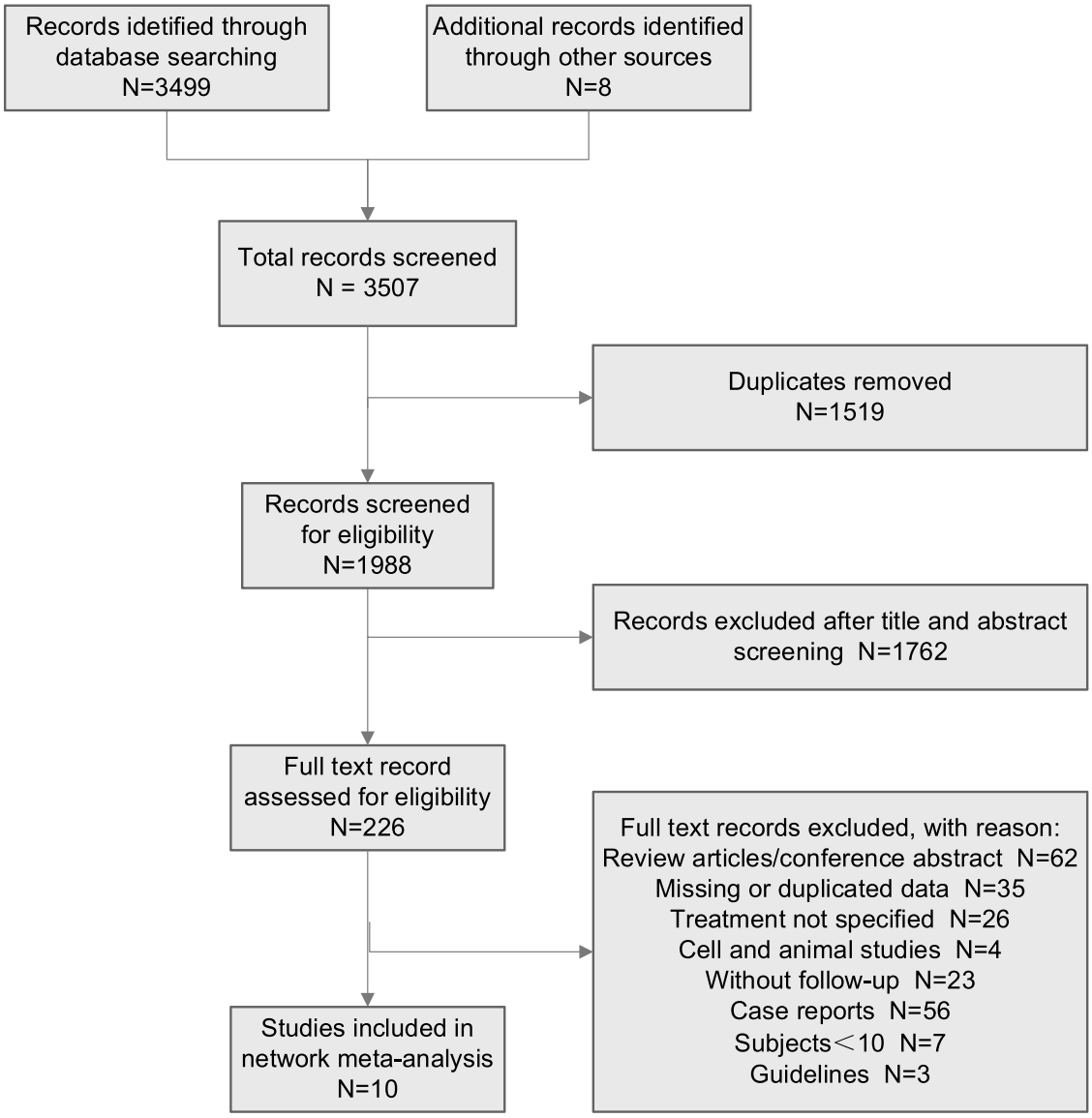

FIGURE 1
Flow diagram for the selection of eligible studies.

3.5 Network meta-analysis

The network meta-analysis results are presented in Figure 2. In terms of stroke, there was no significant difference between patients treated with DAPT, DOACs, and VKA after LAAO (DOACs vs. DAPT: RR 0.60; 95% CI, 0.16–2.24; VKA vs. DAPT: RR 0.44; 95% CI, 0.08–2.39; VKA vs. DOACs: RR 0.74; 95% CI, 0.19–2.92). Furthermore, in terms of DRT and major bleeding, no significant difference was found among all strategies. Finally, there was no significant difference in stroke, DRT, and major bleeding among the different antithrombotic strategies (DAPT, DOACs, and VKA) after LAAO. Similar results were observed in the pairwise comparison (Supplementary Figure S2).

3.5.1 Rank probability

The SUCRA and absolute rank probabilities of antithrombotic strategies are shown in Table 2. In terms of stroke, DAPT (SUCRA: 19.8%) had the lowest cumulative ranking probability and VKA (SUCRA: 74.9%) had the highest cumulative ranking probability, followed by DOACs (SUCRA: 55.3%). With respect to DRT, compared with VKA (SUCRA: 82.3%) and DOACs (SUCRA: 64.1%), DAPT (SUCRA: 3.6%) ranked the worst. In regards to major bleeding, DOACs (SUCRA: 72.4%) had the highest cumulative ranking probability, followed by VKA (SUCRA: 71.0%) and DAPT (SUCRA: 6.6%). VKA was the most effective treatment, and DOACs were the safest in patients who experienced LAAO. VKA had similar safety patterns to DOACs.

TABLE 1 Summarized characteristics of the included studies.

Study		Bösche 2015	Cepas-Guillen 2021	Duthoit 2019	Faroux 2021	Kim 2016	Wiebe 2015	Jing Zhu 2021	Enomoto 2017	Chen 2021	Cohen 2019
Age (mean ± SD)		75 ± 7	73.1 ± 9	77.5 ± 8.2	75.9 ± 8.1	65.1 ± 9.4	71.6 ± 8.8	66 (46–86)	75.5 ± 8	64.8 ± 8.2	76.9 ± 8.7
Male (%)		58.0%	65.0%	62.5%	58.2%	61.5%	62.7%	58.6%	34.0%	NR	62.9%
Hypertension		91.0%	91.0%	85.6%	90.5%	70.8%	91.2%	68.6%	NR	NR	89.7%
Diabetes mellitus		34.00%	NR	27.90%	33.00%	38.50%	27.50%	20.00%	NR	16.2%	21.60%
Previous stroke/TIA		31.0%	43.0%	48.1%	38.6%	43.8%	40.1%	74.2%	NR	42.6%	40.2%
Coronary artery disease		53%	NR	10.6%	NR	38.5%	NR	41.4%	NR	33.5%	NR
CHA_2DS_2-VASc score (mean ± SD)		4.0 ± 1.4	4.3 ± 1.5	4.5 ± 1.5	4.6 ± 1.6	3.9 ± 1.6	4.3 ± 1.7	3.9 ± 1.0	3.9 ± 1.6	3.1 ± 1.7	4.7 ± 1.5
HAS-BLED score (mean ± SD)		3.5 ± 0.8	3.6 ± 1.0	3.7 ± 1.0	3.6 ± 1.0	2.7 ± 1.3	2.9 ± 1.2	3.2 ± 0.8	2.5 ± 1.1	1.8 ± 1.2	3.5 ± 1.0
Follow-up (month)		1.5	3	3	3	22	6	1.5	4	1.5	8
Therapeutic regimen	DAPT	27	73	33	190	35	41				
	DOACs	18	40	71	95	61		30	212	170	52
	VKA						57	40	214	170	45

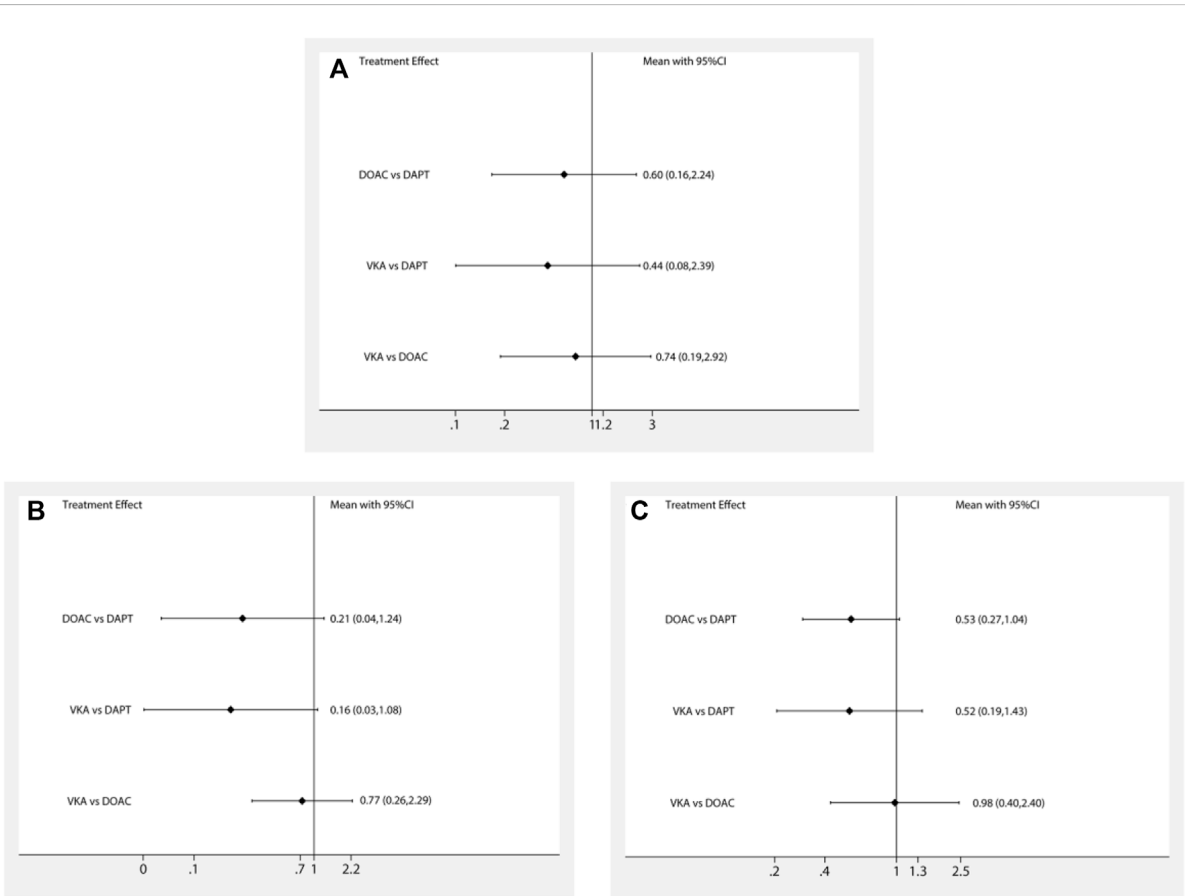

FIGURE 2
Forest plot for the network meta-analysis of all outcomes: **(A)** strokes, **(B)** DRT, and **(C)** major bleeding.

TABLE 2 Surface under the cumulative ranking of the primary outcome.

Intervention	Stroke			DRT			Major bleeding		
	SUCRA (%)	PrBest	MeanRank	SUCRA (%)	PrBest	MeanRank	SUCRA (%)	PrBest	MeanRank
DAPT	19.8	9.6	2.6	3.6	1.8	2.9	6.6	1.5	2.9
DOACs	55.3	28.0	1.9	64.1	31.7	1.7	72.4	46.7	1.6
VKA	74.9	62.4	1.5	82.3	66.6	1.4	71.0	51.8	1.6

DAPT, dual antiplatelet therapy; DOACs, direct oral anticoagulants; VKA, vitamin K antagonist; SUCRA, surface under the cumulative ranking.

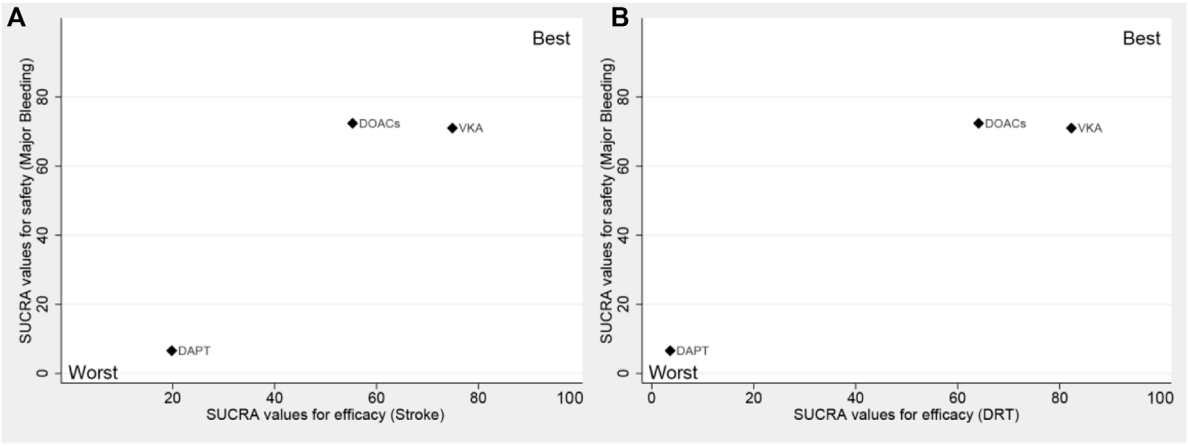

FIGURE 3
Surface under the cumulative ranking (SUCRA) plot. Ranking of strategies expresses the probability associated with each one being the best with respect to stroke and major bleeding **(A)**, as well as DRT and major bleeding **(B)**. The strategies in the upper right corner are more effective and safer than the other strategies. DAPT, dual antiplatelet therapy; DOACs, direct oral anticoagulants; VKA, vitamin K antagonist.

3.5.2 Trade-off analysis

Trade-off analyses of different antithrombotic strategies are shown in Figure 3. The clustered ranking plot according to SUCRA values indicated that DAPT occupied the most unfavorable position with respect to efficacy and safety. VKA formed a cluster of "the most effective and reasonably safe" treatment, whereas DOACs presented a cluster of "the most safe and reasonably effective" treatment.

3.6 Assessment of inconsistency

The results of inconsistency assessments between direct and indirect estimates indicated that the overall level of each antithrombotic strategy satisfied the assumption of consistency (p >0.05). There were no significant differences among all comparisons (p >0.05). Supplementary Table S2 shows the details of loop-specific heterogeneity.

3.7 Meta-regression

The subgroup meta-regression analyses indicated that the device type did not substantially influence the occurrence of thrombosis and bleeding events (p >0.05 for each outcome). There was no significant difference regarding the outcomes of interest between patients who received the WATCHMAN device and patients who received the Amulet or ACP device (Supplementary Table S3).

3.8 Publication bias

Comparison-adjusted funnel plots were performed to test the publication bias among the enrolled studies. The results showed that the statistically symmetrical funnel plots did not indicate evidence of publication bias (Supplementary Figure S3). However, for the comparison of DAPT and VKA, only one study was included, which may make the assessment of publication bias somewhat unreliable.

4 Discussion

Transcatheter left atrial appendage occlusion has become an emerging, effective intervention for preventing stroke and embolic events in patients with NVAF (Reddy et al., 2013; Kirchhof et al., 2016; Boersma et al., 2019; Osmancik et al., 2020; Hindricks et al., 2021). However, the occurrence of DRT and stroke complications after the implantation of the left atrial occluder device has always been an unavoidable clinical problem for most doctors and device

developers, causing great controversy (Reddy et al., 2013; Main et al., 2016; Boersma et al., 2019; Holmes et al., 2019). It is reported that the prevention of thrombosis may be an important segment of reducing the incidence of complications after LAAO (Tung et al., 2017; Dukkipati et al., 2018; Fauchier et al., 2018). However, the optimal antithrombotic strategies have not been adequately studied, which has aroused great concerns and heated discussions (Nakajima, 2022).

The present network meta-analysis, based on 10 observational studies involving 1,674 patients, observed no significant differences in the interested outcomes among all antithrombotic treatments. Furthermore, the SUCRA of our analysis indicated that DAPT was ranked the worst among all antithrombotic strategies due to the higher risk of stroke, DRT, and major bleeding events, while VKAs were ranked the preferred antithrombotic strategy; in addition, the efficacy and safety of DOACs were appreciable for LAAO patients.

Although the results of a few studies illustrated the safety and efficacy of administering DAPT after LAAO, they remain inconsistent (Chun et al., 2013). The results of a subgroup analysis of five studies by Søndergaard et al. (2019) also showed that patients who received APT treatments reported more DRT events compared with those who received DOAC treatments after LAAO. Moreover, the use of VKA has been limited due to its high requirements for patient compliance, narrow therapeutic window, and interaction with multiple foods and drugs (Shendre et al., 2018). Furthermore, previous studies deduced that DOACs play an important role in the treatment of patients who underwent LAAO (Asmarats et al., 2020; Li et al., 2020). Several clinical trials have demonstrated the efficacy and safety of DOACs in preventing post-PCI and stent thrombosis in NVAF patients and AF patients with coronary heart disease, particularly showing a lower incidence of major bleeding events than warfarin (VKA) (Cimmino et al., 2020). Therefore, DOACs are increasingly being used in antithrombotic strategies after LAAO. A multicenter, randomized, controlled trial comparing the efficacy and safety of apixaban (DOACs) and DAPT post-LAAO was conducted, which looked forward to adding evidence for the safety and efficacy of receiving DOACs or DAPT after LAAO (Flores-Umanzor et al., 2020).

Two landmark trials of LAAO, the PREVAIL trial and the PROTECT-AF trial, were published in 2014 and 2016, respectively, and mainly explored the efficacy and safety of using warfarin (VKA) as antithrombotic therapy in LAAO patients (Holmes et al., 2014; Main et al., 2016). These two large multicenter, randomized trials indicated that VKA followed by DAPT, was feasible for use in patients without anticoagulant contraindications post-LAAO. However, both the PROTECT-AF and PREVAIL trials did not enroll patients with contraindications and had controversial conclusions. Meanwhile, there is a lack of high-quality meta-analyses that explored different antithrombotic regimens. Meta-analyses, which have been published previously, included a total of 32 studies with 4,474 patients, indicating that DOACs have good prospects for development and may serve as alternatives to VKAs in the future. However, the study had several limitations that should not be overlooked; most of the studies included in the meta-analysis were single-arm studies and the level of evidence was not high; in addition, heterogeneity was analyzed, but no source of heterogeneity was identified for all-cause mortality (Li et al., 2020). Therefore, more extensive RCTs are needed to confirm the efficacy and safety of DOACs in post-LAAO patients. In summary, whether using VKAs or DOACs, the optimal antithrombotic strategy after LAAO requires extensive exploration.

In addition, to explore whether the device type plays an important role in postoperative outcomes during follow-ups, which remains controversial, we conducted a meta-regression in direct comparative subgroups using the proportion of the device type. The results of the subgroup meta-regression showed that the device type did not substantially influence the occurrence of thrombosis and bleeding events. Meanwhile, a real-world study compared the WATCHMAN and Amulet devices in an independent registry and concluded that the two devices showed similar efficacy and safety during long-term follow-ups (Saad et al., 2021).

Nevertheless, several limitations should be considered in this analysis. First, most of the studies enrolled in this network meta-analysis are observational studies. The lack of randomization in observational studies and poor transitivity among studies may lead to bias in the results of the network meta-analysis. Furthermore, most of the studies included reported event rates only based on the follow-up period, and we could not show the relationship between the events and time. In addition, there was a considerable gap in regard to the number of studies that included each antithrombotic regimen, and only one adapted study compared VKA and DAPT. Finally, this analysis just evaluated the efficacy and safety of different antithrombotic regimens, and the effect of individual drugs on postoperative outcome events was not considered.

5 Conclusion

Overall, no significant difference was found in the network meta-analysis among different antithrombotic strategies. Furthermore, the SUCRA indicated that DAPT is the worst antithrombotic strategy, while VKAs were the best. However, DOACs are a strategy worth considering due to their advantages of fixed-dose and no need for regular monitoring. This finding must be validated in larger prospective clinical studies.

Author contributions

HX, Z-CG, and Y-JZ are the guarantors of the entire manuscript. L-MW and YC contributed to the study conception and design, the critical revision of the manuscript for important intellectual content, and the final approval of the version to be published. L-LX, M-FD, Y-JK, B-YW, LZ, J-FZ, and Z-QW contributed to data acquisition, analysis, and interpretation. All authors contributed to the article and approved the submitted version.

Funding

The authors disclosed the receipt of the following financial support for the research, authorship, and/or publication of this article: this study was funded by the Project of Chinese Hospital Reform and Development Institute, Nanjing University, and the Aid Project of Nanjing Drum Tower Hospital Health, Education, and Research Foundation (NDYG2022050).

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/fphar.2023.1159857/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Case Report
PUBLISHED 06 September 2023
DOI 10.3389/fphar.2023.1246914

OPEN ACCESS

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RECEIVED 25 June 2023
ACCEPTED 28 August 2023
PUBLISHED 06 September 2023

CITATION
Soghomonyan N, Khachatryan H, Soghomonyan G and Fleming Q (2023), Thrombosis of portal, superior mesenteric, and splenic veins: a case report.
Front. Pharmacol. 14:1246914.
doi: 10.3389/fphar.2023.1246914

Thrombosis of portal, superior mesenteric, and splenic veins: a case report

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Patients with venous thrombosis of splanchnic circulation represent a group of high risk with significant morbidity and mortality, if treatment is delayed. We present a patient with thrombosis of portal vein and its tributaries combined with deep venous thrombosis (DVT) of the lower extremities who was successfully treated with conservative management. This patient case highlights the importance of early empiric anti-inflammatory therapy along with systemic anticoagulation to reduce the intestinal inflammation and enteritis and break the vicious circuit resulting in secondary progressive thrombosis of the splanchnic veins, fluid shifts, and functional ileus. *Case presentation*: A previously healthy 61-years-old female patient with no significant medical history was admitted with progressive upper abdominal pain, nausea and vomiting, low-grade fever, mild signs of ileus, and malaise. Imaging studies revealed portal venous dilation reaching ~20 mm with near-total obliteration of the lumen by a thrombus. In addition, thrombosis of superior mesenteric and splenic veins with thrombophlebitis was found. Imaging studies also confirmed the presence of DVT of lower extremities including thrombus propagation into the iliac veins. An immediate therapy was started with parenteral antibiotics, anti-inflammatory medications, systemic anticoagulants, and intravenous fluid infusions to restore the circulating volume deficit and treat electrolyte disbalance. With such therapy, the patient's symptoms resolved within a month, and she was discharged from the hospital with full recovery. Heparin infusion was started to reach systemic anticoagulation. With resolution of symptoms, anticoagulation was continued with warfarin. We used non-steroidal anti-inflammatory drugs (NSAIDs) as a component in management of intestinal and systemic inflammation and multifocal thrombosis when the antiphospholipid syndrome was also on the list of differential diagnoses. *Conclusion*: We present a previously asymptomatic patient with progressive portal venous thrombosis and ascending DVT. Early establishment of diagnosis and initiation of therapy with systemic anticoagulants, anti-inflammatory and antibacterial drugs helped to stop thrombus progression, prevent irreversible intestinal ischemia, and allow for re-canalization of the occluded veins. This case highlights the importance of early interventions to improve the treatment outcome.

KEYWORDS

portal venous thrombosis (PVT), intestinal ischaemia, anticoagulation, deep vein thrombosis (DVT), systemic inflammation

Introduction

The interplay of chronic disease, inflammation and coagulation with thrombosis has always been in the focus of researchers and practitioners taking care of critically ill patients. If left untreated, these processes may eventually result in hemorrhagic and thrombotic complications, disseminated intravascular coagulation (DIC), and multi-organ failure with high morbidity and mortality (Yanuck et al., 2019). Thrombosis of portal vein and its tributaries is a condition requiring immediate action to reduce the risk of serious complications as splanchnic infarction and organ perforation (Sanyal et al., 2022). Rarely, this complication takes place without any history of significant disease in the past, or it may manifest as an ongoing inflammatory disease.

We present a patient, who was admitted with signs of lower extremity DVT, abdominal discomfort, and functional ileus. Aside from the DVT, further examination revealed splanchnic venous thrombosis with progressive abdominal complaints. Immediate conservative treatment was initiated with antimicrobial, anti-inflammatory, and anticoagulant therapy as well as intravenous fluid replacement to restore the volume deficit and eliminate electrolyte disbalance.

This case presentation highlights the importance of systemic approach to this complex pathological condition requiring early diagnosis and immediate intervention to stop thrombus progression and allow for time to restoration of the venous blood flow thus preventing bowel infarction and perforation. The therapeutic goals included early anticoagulation with anti-inflammatory and antimicrobial treatment to counteract thrombus formation, intestinal inflammation to break the pathophysiological circuits resulting in secondary progressive thrombosis of the splanchnic vessels: portal, superior mesenteric, and splenic veins.

Case presentation

A previously healthy 61-years-old female patient with no significant past medical history was admitted with DVT, upper abdominal tenderness, nausea and vomiting, subfebrile fever, mild signs of ileus, and progressive malaise. The ultrasound examination revealed portal venous dilation with a diameter of 20 mm with a near-total occlusion of the lumen by intraluminal thrombi, presence of mild abdominal exsudation. The patient underwent an emergent abdominal computerized tomographic (CT) examination, which revealed thrombosis of portal, upper mesenteric, and splenic veins with small bubbles of gas located in the adipose tissue of the abdominal wall in the upper quadrant. Splenomegaly was excluded, but the splenic vein was dilated (11 mm) and entirely occluded by a longitudinal thrombotic mass with linear hypodense filling defect near the splenic hilum with a high probability of venous infarction. Identical changes were described in the superior mesenteric vein, the diameter of which reached 14 mm. Within the vein, there was a filling defect due to thrombotic occlusion with intraluminal thrombi involving larger venous mesenteric branches with a spread to smaller branches with adequate contrast filling. The remaining mesenteric and pancreatic veins were intact. There were no signs of cirrhosis or pancreatitis. The portal venous thrombi reached the intrahepatic venous branches including the bifurcation. The walls of all affected veins were markedly thickened, and overloaded portocaval anastomoses were observed. The patient's clinical symptoms correlated with the imaging data and were suggestive of portal hypertension and thrombophlebitis. The laboratory tests correlated with an acute inflammatory reaction with elevation of erythrocyte sedimentation rate (46 mm/h), C-reactive protein (218 mg/L), and D-dimer (10.8 μg/mL).

An immediate treatment was started to control progression of splanchnic thrombosis and avoid life-threatening complications. The following treatment was initiated without delay:

- ✓ Intravenous hydration to restore the fluid deficit, treat the electrolyte imbalance, and maintain adequate diuresis.
- ✓ Systemic wide-spectrum antibacterial therapy was started with intravenous ceftriaxone, 2.0 g/day combined with Metronidazole, 500 mg, three times a day. Once the urine cultures came back positive for hemolytic Streptococci sensitive to Amoxicillin and Ciprofloxacin, further antibiotic therapy was continued with these drugs for additional 2 weeks.
- ✓ Non-steroidal anti-inflammatory therapy was initiated with Ibuprofen 400 mg three times a day.
- ✓ Systemic anticoagulation with intravenous infusion of unfractionated heparin with a goal to maintain the international normalized ratio (INR) between 2.0–3.0. After resolution of symptoms with restoration of venous blood flow verified by imaging studies, further anticoagulation was continued with oral Warfarin 5 mg for 6 months with periodic monitoring of the coagulation status.

With provided therapy, the patient's symptoms gradually resolved, and the blood flow in splanchnic veins was re-established within a few days. In 3 days, once the clinical signs of ileus resolved, enteral feeding was started. The patient was discharged from the hospital with complete resolution of the symptoms. Her medical management was continued as an outpatient.

Serial clinical assessments, laboratory tests, ultrasound and CT imaging showed regression of portal hypertension and thrombophlebitis. Complete resolution of symptoms and return to normal daily activities became possible in 2 months after discharge from the hospital.

Discussion

Thrombosis of portal and other veins in the splanchnic system, if not diagnosed and treated in time, carries the risk of intestinal ischemia with perforation of the affected portions of gut creating a life-threatening situation. Etiologically, portal thrombosis is more commonly seen in patients with liver cirrhosis, systemic pro-thrombotic conditions, malignancies, and several other conditions (Sanyal et al., 2022).

The clinical picture varies with acuity of the process and the extent of occlusion. The patients may be completely asymptomatic or may complain on abdominal tenderness, have signs of developing

ileus, pancreatitis, variceal bleeding, etc. When mesenteric vessels are involved, the patients may develop a picture of overt mesenteric ischemia, infarction, peritonitis, and septic shock (Sanyal et al., 2022).

Early systemic anticoagulation to counteract the expansion of the venous thrombi and allow for recanalization of the major veins is the mainstay of therapy (Sanyal et al., 2022). It is also important to diagnose and treat the underlying conditions predisposing to venous thrombosis. Inflammatory bowel disease, infections, malignancy, systemic inflammatory reaction, antiphospholipid syndrome, pancreatitis, cirrhosis, hepato-portal sclerosis, and other conditions, including anatomical variants, may predispose or even trigger portal venous thrombosis (Beyazit et al., 2011; Talebi-Taher et al., 2018; Fan et al., 2019; Leitão et al., 2019). Our patient had no previous history of the above-mentioned pathologies, nevertheless, all of them were on our list of differential diagnoses. Laboratory tests and diagnostic studies were carried out to rule out autoimmune diseases, chronic infections, and malignancy. Since the patient presented with progressive signs of ileus and inflammation, systemic wide-spectrum antibiotics along with NSAIDs were given. Once the results of blood and urinary cultures became available indicating urinary infection with hemolytic Streptococci sensitive to Amoxicillin and Ciprofloxacin, further antimicrobial therapy was continued based on the microbial sensitivity. With improvement of symptoms and imaging evidence of partial recanalization of the portal and splanchnic venous blood flow, systemic anticoagulation was continued with warfarin.

While selecting the drug for chronic anticoagulation therapy, we considered the ample clinical experience and literature evidence on warfarin's efficacy for patients with portal thrombosis and cirrhosis. While there are reports of potential efficacy of direct oral anticoagulants in patients with cirrhosis, there are also reports suggesting decreased efficacy of rivaroxaban and apixaban in those patients (Elhosseiny et al., 2019; Sanyal et al., 2022). There are also concerns for increased risk of bleeding, especially, when used with NSAIDs, which are used to treat local and systemic inflammatory processes predisposing to vascular thrombosis.

In addition to restoration of portal venous blood flow, therapeutic measures helped to control the progressive DVT with occlusion of the iliac veins. As in our patient, the management of DVT of the lower extremities and inferior vena cava is mainly conservative and includes systemic anticoagulation, compression stockings and treatment of complications (Talebi-Taher et al., 2018). Some patients will benefit from placement of an IVC filter to decrease the risk of thromboembolism. Invasive surgical interventions with successful endovascular thrombectomy, stenting, and prosthetic replacement of the inferior vena cava have also been reported, even though the procedures are not without risk (Gwozdz et al., 2018; Wei et al., 2018; Che et al., 2019; Mityul et al., 2019; Wagenhäuser et al., 2019; Yang et al., 2019).

At 5-month follow-up, the patient remained asymptomatic. She continued receiving anticoagulant therapy. She used compression stockings and postural measures for her DVT. Repetitive imaging confirmed partial recanalization of the iliac veins.

Conclusion

Thrombosis of the portal vein and its branches is a serious complication and any delays in establishing the diagnosis and early intervention may be life-threatening. Pre-existing autoimmune disorders, malignancy, inflammatory bowel disease, infection, systemic inflammation with a surge in inflammatory cytokines should be considered as potential mechanisms for development of portal and splanchnic venous thrombosis. The time for diagnostic procedures should be minimized and therapeutic measures should be started early to avoid irreversible organ damage with increased morbidity and mortality. The presented patient case demonstrates that systemic anticoagulation along with anti-inflammatory and antimicrobial therapy, when an infectious etiology is suspected, helps to stop the thrombus progression, and allows for recanalization of the occluded veins. Timely interventions help to save lives and improve its quality.

Data availability statement

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

Ethics statement

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

NS and HK treated the patient, discussed the treatment plan with the other authors, and participated in preparation of the manuscript. GS conducted literature search, participated in medical discussions and writing of the manuscript. QF discussed the treatment plan with the responsible physicians taking care of the patient as an expert, led the team during the preparation of the manuscript as a senior author.

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 Pharmacology

TYPE Review
PUBLISHED 31 October 2023
DOI 10.3389/fphar.2023.1274214

OPEN ACCESS

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RECEIVED 08 August 2023
ACCEPTED 20 October 2023
PUBLISHED 31 October 2023

CITATION
Elias M, Gombert A, Siddiqui S, Yu S, Jin Z and Bergese S (2023), Perioperative utility of amisulpride and dopamine receptor antagonist antiemetics-a narrative review.
Front. Pharmacol. 14:1274214.
doi: 10.3389/fphar.2023.1274214

Perioperative utility of amisulpride and dopamine receptor antagonist antiemetics-a narrative review

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Despite advances in antiemetics and protocolized postoperative nausea vomiting (PONV) management, it remains one of the most common postoperative adverse events. In patients who developed PONV despite antiemetic prophylaxis, giving a rescue treatment from the same class of medication is known to be of limited efficacy. Given the widespread use of 5-HT3 antagonists as PONV prophylaxis, another class of effective intravenous rescue antiemetic is in dire need, especially when prophylaxis fails, and rescue medication is utilized. Dopamine antagonists were widely used for the treatment of PONV but have fallen out of favor due to some of their side effect profiles. Amisulpride was first designed as an antipsychotic medication but was found to have antiemetic properties. Here we will review the historical perspective on the use of dopamine receptor antagonist antiemetics, as well as the evidence on the efficacy and safety of amisulpride.

KEYWORDS

amisulpride, antiemetics, dopamine receptor antagonist, haloperidol, droperidol, post-operative nausea and vomiting

Introduction

Postoperative nausea and vomiting (PONV) is one of the most common adverse events to occur postoperatively, occurring in up to 30% of patients. In high-risk patients, this number can be as high as 70% (Gress et al., 2020). It is second only to postoperative pain in terms of the most common complaints by patients following surgery. Furthermore, it is a significant source of distress and patient dissatisfaction (Eberhart et al., 2002). With a growing trend towards ambulatory and same day surgeries, it is also a major source of delaying discharges from post-anesthesia care units (PACU) (Chatterjee et al., 2011). A single episode of PONV can delay discharge from the PACU by about 25 min (Habib et al., 2006). This can sometimes lead to unanticipated hospital admission and ultimately lead to an overall increase in healthcare costs (Hill et al., 2000). Being able to identify high-risk patients and treat them with the appropriate prophylaxis can greatly improve patient care and satisfaction.

Risk factors for PONV can typically be grouped into three categories: patient factors, type of anesthetic drug, and surgery-related factors. Patient-specific risk factors for PONV in adults are well established in the literature, with the Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting stating that female sex, non-smoking

status, young age, and a history of PONV/motion sickness all increase the risk of PONV. Anesthesia-related risk factors include the use of general versus regional anesthesia, postoperative opioid use, and the use of volatile anesthetics and nitrous oxide. Surgery-related factors include the duration of surgery and type of surgery being performed (laparoscopic, intra-abdominal, gynecologic) (Gan et al., 2020).

The Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting by Gan et al. (2020) state the following in terms of guidelines and recommendations for the prevention and management of PONV: 1) Identify Patients' Risk For PONV, 2) Reduce Baseline Risk For PONV, 3) Administer PONV Prophylaxis Using 2 Interventions in Adults at Risk for PONV, 4) Administer Prophylactic Antiemetic Therapy to Children at Increased Risk for POV/PONV; As in Adults, Use of Combination Therapy Is Most Effective, 5) Provide Antiemetic Treatment to Patients With PONV Who Did Not Receive Prophylaxis or When Prophylaxis Failed, 6) Ensure General Multimodal PONV Prevention and Timely Rescue Treatment Is Implemented in the Clinical Setting, 7) Administer Multimodal Prophylactic Antiemetics in Enhanced Recovery Pathways.

Weibel et al. (2020) conducted a network meta-analysis of antiemetic for PONV prevention, which found significant difference in the efficacy of available therapeutic options. Some monotherapy options such as aprepitant are of equivalent efficacy to the commonly used combination prophylaxis (ondansetron plus dexamethasone); while other antiemetics (such as metoclopramide and domperidone) have comparable efficacy to placebo. Thus, the choice of antiemetic may be just as important as the number of antiemetics that is administered.

Despite these robust guidelines and advances in antiemetics and protocolized PONV management, PONV remains one of the most common adverse postoperative events. In terms of rescue treatment of PONV after failure of prophylaxis, there are very few prospective trials on this topic. Therefore, there is limited evidence to guide clinical management. Moreover, administering rescue antiemetics from the same drug class in patients who have failed prophylaxis has been found to be ineffective, although very commonly practiced.

A 2022 systematic review on the rescue treatment of postoperative nausea and vomiting was conducted by Gan et al. (2022) to summarize the current evidence on this topic. Using the evidence from their review, they created an algorithm for the treatment of PONV in patients with and without prophylaxis. In patients who received no prophylactic antiemetics, 5-HT3 antagonists (ondansetron) remain first-line therapy for established PONV. If ondansetron was used as prophylaxis, it is not beneficial to re-administer ondansetron or another 5-HT3 antagonists unless it was given greater than 6 h prior to the episode of PONV. Although the optimal combination has not yet been established, it appears that combining antiemetics increases efficacy compared to a single agent. Last, if pharmacologic options fail, certain treatments such as acupuncture, acupressure, ginger, and aromatherapy can be considered, although there is a weak level of evidence behind this. They found the following antiemetics to be the most effective: dopamine antagonists (amisulpride 10 mg or droperidol 1.25 mg), 5-HT3 antagonists (ondansetron 4 mg, palonosetron 0.075 mg, granisetron 1 mg, ramosetron 0.3 mg, or tropisetron 0.5 mg), histamine antagonists (diphenhydramine 12.5 mg, dimenhydrinate 25 mg, or promethazine 6.25 mg), and propofol 20 mg bolus.

Before discussing dopamine receptor antagonist antiemetics in this chapter, it is important to briefly review the pathophysiology behind nausea and vomiting. The nucleus tractus solitarius, a region within the brainstem is the site that controls nausea and vomiting. It receives afferent inputs from multiple sources, such as the glossopharyngeal and vagus nerves, vestibular apparatus, cerebellum, and higher cortical centers. All these inputs further interact within the nucleus tractus solitarius as well as the chemoreceptor trigger zone in the floor of the fourth ventricle. The chemoreceptor trigger zone, also known as the area postrema, lies outside the blood-brain barrier and is in direct contact with the cerebrospinal fluid. This allows substances in the blood and cerebrospinal fluid to interact. These areas have been found to contain histamine (H1), serotonin (5-HT3), cholinergic (M1), neurokinin-1, and D2 dopamine receptors (Horn et al., 2014).

Regarding the antiemetics that are used for PONV prophylaxis, there are four major receptor systems involved: cholinergic (muscarinic), dopaminergic (D2), histaminergic (H1), and serotonergic (5-HT3). Neurokinin-1 (NK-1) receptors are also thought to be involved, as NK-1 antagonists such as aprepitant have been used for PONV. These different receptors can be found in areas that are responsible for nausea and vomiting. For example, there are cholinergic receptors in the vestibular nuclei as well as the vomiting centers. The area postrema contains dopamine, serotonin, and opioid receptors. The nucleus tractus solitarius contains μ-opioid receptor, histamine (H1), cholinergic (M1), and neurokinin-1 receptors (Gress et al., 2020). Finally, cannabinoid receptors (CB1) are also found in nucleus tractus solitaries and area postrema.

Since several pathways exist behind PONV, the current consensus guidelines recommend that high risk patients should be given a combination of antiemetics with different mechanisms of action (Weibel et al., 2020; Gan et al., 2022). When choosing an appropriate antiemetic, both the class of drug and the timing of administration should be considered. For example, steroids such as dexamethasone are effective when given prophylactically at the beginning of surgery, whereas 5-HT3 antagonists such as ondansetron are most effective when given 30 min before the end of anesthesia (Gan et al., 2020). This review will focus on dopamine receptor antagonist agents such as amisulpride, haloperidol, and droperidol.

Dopaminergic secantiemetics

Haloperidol

Haloperidol is a butyrophenone and typical antipsychotic approved by the Food and Drug Administration (FDA) in 1967 for the treatment of schizophrenia. Haloperidol has high levels of antagonism towards D2 receptors in the central nervous system, leading to its strong antipsychotic effects. At lower doses, haloperidol has also been used as an antiemetic, particularly in palliative care. This effect may be due to antagonism of dopaminergic receptors within the area postrema (Dağ et al., 2019). Within the body, haloperidol is confined to the blood with 90% bound to plasma due to its high intrinsic protein binding capacity. The half-life of haloperidol once administered is around 18 h. Once in the bloodstream, haloperidol undergoes metabolism

TABLE 1 Pharmacokinetics and notable side effects of dopamine receptor antagonist antiemetics.

Drug name	Volume of distribution	Metabolism	Half-life	Notable side effects
Haloperidol Kudo and Ishizaki, (1999)	9.5–21.7 L/kg	Hepatic	Oral: 14–37 h IM: 20 h IV: 14–26 h	Extrapyramidal Reaction, Parkinsonism, Abdominal Pain, Constipation, Drowsiness, Headache, Sialorrhea
Droperidol Cisewski et al., (2022)	1.5L/kg	Hepatic	IM: 2–4 h	Extrapyramidal Reaction, Dizziness, Neuroleptic Malignant Syndrome, Cardiac Arrhythmia, Prolonged QT interval, Laryngospasm, Bronchospasm
Amisulpride Rosenzweig et al., (2002)	5.8 L/kg	Undergoes minimal metabolism and its metabolites in plasma are largely undetectable	Oral: 12 h IV: 4–5 h	Infusion Site Pain, Hypokalemia, Increased Serum Prolactin, Hypotension

by the liver through glucuronidation, reduction, and oxidation by cytochrome P450, specifically as a substrate of CYP3A4, prior to excretion in bile (Table 1) (Kudo and Ishizaki, 1999).

Several studies have investigated the use of haloperidol as an antiemetic within the dose range of 0.5–4 mg. A 2004 meta-analysis of 15 studies and randomized controlled trials conducted between 1962 and 1988 found that both 1 and 2 mg intramuscular haloperidol were effective at limiting PONV 2–4 h after treatment at similar efficacy and with a similar side effect profile to 5-HT3 receptor antagonists (Büttner et al., 2004).

Haloperidol has been linked to several significant side effects, mostly at high doses. Because haloperidol is not selective for the D2 receptor and blocks other receptors such as cholinergic, noradrenergic, histaminergic receptors, it can cause a multitude of side effects (Gao et al., 2008). Like other typical antipsychotics, haloperidol may cause dopaminergic blockage of the substantia nigra. This can cause extrapyramidal side effects including acute dystonia, Parkinsonism, and tardive dyskinesia. Haloperidol, compared to other drugs in its class, has a high affinity to dopamine receptors, which has been linked to lower side effects overall but higher rates of extrapyramidal symptoms (Gao et al., 2008). Another complication of haloperidol is neuroleptic malignant syndrome (Dixit et al., 2013). Haloperidol also has been demonstrated to prolong the QT interval in a dose-dependent manner which may precipitate torsade de pointes. Torsade de pointes has been reported with intravenous, intramuscular and oral administration of haloperidol (Sharma et al., 1998). However, at lower doses such as the 1–2 mg recommended for PONV prophylaxis, haloperidol has lower toxicity. Buttner et al. reported zero records of cardiac adverse reactions and one case of extrapyramidal symptoms at 4 mg out of 1800 patients. The most significant side effect was increased sedation at 5 mg, with a relative risk of 2.09 (95% confidence interval, 1.73–2.52; number needed to treat, 4.4) (Büttner et al., 2004).

Droperidol

Droperidol is a butyrophenone and central dopamine antagonist approved by the FDA in 1970 for clinical use as an antiemetic and general anesthesia adjuvant, as well as an antipsychotic agent. It is an analogue of haloperidol with a shorter half-life and rapid sedating effects. Additionally, it possesses significant dopamine receptor antagonistic activity. Although its exact mechanism is unknown, droperidol's effects come from its high affinity for and selective inhibition of dopamine D2 receptors, resulting in reduced dopaminergic transmission within the four dopaminergic pathways. To a lesser extent, it is also thought to inhibit serotonin (5-HT3), muscarinic, and alpha-2 adrenergic receptors (Table 1) (McKeage et al., 2006).

Droperidol is primarily metabolized by the hepatic CYP3A4 system with inactive metabolites excreted via urine and feces. It has a rapid onset of 3–10 min, with a peak effect occurring at approximately 30 min. The elimination half-life of droperidol is between 2–4 h, however its sedative effects can be observed up to 12 h (Cisewski et al., 2022). The onset of its sedative effects is essentially identical when administered intravenously (IV) versus intramuscularly (IM), which provides clinical advantage when IV access is unobtainable. Droperidol has a high volume of distribution and is highly protein-bound, with up to 90% of it bound to plasma protein (Cisewski et al., 2022). Overall, droperidol is characterized by rapid distribution, extensive protein binding, hepatic metabolism, and a relatively short elimination half-life.

The efficacy of droperidol as an antiemetic for the prevention and treatment of PONV has been investigated across multiple studies. In 1998, a randomized, double-blind, placebo-controlled, multi-site study of 2061 adult surgical outpatients at high risk of PONV was carried out by Fortney et al. to observe the effects of droperidol at doses 0.625–1.25 mg in comparison to 4 mg ondansetron and a placebo as a preventative in PONV. Eligibility criteria were based on ASA physical status I or II, between the ages of 19- and 65-years old with a history of motion sickness or PONV after general anesthesia scheduled for outpatient surgery less than 2 h duration. Study patients were limited to those undergoing procedures with high emetogenic potential such as laparoscopic, genitourinary, lower extremity orthopedics, partial mastectomies, or lumpectomies. Individuals were randomly assigned to one of four treatments: placebo (normal saline), droperidol 0.625 mg, droperidol 1.25 mg, or ondansetron 4 mg. IV administration of the assigned drug was conducted 20 min prior to anesthesia induction. A complete response was defined as no emetic episodes and no requirement for rescue antiemetic medications. At 0–2 h postoperatively, a complete response was observed in

320 of 512 patients (63%) in the 0.625 mg droperidol group and 348 of 505 (69%) in the 1.25 mg droperidol group which was significantly higher compared to 236/510 (46%) in the placebo group ($p < 0.05$). The incidence of complete responses at 0–2 h was similar in the ondansetron and droperidol 0.625 groups (62% and 63%, respectively), but significantly greater in the droperidol 1.25 mg group (69%, $p < 0.05$). In the 0–24 h postoperative period, there was no significant difference in complete response between the ondansetron and droperidol 0.625 or 1.25 mg groups, however all groups remained superior to placebo (Fo et al., 1998).

The proportion of patients without nausea in the first 24 h postoperatively was significantly greater with droperidol 1.25 mg when compared with ondansetron 4 mg or droperidol 0.625 mg (43% vs. 29% or 29%, respectively). Rescue medication was used in 164 of 518 patients (32%) in the 0.625 mg droperidol group, 133 of 510 patients (26%), 174 of 515 patients (34%) in the 4 mg ondansetron group, and 235 of 518 patients (45%) in the placebo group. In regard to adverse event reporting and safety, there was no significant difference in adverse events in the droperidol groups compared to the ondansetron group (Fo et al., 1998). Overall, research suggests that 1–1.25 mg droperidol has comparable efficacy as 4–8 mg ondansetron but is significantly superior to placebo when preventing PONV (Fo et al., 1998).

Domino et al. (1999) compared the efficacy and safety of droperidol, ondansetron, and metoclopramide in preventing PONV in meta-analysis. Droperidol was found to be 34% more effective than metoclopramide in reducing postoperative nausea (pooled OR 0.66, 95% CI 0.48, 0.90; $p = 0.008$). Droperidol was 32% more effective than metoclopramide in reducing postoperative vomiting (pooled OR 0.68, 95% CI 0.54, 0.85; $p < 0.001$). Droperidol was found to be equally effective as metoclopramide in preventing postoperative nausea (Pooled OR 0.99); however, ondansetron was found to be 30% more effective than droperidol in preventing postoperative vomiting (pooled OR 0.70, 95% CI 0.52, 0.94; $p = 0.018$). Furthermore, the study recognized that data was substantially variable across studies that compared efficacy of ondansetron and droperidol (Domino et al., 1999).

When comparing the efficacy of odansetron-droperidol combination therapy versus monotherapy in treating PONV, Matsota et al. (2015) found that combination therapy is superior to monotherapy of either drug alone. 127 patients who underwent laparoscopic cholecystectomy while under general anesthesia were included in this study and assigned to Group D (droperidol only), O (ondansetron only), or D + O (droperidol plus ondansetron). Researchers found that throughout the 24-h study period, 35 patients experienced vomiting in group D, 30 in group O and 11 in group D + O [(D + O vs. D, $p < 0.05$), (D + O vs. O, $p < 0.05$)]. Their analysis also revealed that the combination therapy was significantly more effective than monotherapy of agents alone in preventing PONV at 30 min, 3 h and 6 h postoperatively (Matsota et al., 2015).

In a 2022 systematic review of rescue treatment of PONV by Gan et al. (2022), 1–1.25 mg of droperidol demonstrated similar efficacy to 4–8 mg ondansetron in prophylaxis naïve patients. Droperidol was also suggested to be superior to dexamethasone and metoclopramide in these studies, however risks of bias may outweigh these findings.

In 2001, FDA to issue a black box warning due to concerns over the proarrhythmic risks of droperidol. Droperidol was specifically thought to be associated with dose dependent prolonged QTc and torsade de pointes (McKeage et al., 2006). However, various retrospective studies disclosed that there is insufficient evidence to support the FDA's issued warning against the use of the cost-effective drug. Under the Freedom of Information Act, researchers in the Department of Anesthesiology at Duke University reviewed all individual case reports that led to the issuance of the black box warning on droperidol. They determined only 10 cases in which serious cardiovascular events were reported at appropriate doses of 1.25 mg or less. A review of the case reports revealed multiple confounding factors in each case that show no definitive causation to the adverse cardiac event (Habib and Gan, 2003). Most deaths associated with cardiac arrythmias occurred at doses ranging from 25 to 250 mg (White, 2002). However, clinicians are still weary to reimplement the use of droperidol back into their practice.

As with most typical antipsychotics, extrapyramidal symptoms can be observed as a side effect of droperidol use. These include akathisia, tardive dyskinesia, tremors, and muscle rigidity. Additional side effects associated with the use of droperidol include hypotension, sedation, restlessness, dysphoria, and anxiety (Habib and Gan, 2003).

Amisulpride

Amisulpride is a selective antagonist of dopamine D2 and D3 receptors. It belongs to the benzamide atypical antipsychotic drug class. It has a much higher affinity for dopamine receptors compared to other receptors, such as serotonin or histamine receptors. This selectivity is thought to be responsible for its relatively lower incidence of side effects compared to other antipsychotic medications such as haloperidol and droperidol. Amisulpride displays linear pharmacokinetics, has a bioavailability of 48%, displays low protein binding (17%), and has an elimination half-life of approximately 12 h. It is predominantly eliminated in the urine as the parent compound (Table 1) (Rosenzweig et al., 2002).

Depending on the dose of amisulpride, it can preferentially block presynaptic D2/D3 receptors versus postsynaptic D2/D3 receptors. Low doses preferentially block presynaptic receptors (enhancing dopaminergic transmission) whereas higher preferentially block postsynaptic receptors (inhibiting dopaminergic hyperactivity) (Rosenzweig et al., 2002). This makes it useful at targeting the negative symptoms of schizophrenia at lower dosages of 50–300 mg/day and the positive symptoms at higher dosages of 400–800 mg/day.

Amisulpride has been used orally for the past 30 years in Europe for psychotic disorders such as schizophrenia. At doses between 50–1,200 mg/day, it has a relatively benign safety profile, even in chronic usage (Rein et al., 2000). The effect of amisulpride on the QT interval and consequent risk of Torsades de pointes appear to be minimal other than at extreme overdoses. At doses up to 300 mg/day, its extrapyramidal side effects did not occur more frequently than placebo (Joy et al., 2011). Recently, an injectable form of the drug (single 5 mg IV dose) was shown to be effective at preventing PONV. It did not have more toxicity than placebo and did not prolong the QT interval enough for it to be clinically relevant,

according to a randomized, double-blinded, placebo-controlled, multi-center trial published in 2013 (Kranke et al., 2013).

Since then, there have been several randomized, double-blinded, placebo-controlled trials demonstrating the effectiveness of amisulpride in the prevention of PONV in high risk patients, such as a study published in 2018 by Kranke et al. (2018). In their study, they conducted a randomized, double-blinded, placebo-controlled, international multicenter trial in 1,145 adult surgical patients. These patients had three or four risk factors for PONV, as described in the Fourth Consensus Guidelines (Weibel et al., 2020) (female sex, non-smoking status, young age, and a history of PONV/motion sickness as the main risk factors). Patients were randomized to either receive placebo or 5 mg intravenous amisulpride, at the induction of general anesthesia, in addition to one standard, non-dopaminergic anti-emetic (most commonly ondansetron or dexamethasone). The following was recorded for up to 24 h after wound closure: nausea, retching/vomiting, and the use of rescue medication. The primary endpoint of the study was a complete response, which was described as no emesis or rescue medication use for up to 24 h in the postoperative period.

A complete response was observed in 330 of 572 patients (57.7%) in the amisulpride group and 268 of 575 patients (46.6%) of the control group. This was a difference of 11.1%, with a 95% 5.3–16.8, $p < 0.001$. The incidence of emesis was 13.8% in the amisulpride group versus 20.0% in the control group, $p = 0.003$. Nausea was seen in 50% of the amisulpride group, compared to 58.3% of the control group, $p = 0.002$. Rescue medication was used in 40.9% of the amisulpride group, versus 49.4% of the control group, $p = 0.002$. There were statistically significant differences seen in all the endpoints of the study when comparing the amisulpride to the control group. In terms of adverse events, laboratory and electrocardiogram abnormalities occurred no more frequently in the amisulpride group when compared to the control group. The conclusion of the study was that amisulpride was safe and effective as prophylaxis of PONV when given in combination with an antiemetic from a different class to high-risk adult patients undergoing elective surgeries under general anesthesia with inhalational agents (Kranke et al., 2018).

Several other studies have also concluded the safety and efficacy of amisulpride as not only an agent that can be used for prevention of PONV, but also as a rescue treatment. A systematic review and meta-analysis published by Zhang et al. (2020) in 2020 concluded that intravenous amisulpride was safe and efficacious for the prevention and treatment of PONV compared to placebo.

Habib et al. (2019) conducted a randomized, placebo-controlled phase III clinical trial in 2019 investigating the efficacy of amisulpride as a rescue therapy after failed prophylaxis. The study included over 2,200 surgical patients with moderate to high PONV risks, undergoing open and laparoscopic surgeries. Patients were given standard PONV prophylaxis, with the majority of patients receiving ondansetron or dexamethasone. Patients experiencing PONV within 24 h of surgery were randomized to receive a single dose of 5 or 10 mg intravenous amisulpride or matching placebo. Results showed a higher level of response, measured by incidence of post operative emesis and use of rescue medication within 24 h, in patients given the 10 mg dose of intravenous amisulpride as compared to placebo (41.7% vs. 28.5%; $p = 0.006$), and no significant difference between the group given the 5 mg dose compared to placebo (33.8%; $p = 0.109$). Total number of adverse events were similar between groups. The conclusion of the study was that 10 mg intravenous amisulpride was safe and efficacious for the prevention and treatment of PONV compared to placebo.

A 2019 randomized, double-blinded, placebo-controlled study conducted by Candiotti et al. (2019) investigated amisulpride as a rescue option for patients who received no prior PONV prophylaxis. The study included 1988 men and women aged over 18 years undergoing inpatient and outpatient procedures under inhalational anesthesia, selecting for patients who had low to moderate risks for PONV. Five hundred and sixty patients experienced PONV and were randomized equally to placebo or 5 or 10 mg amisulpride administered intravenously. The primary efficacy end point was complete response, defined as no episodes of emesis or use of rescue medication within 24 h after administration of study medication. Results showed complete response in 31.4% in both the amisulpride 5 and 10 mg groups compared to 21.5% in placebo ($p = 0.016$). The adverse event profile of amisulpride at either dose was similar to placebo.

Notably, the two studies differed in their conclusion regarding 5 mg dose as PONV rescue treatment, with Candiotti et al. (2019) reporting significantly higher efficacy over placebo, while Habib et al. (2019) found no significant difference. There are several possible explanations for the differing results, including the higher baseline PONV risks in Habib's patient cohort, as well as the PONV prophylaxis they received.

In 2017, two concurrent, randomized, double-blind, placebo-controlled trials were investigated by Gan et al. (2017). The authors found that nausea occurred less often in patients who received amisulpride compared to placebo in at least one of the trials (46.9% vs. 33.8%, $p = 0.026$; 57.6% vs. 46.6%, $p = 0.070$). Furthermore, in terms of safety profile, there were no differences in terms of QT prolongation, extrapyramidal side effects, or sedation in the amisulpride versus placebo arms. Moreover, in one of the two trials, they found that amisulpride was superior to placebo in reducing the incidence of PONV in moderate to high-risk patients. Further studies investigated the side effect in safety profile, such as a 2021 randomized, double-blind, placebo-controlled study of healthy volunteers conducted by Fox et al. (2021), which concluded that a single 10 mg dose of IV amisulpride does not have a clinically significant effect on the QT interval, when given alone or in combination with ondansetron.

There is robust literature supporting the efficacy and safety profile of amisulpride for PONV prophylaxis as well as rescue treatment in adult patients (Rein et al., 2000; Joy et al., 2011; Kranke et al., 2013; Gan et al., 2017; Kranke et al., 2018; Candiotti et al., 2019; Habib et al., 2019; Zhang et al., 2020; Fox et al., 2021). Further studies need to be conducted to evaluate the efficacy and safety profile of amisulpride for PONV in the pediatric population. Currently, there is a need for randomized, double-blinded, placebo-controlled studies in the pediatric population.

Other dopamine receptor antagonist antiemetics

When discussing the efficacy of antiemetics that antagonize dopamine receptors, it is notable to mention the marginally used therapeutics promethazine, perphenazine, prochlorperazine, and metoclopramide. Promethazine is a phenothiazine derivative with

antidopaminergic, antihistamine, and anticholinergic properties. Prochlorperazine is also a phenothiazine derivative with similar properties to that of promethazine. Promethazine and prochlorperazine function as direct antagonists at the mesolimbic dopamine receptors and alpha-adrenergic receptors in the brain. Additionally, promethazine acts as an H1-receptor blocker, exhibiting antihistamine effects (Sharma and Hamelin, 2003; Tan et al., 2010).

Perphenazine, a piperazine phenothiazine derivative, operates through postsynaptic inhibition of dopamine receptors. It exerts central and peripheral nervous system effects by stimulating alpha adrenergic receptors and inhibiting histamine and serotonin receptors. Perphenazine has a substantial first-pass effect resulting in a bioavailability of only about 40%. Approved as an antipsychotic medication in 1957 in the United States, it has been largely supplanted by atypical antipsychotics due to their more favorable side effect profile (Hartung et al., 2015).

Metoclopramide is another dopamine receptor antagonist which has been used as an antiemetic and prophylactic agent for postoperative nausea and vomiting for over 40 years. While extrapyramidal side effects are rare at typical doses (10 mg or less), higher doses are often required for effective antiemetic action. Consequently, it is not as frequently employed as other agents in preventing postoperative nausea and vomiting (Henzi et al., 1999).

Conclusion

Appropriately screening patients for PONV risk factors and treating them with the appropriate prophylaxis and rescue treatment if needed is an integral component to providing anesthesia care. Despite advances in antiemetics and protocolized postoperative nausea vomiting (PONV) management, it remains one of the most common postoperative adverse events. In patients with multiple risk factors for PONV, this number has been reported to be as high as 70% (Gress et al., 2020). It is a significant source of distress, patient dissatisfaction, delaying discharges from post-anesthesia care units, increases in healthcare costs, and a cause of unanticipated hospital admission (Hill et al., 2000; Eberhart et al., 2002; Chatterjee et al., 2011; Gan et al., 2020).

Current consensus guidelines support the use of multimodal PONV prophylaxis in patients who are at high risk (one or two risk factors or greater) in attempts to reduce the risk of inadequate prophylaxis. Multimodal therapy should consist of drugs from different classes, while utilizing the minimum effective doses. Patient factors, drug availability, and institutional policy will guide what medications are utilized. In children, it is recommended to use a 5-HT3 receptor antagonist such as ondansetron plus dexamethasone, while also minimizing opioids and volatile anesthetics (Weibel et al., 2020).

Although dopamine receptor antagonist agents such as haloperidol and droperidol demonstrate efficacy in PONV prophylaxis, they have undesirable side effects at higher doses, such as excessive sedation, extrapyramidal symptoms, neuroleptic malignant syndrome, torsades de pointe, hypotension, dysphoria (Sharma et al., 1998; Habib and Gan, 2003; Gao et al., 2008; Dixit et al., 2013). Amisulpride, a selective D2 and D3 receptor antagonist has been extensively studied in its use in PONV prophylaxis and treatment. In several studies it displayed superior efficacy when compared to placebo (Habib et al., 2019), while having minimal side effects (Fox et al., 2021). Amisulpride is a safe and effective agent for PONV prophylaxis and rescue treatment in established PONV in the adult population. In the pediatric population, the literature is sparse and further studies should be conducted to evaluate its safety and efficacy when used for PONV prophylaxis and rescue treatment.

Author contributions

ME: Writing–original draft, Conceptualization. AG: Writing–original draft. SS: Writing–original draft. SY: Writing–original draft. ZJ: Conceptualization, Writing–review and editing. SB: Conceptualization, Supervision, Writing–review and editing.

Funding

The authors 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.

The authors declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 14 November 2023
DOI 10.3389/fphar.2023.1270787

OPEN ACCESS

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RECEIVED 01 August 2023
ACCEPTED 31 October 2023
PUBLISHED 14 November 2023

CITATION
Xu Y-P, Lu X-Y, Song Z-Q, Lin H and Chen Y-H (2023), The protective effect of vagus nerve stimulation against myocardial ischemia/reperfusion injury: pooled review from preclinical studies. *Front. Pharmacol.* 14:1270787. doi: 10.3389/fphar.2023.1270787

The protective effect of vagus nerve stimulation against myocardial ischemia/reperfusion injury: pooled review from preclinical studies

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Aims: Myocardial ischemia-reperfusion (I/R) injury markedly undermines the protective benefits of revascularization, contributing to ventricular dysfunction and mortality. Due to complex mechanisms, no efficient ways exist to prevent cardiomyocyte reperfusion damage. Vagus nerve stimulation (VNS) appears as a potential therapeutic intervention to alleviate myocardial I/R injury. Hence, this meta-analysis intends to elucidate the potential cellular and molecular mechanisms underpinning the beneficial impact of VNS, along with its prospective clinical implications.

Methods and Results: A literature search of MEDLINE, PubMed, Embase, and Cochrane Database yielded 10 articles that satisfied the inclusion criteria. VNS was significantly correlated with a reduced infarct size following myocardial I/R injury [Weighed mean difference (WMD): 25.24, 95% confidence interval (CI): 32.24 to 18.23, $p < 0.001$] when compared to the control group. Despite high heterogeneity (I^2 = 95.3%, $p < 0.001$), sensitivity and subgroup analyses corroborated the robust efficacy of VNS in limiting infarct expansion. Moreover, meta-regression failed to identify significant influences of pre-specified covariates (i.e., stimulation type or site, VNS duration, condition, and species) on the primary estimates. Notably, VNS considerably impeded ventricular remodeling and cardiac dysfunction, as evidenced by improved left ventricular ejection fraction (LVEF) (WMD: 10.12, 95% CI: 4.28; 15.97, $p = 0.001$) and end-diastolic pressure (EDP) (WMD: 5.79, 95% CI: 9.84; –1.74, $p = 0.005$) during the reperfusion phase.

Conclusion: VNS offers a protective role against myocardial I/R injury and emerges as a promising therapeutic strategy for future clinical application.

KEYWORDS

myocardial I/R injury, vagus nerve stimulation, cardioprotection, meta-analysis, molecular mechanisms

Introduction

Myocardial infarction (MI) remains a primary global cause of mortality and disability. Prompt and successful reperfusion of the ischemic myocardium through thrombolytic therapy or primary percutaneous coronary intervention is the most efficacious strategy to salvage ischemic myocardium, mitigate myocardial injury, and enhance clinical outcomes (Hausenloy and Yellon, 2013). However, the process of myocardial reperfusion may trigger cardiomyocyte death and exacerbate cardiac dysfunction. This paradoxical occurrence, known as myocardial ischemia/reperfusion (I/R) injury, curtails the beneficial effects of revascularization strategies (González-Montero et al., 2018; Yang, 2018). While the exact molecular mechanisms of reperfusion-related cardiomyocyte death remain not fully clarified, it thus implicates a pressing need for deep exploration and succedent unmarked novel therapeutic targets (Piper et al., 1998).

Vagus nerve stimulation (VNS) was originally employed for treating refractory epilepsy and depression, leveraging its potential advantages in autonomic neuromodulation (George et al., 2007; González et al., 2019). Subsequent research has increasingly suggested that VNS can also confer protection against heart failure progression, due to the restoration of autonomic balance, baroreceptor sensitivity, and electrical stability (Capilupi et al., 2020; Verrier et al., 2022; Elamin et al., 2023). Recent studies have progressively unveiled the role of VNS in mitigating myocardial I/R injury through the activation of the cholinergic anti-inflammatory pathway, anti-oxidative stress response, or anti-apoptotic response (Chen et al., 2020; Wang et al., 2020; Deng et al., 2022). However, the intricate mechanisms underlying VNS-mediated cardioprotection in experimental studies, along with limited clinical evidence, pose obstacles to its broader application in clinical practice.

Hence, a comprehensive systematic review and meta-analysis are warranted to evaluate the effectiveness of VNS during myocardial I/R injury and provide a deeper understanding of the underlying mechanisms of this therapeutic approach.

Materials and methods

Search strategy

We conducted a systematic literature search for animal studies assessing the cardioprotection of VNS in myocardial I/R injury in MEDLINE, PubMed, Embase, and Cochrane Database from the inception to July 2023, with no language restriction. The following search terms were used: “myocardial ischemia/reperfusion injury” OR “myocardial I/R injury” OR “myocardial ischemia-reperfusion injury” AND “vagal nerve stimulation”. Moreover, we searched the references of comments, meeting abstracts, and review articles for additive studies.

Inclusion and exclusion criteria

Studies were included based on the following criteria: (a) reported the infarct size measured by triphenyl tetrazolium chloride (TTC) and Evan’s blue double staining method, (b) analyzed intervention received VNS treatment merely; comparator intervention received or no treatment, (c) with no cardiovascular-related comorbidity. We excluded studies that did not express infarct size as the percentage of infarct area over the area at risk (AAR) or did not quantify the ischemic area by Evans blue/TTC staining.

Data extraction

The data were extracted independently by two authors (Yu-Peng Xu and Xin-Yu Lu) from included studies, with discrepancies resolved by consensus. The following details were recorded in Table1: (1) studies’ information, including first author’s name, country, year of publication number of included animals, and duration of I/R injury; (2) animals’ characteristics, including species, gender and anesthetics; (3) the vagal nerve stimulation protocol, including stimulation site, duration, parameters and heart rate reduction; (4) methods for determining the infarct size. The results were expressed in terms of mean and standard deviation to minimize publication bias. The digital ruler software was used to measure the value when some data were only represented by graphs.

Quality assessment

Two reviewers independently evaluated and graded the quality of included studies based on published criteria for animal experiments. One point for each of the following: a peer-reviewed publication, random allocation to groups, blinded assessment of outcome, sample size calculation, compliance with animal welfare regulations, and a statement of a potential conflict of interest. Any discrepancies were arbitrated by a third reviewer.

Statistical analysis

All outcome data were treated as continuous variables in this meta-analysis, presented as the mean and standard deviation. DerSimonian and Laird random effects meta-analysis was used to measure the WMD and the related 95%CIs. Heterogeneity between studies results was evaluated by Cochran’s Q test and quantified by I^2 statistics test. Begger’s and Egger’s test was used to assess the potential publication bias.

Results

A total of 61 studies were initially screened and 10 studies comprising 238 animals matched the inclusion criteria for further quantitative analysis (Figure 1). Of these, 123 animals were treated with VNS and 115 animals were treated with control therapy. Cohort characteristics were presented in Table 1. Half of the studies used rodents with the remaining used rabbits, dogs and

TABLE 1 Characteristics of included studies, animals and VNS treatment.

Author	Year	Country	Animals	Sample size		I/R duration	Anesthetic agent	Infarct size measurement	VNS protocols			
				Control	VNS				Site of stimulation /Duration	Parameters	HR reduction	Timing of VNS
Bruno et al.Buchholz et al. (2015)	2015	Argentina	Rabbits, NZ, M	10	20	30min/3 h	Pentobarbital	Evans blue/TTC	RVN, 10m, int or con	0.1 m, 10HZ	10%–20%	10min before ischemia
Nederhoff et al.Nederhoff et al. (2019)	2019	Netherland	Mice, C57BL/6, M	19	18	30min/48 h	Fentanyl/Dormicum	Evans blue/TTC	RVN, 30s, con	0.5 m, 10HZ	15%	10min before ischemia
Krekwit et al.Shinlapawittayatorn et al. (2013)	2013	Thailand	Swines	8	16	60min/2 h	Zoletil/Xylazine	Evans blue/TTC	LVN, 3h, int or con	0.5 m, 20HZ	NA	0min after ischemia
Chen et al.Chen et al. (2016)	2016	China	Dogs, mongrel, M	12	9	60min/1 h	Pentobarbital	Evans blue/TTC	LVN, 2h, con	0.1 m, 20HZ	NA	0min after ischemia
Wang et al. (Wang et al., 2014)	2014	China	Rats, SD, M	20	20	30min/2 h	Pentobarbital	Evans blue/TTC	RVN, 30min, con	2.0 m, 10 Hz	10%	15min after ischemia
Zhao et al.Zhao et al. (2013)	2013	China	Rats, SD, M	8	8	60min/2 h	Pentobarbital	Evans blue/TTC	RVN, 3.25h, con	1.0 m, 5HZ	10%	15min before ischemia
Calvillo et al.Calvillo et al. (2011)	2011	Italy	Rats, SD, M	13	6	30min/24 h	Isoflurane	Evans blue/TTC	RVN, 24.7h, con	0.5 m, 8-10HZ	10%	5min before ischemia
Yi et al. (Yi et al., 2016)	2015	China	Rats, SD, M	12	12	30min/4 h	Pentobarbital	Evans blue/TTC	RVN, 30min, con	0.2 m, 10HZ	10%	15min after ischemia
Nuntaphum et al.Nuntaphum et al. (2018)	2018	Thailand	Swines	6	6	60min/2 h	Zoletil/Xylazine	Evans blue/TTC	LVN, 3h, int	0.5 m, 20HZ	NA	0min after ischemia
Krekwit et al.Shinlapawittayatorn et al. (2014)	2014	Thailand	Swines	7	8	60min/2 h	Zoletil/Xylazine	Evans blue/TTC	LVN, 2.5h, int	0.5 m, 20HZ	NA	30min after ischemia

VNS, vagus nerve stimulation; I/R, ischemia/reperfusion; SD, Sprague-Dawley rats; NZ, new zealand rabbit; M, male; RVN, right vagus nerve stimulation; LVN, left vagus nerve stimulation, TTC, triphenyl tetrazolium chloride; HR, heart rate; con, continuous; int, intermittent; NA, none available.

10.3389/fphar.2023.1270787

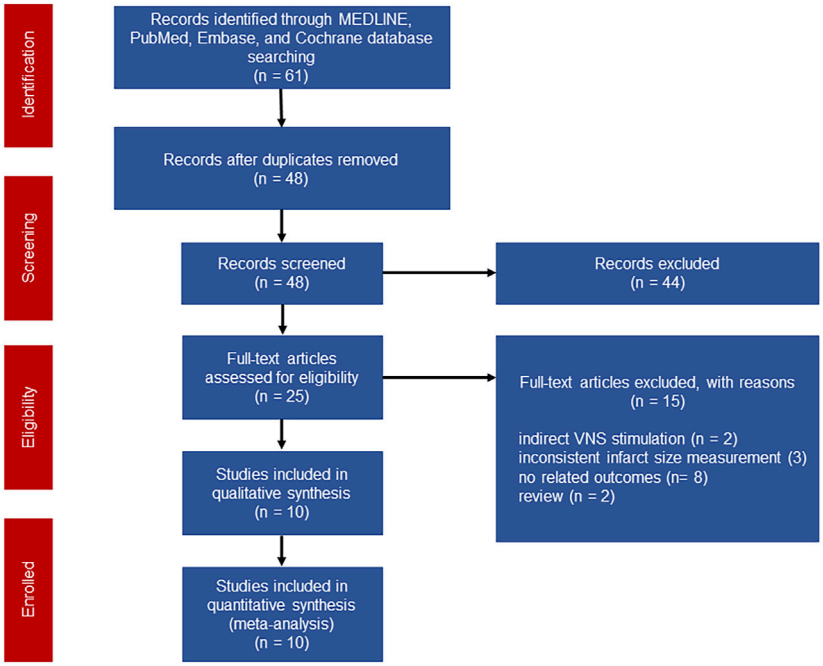

FIGURE 1
Flow chart of the literature screening.

TABLE 2 The underlying mechanisms involved in the protective effects of VNS against myocardial I/R injury.

Studies	Year	Proposed mechanisms
Bruno et al	2015	Consistent vagal stimulation: co-activation of the sympathetic nervous system Intermittent vagal stimulation: activation of the Akt/GSK-3β signaling pathway
Nederhoff et al	2019	A less inhibiting effect on inflammatory responsiveness
Krekwit et al	2013	Prevent mitochondrial dysfunction during myocardial I/R
Chen et al	2016	inhibiting oxidative stress and reducing cellular apoptosis
Wang et al	2014	Alleviating inflammatory responsiveness in early phase of myocardial I/R
Zhao et al	2013	Endothelial function and structure protection, anti-inflammatory activity via STAT3 signaling and NF-κB cascade
Calvillo et al	2011	anti-inflammatory and anti-apoptotic activity
Yi et al	2015	Restraining inflammatory cytokines, oxidative stress and apoptosis via IL-17A
Nuntaphum et al	2018	Attenuation of mitochondrial dysfunction, oxidative stress, apoptosis and metabolic abnormalities
Krekwit et al	2014	Protect mitochondrial integrity by mitigating cytochrome c induced apoptosis

VNS, vagus nerve stimulation; I/R, ischemia/reperfusion.

swine. Continuous, right cervical vagal trunk stimulation was conducted in most of enrolled studies for VNS, the remaining studies performed VNS in left vagal nerve with either continuous or intermittent regimen. The parameters of VNS varied substantially among the studies. The majority of studies reported a 10%–20% heart rate reduction during the procedure to guarantee the biological effect of VNS. Additionally, the potential mechanisms of action of VNS in myocardial I/R injury were detailed in Table 2, predominantly involving anti-inflammatory, oxidative stress, mitochondrial dysfunction anti-apoptosis.

Infarct size

Data on infarct size were available in 10 studies. VNS was associated with a dramatic reduction of infarct size assessed by Evans blue/TTC staining post myocardial I/R injury (WMD: 25.24, 95% CI: 32.24 to −18.23, $p < 0.001$, Figure 2), accompanied by high heterogeneity ($I^2 = 95.3\%$, $p < 0.001$). There was no evidence of publication bias according to Begg's and Egger's test. Subsequent sensitivity analysis utilizing the one-study-omit method showed similar findings (Table 3). In addition, stratified analysis according to vagal stimulation site, duration, animal species and

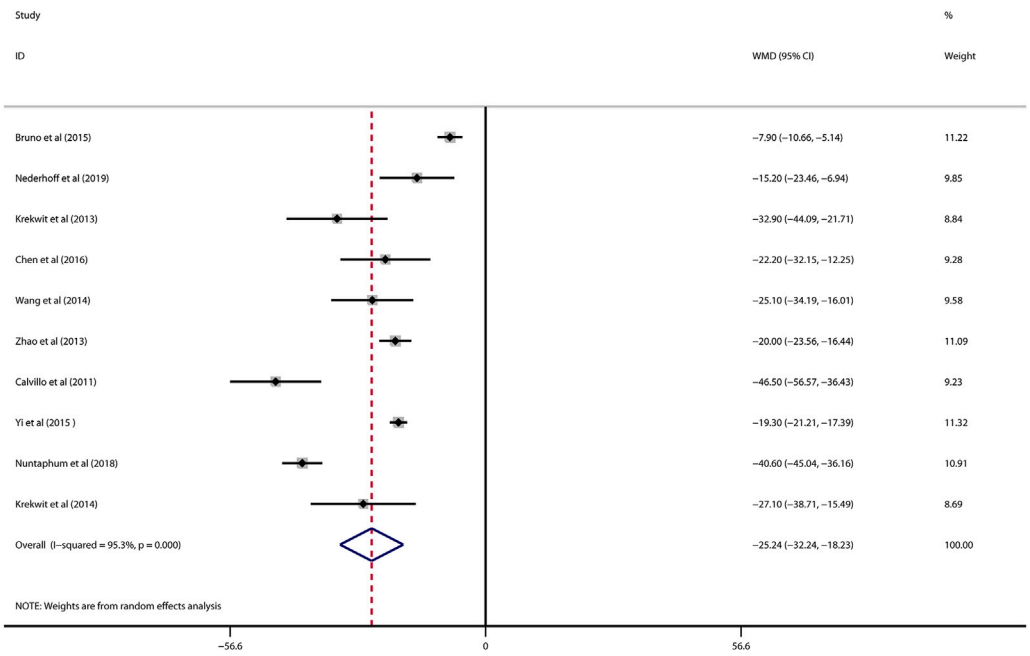

FIGURE 2
Forest plot of infarct size for VNS treatment against myocardial I/R injury. VNS, vagus nerve stimulation.

TABLE 3 Sensitivity analysis for pooled estimates of infarct size by leaving each study out.

Omitted studies	Pooled estimate	95% CI	*p*-Value
Buchholz et al. (2015)	−27.375332	−34.116432; −20.634233	<0.001
Nederhoff et al. (2019)	−26.351851	−33.873882; −18.829815	<0.001
Shinlapawittayatorn et al. (2013)	−24.491714	−31.822363; −17.161068	<0.001
Chen et al. (2016)	−25.56126	−33.027866; −18.094656	<0.001
Wang et al. (2014)	−25.26421	−32.741207; −17.787214	<0.001
Zhao et al. (2013)	−25.974266	−34.273678; −17.674858	<0.001
Calvillo et al. (2011)	−23.037252	−29.975634; −16.098871	<0.001
Yi et al. (2016)	−26.155228	−35.789894; −16.520563	<0.001
Nuntaphum et al. (2018)	−22.940166	−28.790264; −17.090067	<0.001
Shinlapawittayatorn et al. (2014)	−25.065401	−32.455986; −17.674816	<0.001
Combined	−25.235	−32.238; −18.232	<0.001

CI, confidence interval.

state region and myocardial I/R regimen did not influence the efficacy results of infarct size after I/R assaults (Table 4). Further meta-regression also did not reveal any interaction between the pre-specified covaries and VNS-mediated reduction in myocardial I/R damage (Table 5).

Cardiac function

Data on left ventricular ejection fraction (LVEF) was available in 4 studies. VNS was associated with a significantly improved systolic function after myocardial I/R injury (WMD: 10.12, 95% CI: 4.28 to 15.97, $p < 0.001$, Figure 3), with high heterogeneity ($I^2 = 71.6\%$, $p < 0.001$). Data on left ventricular end-diastolic pressure (LVEDP) were available in 5 studies. In accordance with the results for LVEF, there was also a significantly diminished LVEDP in VNS treated group (WMD: 5.79, 95% CI: 9.84 to −1.74, $p = 0.005$, Figure 4), despite high heterogeneity ($I^2 = 90.2\%$, $p < 0.001$). One-study-omit sensitivity analysis presented similar results (Table 6). Moreover, there were no signs of any correlation between the pre-specified covaries and both pooled estimates for LVEF and LVDEP, respectively (Table 7).

TABLE 4 Subgroup analysis for pooled estimates of infarct size according to vagal stimulation site, duration, animal species, state region and myocardial I/R regimen.

Pooled estimates	No. of studies	WMD (95% CI)	*p*-Value
VNS type			
Intermittent	4	−32.49 (−44.51; −20.47)	<0.001
Consistent	8	−19.23 (−31.91; −6.55)	0.003
Site of vagus nerve			
RVN	6	−21.24 (−28.15; −14.33)	<0.001
LVN	4	−31.38 (−40.97; −21.79)	<0.001
VNS duration			
>60min	6	−31.49 (−41.67; −21.30)	<0.001
≤60min	4	−16.39 (−24.21; −8.58)	<0.001
Animal			
Small animals	6	−21.24 (−28.15; −14.33)	<0.001
Large animals	4	−31.38 (−40.97; −21.79)	<0.001
Region			
Asian	7	−26.58 (−33.74; −19.42)	<0.001
Europe/America	3	−22.75 (−42.29; 10.14)	0.029
Ischemic duration			
30min	5	−21.83 (−30.66; −13.00)	<0.001
60min	5	−28.62 (−39.31; −17.92)	<0.001
Reperfusion duration			
≥2 h	4	−21.14 (−31.12; −11.15)	<0.001
<2 h	6	−28.05 (−37.16; −18.93)	<0.001
Total	10	−25.24 (−32.24; −18.23)	<0.001

VNS, vagus nerve stimulation; RVN, right vagus nerve stimulation; LVN, light vagus nerve stimulation; WMD, weighed mean difference; CI, confidence interval.

TABLE 5 Meta-regression for infarct size.

Covariates	Coefficient	95% CI	*p*-Value
Stimulation type	−7.89749	−20.84117; 5.046191	0.197
Site of vagus nerve	−9.519369	−26.61292; 7.574181	0.235
Duration of VNS	−2.451402	−7.261435; 2.358632	0.274
Species	−3.103634	−9.256419; 3.049152	0.278
Region	−5.766457	−12.56464; 1.031722	0.086
Ischemic duration	−6.530279	−23.95324; 10.89268	0.413
Reperfusion duration	−6.654516	−24.30372; 10.99469	0.410

VNS, vagus nerve stimulation; CI, confidence interval.
Coefficient* indicates the estimates (WMD) of corresponding covariates for infarct size in the context of meta-regression.

Discussion

As far as we are aware, this is the first meta-analysis ever conducted to demonstrate that VNS is beneficial in protecting the myocardium from ischemia-reperfusion (I/R) injury. By incorporating data from 10 distinct studies, our research evaluated the efficacy of VNS in preclinical studies. These findings indicated that VNS could significantly reduce infarct size during myocardial I/R injury and also improve heart function by reducing LVEDP and increasing LVEF. Intriguingly, these benefits

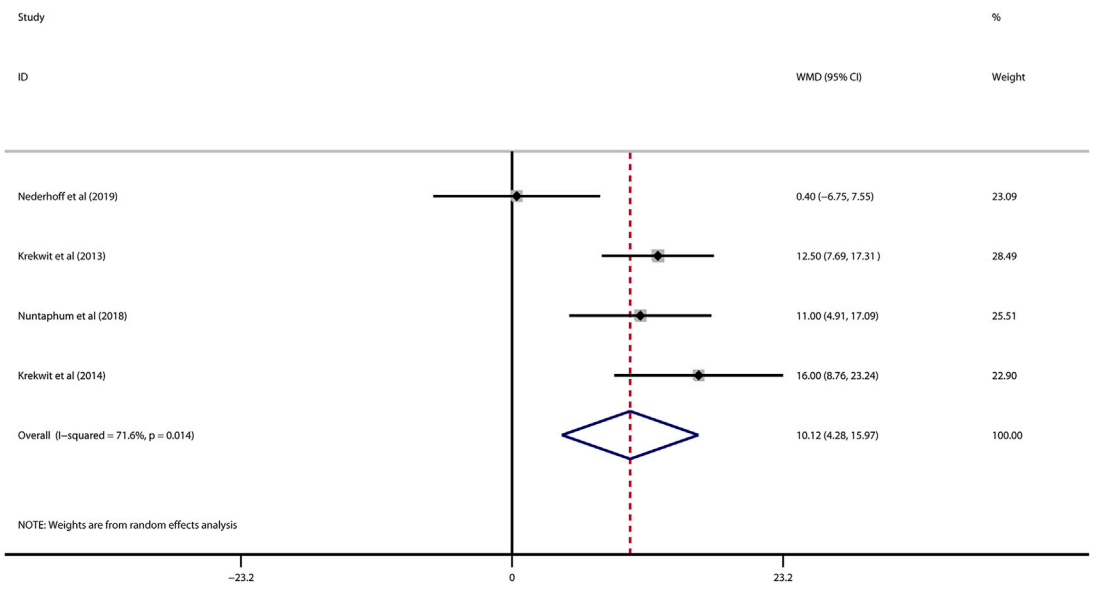

FIGURE 3
Forest plot of LVEF for VNS treatment in myocardial I/R injury. LVEF: left ventricular eject fraction; VNS, vagus nerve stimulation.

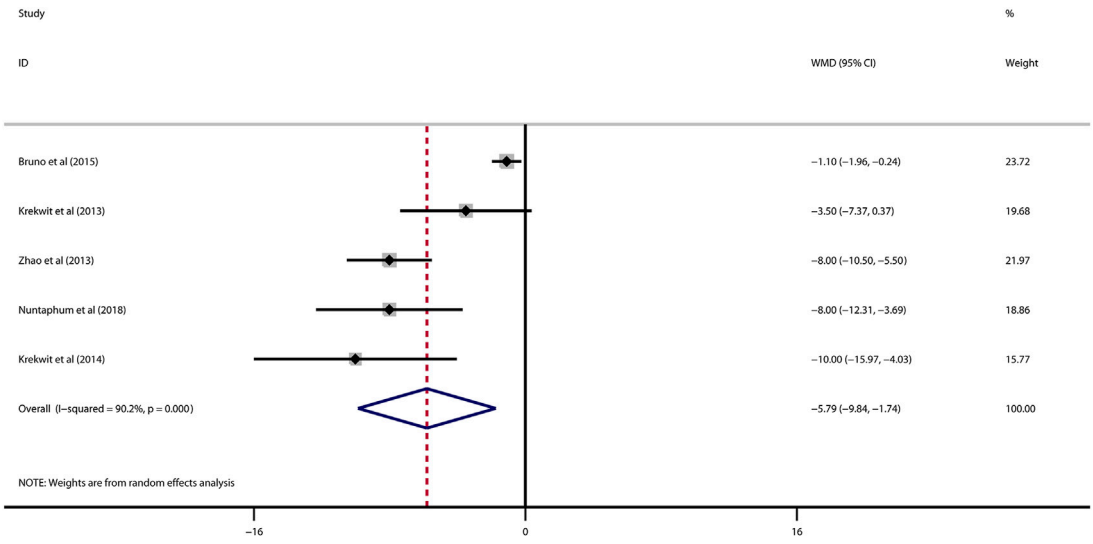

FIGURE 4
Forest plot of LVEDP for VNS treatment in myocardial I/R injury. LVEDP, left ventricular end-diastolic pressure; VNS, vagus nerve stimulation.

were observed to be independent of the type and site of VNS or the animal size.

Myocardial I/R injury remains a significant clinical challenge despite advancements in reperfusion therapies such as thrombolysis and PCI(Férez Santander et al., 2004). This is primarily because of the intricated pathophysiologic process underlying reperfusion injury, including oxidative stress, calcium overload, inflammation, mitochondrial dysfunction, and cell apoptosis (Davidson et al., 2019). During the reperfusion, excessive reactive oxygen species (ROS) production due to the abrupt increase in oxygen supply and corresponding antioxidant enzyme insufficiency are the critical factor of cardiomyocyte death (Férez Santander et al., 2004; Hausenloy and Yellon, 2013). Meanwhile, previous studies reported that mitochondria are the main source of ROS and mitochondrial damage affects post-injury cardiac function by dysregulated ROS modulation. In a vicious cycle, ROS can also impair the mitochondrial respiratory chain and promote mitochondrial membrane depolarization, leading to impaired ATP production and further exacerbating cell death (Murphy and Steenbergen, 2008; Ong and Hausenloy, 2010; Ong and Gustafsson, 2012). Moreover, non-coding RNA, including mi-RNA and Lnc-RNA have increasingly emerged as key regulators

TABLE 6 Sensitivity analysis for left ventricular ejection fraction (LVEF) and left ventricular end-diastolic pressure (LVDEP).

LVEF				LVDEP			
Omitted studies	Pooled estimate	95% CI	*p*-value	Omitted studies	Pooled estimate	95% CI	*p*-value
Nederhoff et al. (2019)	12.795615	9.4486408; 16.14259	<0.001	Buchholz et al. (2015)	−7.1386299	−9.619873; −4.6573863	<0.001
Shinlapawittayatorn et al. (2013)	9.1613674	0.56876612; 17.753969	0.037	Shinlapawittayatorn et al. (2013)	−6.4334135	−11.459242; −1.4075845	0.012
Nuntaphum et al. (2018)	9.7538939	1.3396233; 18.168163	0.023	Zhao et al. (2013)	−5.08149	−9.2801981; −.88278198	0.018
Shinlapawittayatorn et al. (2014)	8.3556633	1.491866; 15.21946	0.017	Nuntaphum et al. (2018)	−5.2803035	−9.7766495; −.78395754	0.021
				Shinlapawittayatorn et al. (2014)	−4.9952269	−9.2649097; −.7255435	0.022
Combined	10.124	4.277; 15.971	0.001	Combined	−5.793	−9.842; −1.744	0.005

LVEF, left ventricular eject fraction; LVEDP, left ventricular end-diastolic pressure; CI, confidence interval.

TABLE 7 Meta-regression for left ventricular ejection fraction (LVEF) and left ventricular end-diastolic pressure (LVDEP).

LVEF				LVEDP			
Covariates	Coefficient	95% CI	*p*-value	Covariates	Coefficient	95% CI	*p*-value
Stimulation type	6.042812	−3.079621; 15.16525	0.104	Stimulation type	−3.820668	−7.660276; 0.0189403	0.051
Site of vagus nerve	11.20161	−7.079008; 29.48222	0.119	Site of vagus nerve	−2.525814	−14.33199; 9.280359	0.545
Duration of VNS	11.20161	−7.079008; 29.48222	0.119	Duration of VNS	−6.038574	−12.66625; 0.589101	0.063
Animal	11.20161	−7.079008; 29.48222	0.119	Animal	−3.598583	−8.449862; 1.252697	0.099
Region	11.20161	−7.079008; 29.48222	0.119	Region	−3.598583	−8.449862; 1.252697	0.099
Ischemic duration	11.20161	−7.079008; 29.48222	0.119	Ischemic duration	−6.038574	−12.66625; 0.589101	0.063
Reperfusion duration	11.20161	−7.079008; 29.48222	0.119	Reperfusion duration	−6.038574	−12.66625; 0.589101	0.063

LVEF, left ventricular eject fraction; LVEDP, left ventricular end-diastolic pressure; VNS, vagus nerve stimulation; CI, confidence interval.
Coefficient* indicates the estimates (WMD) of corresponding covariates for LVEF, or LVDEP, in the context of meta-regression.

in various cellular processes such as apoptosis, inflammation, fibrosis, and angiogenesis and have implications for myocardial ischemia-reperfusion (I/R) injury (Ong et al., 2018). Unfortunately, there are currently limited therapeutic options available to prevent heart damage from reperfusion injury. Several pharmacological interventions have been tried to attenuate myocardial I/R injury by targeting the abovementioned cellular and molecular mechanisms. Vitamins C and E, being well-established antioxidant, have been shown to reduce cardiomyocyte death by inhibiting ROS release during the reperfusion injury (Rodrigo et al., 2014). In addition to the anti-inflammatory drugs, calcium channel blockers or cyclosporine also showed similar cardioprotective effects in retarding infarct area extension and subsequent deterioration of systolic function in a preclinical setting (Boden et al., 2000; Piot et al., 2008; Trelle et al., 2011). However, none of them showed the theoretical potential in clinical translation due to the huge gap between compelling experimental evidence and scant clinical data.

The vagus nerves, originating from the medulla oblongata, are the longest cranial nerve and is involved in the regulation of various physiological systems (Berthoud and Neuhuber, 2000). VNS is first identified as a therapeutic approach for Inflammatory disease by activating the cholinergic anti-inflammatory pathway (Bonaz et al., 2016). On the contrary, vagal denervation consistently released the lymphocyte from thymus to spleen and lymph nodes, which indicated the role of vagus nerves in controlling inflammatory status (Antonica et al., 1994; Antonica et al., 1996). Recently, clinical trials and preclinical trials have demonstrated the beneficial effect of VNS in reducing arrhythmias and hospitalizations, improving cardiac contractility and quality of life for patients with heart failure or AF, which suggests a crucial role of VNS in the treatment of heart disease (Li et al., 2004; Zhang et al., 2009; Zannad et al., 2015; Gold et al., 2016). In terms of the physiological properties of VNS, it was also utilized as a promising method for alleviating myocardial reperfusion injury. As expected, VNS modulates inflammatory cytokines and simultaneously inhibits ROS by activation of AMPK cascades (Kong et al., 2012). Additionally, experimental research indicated that VNS preserved the integrity and function of mitochondria by regulating mitochondrial dynamics, biogenesis, and mitophagy, which turns into cardioprotection against myocardial I/R injury (Nuntaphum et al., 2018). Meanwhile, VNS suppresses the sympathetic nerve sprouting and blocks the inflammatory process, which attenuating ventricular remodeling and decreases the incidence of ventricular arrhythmias after reperfusion injury on mechanism, Jak2/STAT3,

NF-κB, Akt/GSK-3β signaling pathway, which are responsible for VNS induced preventive effects on myocardium during reperfusion injury (Buchholz et al., 2015; Zhao et al., 2021). Yoshihiko et al. reveal a PI3K/Akt pathway for HIF-1α induction by vagal stimulation, which minimizes cardiomyocyte apoptosis under hypoxia and normoxia (Kakinuma et al., 2005). Intriguingly, *in vitro* studies also have demonstrated that VNS could impede FoxO3A phosphorylation through P13K/AKT signaling activation, thus optimizing the sequelae of infarct myocardium (Luo et al., 2020). Collectively, preclinical evidence confirms the potential ability of VNS in facilitating heart recovery from I/R damage, and raise the possibility that it may have a role in improving the prognostic endpoints of myocardial infarction patients receiving timely revascularization. In accordance with the animal experimental results, Yu et al. have reported that tragus stimulation significantly reduces the inducibility of reperfusion-induced ventricular tachycardia and the levels of myocardial injury biomarkers, improves systolic function in patients with STEMI undergoing PCI(Yu et al., 2017).It also indicates that suppressed inflammatory response, evidenced by lower IL-6, IL-1β, high-mobility group-box 1 protein 1, and TNF-α, contributes to the favorable effects of tragus stimulation. However, there remains a great challenge to translate the cardioprotective effects of VNS into myocardial infarction patients, and it therefore is still a pressing need for well-designed randomized control trials to further confirm the role of VNS in the setting of myocardial I/R injury, and contemporaneously deeply elucidate the underlying mechanisms.

Limitations

First, there is no standard protocol for myocardial I/R regimen (i.e., different ischemic or reperfusion duration) or VNS treatment (i.e., different parameters, stimulation site, and type), while subgroup analysis shows remarkable consistent outcomes among the studies. Second, the pooled results from this meta-analysis are based on animals without comorbidities which may impede extrapolating these findings to complicated clinical situations. Third, despite significant heterogeneity that may affect the interpretation of the results, sensitivity analysis and subgroup analyses with robust data substantially support the benefits and reliability of VNS in reducing infarct size and improving cardiac function after reperfusion injury. Meanwhile, the prespecified covariates have no impact on pooled results of both infarct size and LVEF by meta-regression. Finally, the majority of outcomes of included studies concentrate on infarct area and LVEF, rather than mortality or other cardiac functional indicators (e.g., 6-min walking or cardiopulmonary exercise testing), which may more precisely reflect the prognosis and symptoms in clinical practice.

Conclusion

In summary, VNS is a promising therapeutic strategy for preventing lethal myocardial reperfusion injury according to the significant advantages in limiting infarct size and cardiac function from basic studies. It thus provides the theoretical feasibility and reliability to extend the utilization of VNS in ST elevation myocardial infarction patients with revascularization, and implicates the future prospects of clinical application.

Data availability statement

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

Ethics statement

Ethical approval was not required for the study involving animals in accordance with the local legislation and institutional requirements because This study is meta-analysis is a re-examination of data from published articles.

Author contributions

Y-HC: Writing–review and editing. Y-PX: Writing–original draft. X-YL: Writing–original draft. Z-QS: Writing–original draft. HL: Writing–original draft.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by Wenzhou Science and Technology Bureau (Grant No: Y20180079) to Y-HC and the 2023 Science and Technology Innovation Activity Plan for Students in Zhejiang Province (No. 2023R413020) to X-YL.

Acknowledgments

We thank Y-HC for providing the idea, designing and subsequent guiding of this article. We thank HL for revising of 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 Pharmacology

TYPE Mini Review
PUBLISHED 23 November 2023
DOI 10.3389/fphar.2023.1284071

OPEN ACCESS

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RECEIVED 27 August 2023
ACCEPTED 13 November 2023
PUBLISHED 23 November 2023

CITATION
Mazzotta E, Soghomonyan S and Hu L-Q (2023), Postoperative sore throat: prophylaxis and treatment.
Front. Pharmacol. 14:1284071.
doi: 10.3389/fphar.2023.1284071

Postoperative sore throat: prophylaxis and treatment

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Postoperative sore throat (POST) is one of the most reported complications after general anesthesia with an incidence of as high as 60% which may impact patient satisfaction and increase the cost of treatment. The aim of this review is to summarize the currently accepted approaches and new trends intended to reduce the risk and increase the treatment efficacy of POST. Difficult intubation, traumatic intubation, and several other factors contribute to the development of POST. Endotracheal intubation using a stylet-loaded tube exerts excessive pressure on the anterior tracheal wall predisposing to mucosal trauma and contributing to development of POST. Pharmacological interventions are aimed at prevention, amelioration of symptoms, and treatment of POST. Medications suggested for this purpose include corticosteroids, topical sprays and creams, non-steroidal anti-inflammatory drugs (NSAID), and N-methyl-D-aspartate (NMDA) receptor antagonists. The use of video-laryngoscopes (VL) for endotracheal intubation improves the glottic view and increases the success rates with less force required to ensure adequate laryngoscopic view. Nevertheless, despite advances in laryngoscopic devices, the incidence of POST remains high. A novel intubation technique with endotracheal tube (ETT) rotation 180 degrees (ETT 180°) has been suggested to overcome stylet related injury and, possibly, decrease the POST. To date, no clinical trials have been conducted to test the efficacy of ETT 180° in reducing the incidence of POST. Undoubtedly, the suggested method deserves further investigation to determine its role in patient care.

KEYWORDS

postoperative sore throat, postoperative complications, intratracheal intubation, endotracheal tube, anesthetic complications

Introduction

POST is a well-documented complication after tracheal intubation with an incidence of as high as 60% with a significant negative impact on patients' recovery and satisfaction (Macario et al., 1999; McHardy and Chung, 1999; Scuderi, 2003; Boghdadly et al., 2016). The term POST is not well defined and usually describes a wide variety of conditions including pharyngitis, laryngitis, tracheitis, cough, hoarseness or dysphagia manifesting in the early postoperative period (Higgins et al., 2002; Boghdadly et al., 2016). Several risk factors for its development have been reported including female sex, younger age, pre-existing lung disease, prolonged duration of anesthesia, size of tracheal tube, double lumen ETT, presence of a blood-stained ETT on extubation, and high ETT cuff pressure exceeding 20 cm H_2O (Boghdadly et al., 2016; Mitobe et al., 2022).

The etiology of POST is complex and multiple mechanisms may contribute including airway trauma and irritation with mucosal injury and inflammation, prolonged ischemia of the mucosa caused by mechanical pressure, regurgitation of the gastric contents, placement

of a gastric tube, etc. (McHardy and Chung, 1999; Roffey et al., 2003; Scuderi, 2003; Liu et al., 2010) Among many factors, mechanical injury of the airway mucosa caused by forceful laryngoscopy and the use of a stylet loaded ETT are considered the main culprits (Komasawa et al., 2017). The available evidence suggests that the mechanical impact on the anterior tracheal wall resulting from the removal of a stylet (Boghdadly et al., 2016; Kusunoki et al., 2016) during endotracheal intubation may be a key factor contributing to POST (Chou and Wu, 2001). Furthermore, the extraction force during stylet removal seems to play a significant role.

A prospective study by Kusunoki et al. (2016) has shown that increased extraction force during stylet removal exceeding 10.3 Newtons is associated with high incidence of POST).

Despite the risks associated with stylets, including POST, their use to facilitate the endotracheal intubation is unavoidable in many cases, and new modifications of intubation techniques aimed at reducing the associated complications should be encouraged (Komasawa et al., 2017). Efforts have been made to decrease the incidence and severity of POST by either modifying the intubation technique or using topical and systemic pharmacotherapy. Nevertheless, POST remains a common complication of anesthesia requiring attention (Boghdadly et al., 2016). This review focuses on current practices in medical treatment of POST as well as a newly suggested modification of endotracheal intubation which has the potential to reduce the incidence of POST.

Pharmacological interventions

In the context of multimodal analgesia, several pharmacological interventions have been tested to reduce the incidence of POST and increase the quality of recovery. In this section we will briefly describe the most updated recommendations for POST prevention.

Steroids and NSAIDs

The use of glucocorticoids and NSAIDs is justified in the management of POST considering the role of inflammation in pathogenesis of POST. An updated meta-analysis on the efficacy of dexamethasone in reducing the incidence of POST showed that dexamethasone 0.2 mg/kg significantly decreased the incidence of POST, whereas dexamethasone at a dose of 0.1 mg/kg was not effective (Jiang et al., 2018). Topical steroids represent an additional therapeutic option. According to literature reports, topical corticosteroids, when applied to the tracheal mucosa, reduce the incidence of POST when compared with non-analgesic control drug, 95% confidence interval (CI) 0.39 (0.32–0.49) (18 trials including 1506 patients) (Kuriyama et al., 2018a).

NSAIDs are very effective in reducing postoperative pain. Benzydamine hydrochloride, a topical NSAID with analgesic and anti-edema properties, has been proposed as a treatment option for prevention of POST. A meta-analysis by Kuriyama et al. assessed the efficacy of Benzydamine. In the study involving 1842 patients, Benzydamine treatment was associated with a significant decrease in POST with a risk ratio (RR) 0.31, 95% CI 0.20–0.47, and the number needed to prevent of 6 (95% CI 5–8), indicating a significant relevant prophylactic effect (Kuriyama et al., 2018b). Subsequently, another RCT tested flurbiprofen lozenge as a preoperative intervention to address POST and dysphagia associated with the use of laryngeal mask airway (LMA). The study found that the use of flurbiprofen lozenge at dose 8.75 mg effectively reduced the severity, but not the incidence of early POST (Uztüre et al., 2014). Evidence assessing the efficacy of intravenous NSAIDs on POST is currently limited, with only one randomized controlled trial (RCT) testing intravenous Diclofenac that showed no protective effect (Thanga et al., 2013).

Lidocaine

According to a 2015 Cochrane meta-analysis of 1940 patients, topical (intracuff lidocaine, lidocaine jelly, and lidocaine spray) and systemic lidocaine appeared to reduce the incidence of POST (16 studies, 1774 participants, RR = 0.64, 95% CI 0.48–0.85). However, the effect was no longer significant, when only high-quality trials were included (eight studies, 814 participants; RR 0.71, 95% CI 0.47–1.09) (Thanga et al., 2013). Similarly, Li et al. (2020) conducted a recent meta-analysis assessing the efficacy of topical and systemic lidocaine. Their study showed that intracuff and intravenous lidocaine (dose 1.5 mg/kg) effectively reduced the risk of POST at 1 h and 24 h, but lidocaine jelly and spray were not. Despite these positive results, the level of heterogenicity among studies was high and results should be interpreted with caution (Li et al., 2020).

NMDA receptor antagonists

Magnesium and ketamine, two NMDA receptor antagonists, are commonly used in anesthesia for their antinociceptive and anti-inflammatory properties and have been studied for their potential to reduce POST. Several meta-analyses looked at the effectiveness of topical magnesium sulfate prior to surgery in preventing POST. One study used the number needed to treat (NNT) to assess the efficacy. Magnesium was administered as gargles (20 mg/kg), lozenges (100 mg) or nebulization (225–500 mg) 15–30 min before surgery in preoperative area. According to the authors, the NNT equaled 5.76 patients to be treated to prevent 1 event of POST (Singh et al., 2019). Similarly, a recent network meta-analysis reported that topical magnesium effectively prevented the POST 24 h after endotracheal intubation (odds ratio 0.10, and 95% credible interval 0.03–0.26) (Singh et al., 2020). Similarly, a meta-analysis of 41 RCT involving over 3000 patients showed that topical ketamine, regardless of the administration method (gargle 20–50 mg, nebulized 0.5–1.5 mg/kg or lubrication of ETT 50 mg) was associated with lower incidence of POST in the first 24 h (RR 0.45; 95% CI 0.37-0.54; $p < 0.001$) (Kuriyama et al., 2020). On the contrary, the use of IV ketamine 0.5 mg/kg bolus follow by a low maintenance infusion in a RCT, did not result in a significant reduction in the incidence of POST (Park et al., 2010).

Other drugs

Liquorice, also spelled as “licorice”, is derived from the root of Glycyrrhiza gabra and has long history of use in medicine due to its

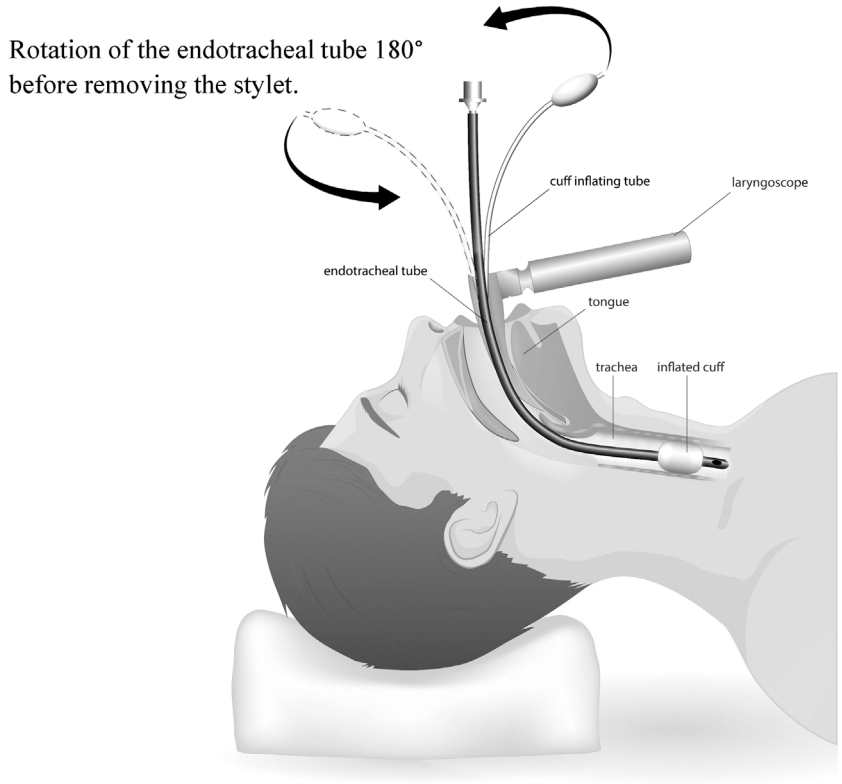

FIGURE 1
ETT 180° intubation technique.

various properties including anti-inflammatory and antitussive effects (Fiore et al., 2005). An early RCT by Arwal et al. showed a reduction in the incidence of POST both at rest and on swallowing after a gargle of 0.5 gr of liquorice made in 30 mL of water (Agarwal et al., 2009). Similarly, a recent meta-analysis of more than 70 trials revealed a reduction of POST with the usage of topical liquorice before induction of anesthesia (Boghdadly et al., 2016).

Non-pharmacological interventions and a novel intubation approach

ETT sizing

Selecting the appropriate endotracheal tube (ETT) size is crucial in minimizing the risk of sore throat and ensuring effective airway management during intubation. Generally, an internal diameter (ID) (6.0–7.5 mm) ETTs are generally suitable for females, whereas 7.0–8.0 mm ID ETTs are suitable for males (Butterworth, 2013). Studies have shown that female patient under general anesthesia with smaller size of ETT (6.0 mm) were associated with a lower incidence of POST (Hu et al., 2013; Jaensson et al., 2014).

Tracheal cuff pressure

Higher cuff pressures in endotracheal tubes (ETTs) and supraglottic airway (SGA) devices can indeed be associated with an increased incidence of sore throat. This is due to the potential for mucosal trauma and pressure-related injuries when the cuff pressure is excessively high (Ansari et al., 2014). To mitigate the risk of sore throat associated with high cuff pressures, monitoring cuff pressures regularly and adjust them as needed to maintain an appropriate range has been suggested. In a prospective randomized control trial on patients undergoing thyroidectomy, the authors showed that monitoring and maintaining cuff pressure at 25 cm H2O was associated with less incidence and severity of POST at 2 (61% vs. 86%; $p = 0.008$) and 24 h postoperatively (43% vs. 66%; $p = 0.032$) (Ryu et al., 2013).

Similarly, another prospective study on patients undergoing maxillofacial surgery, offers further support for the practice of monitoring and adjusting cuff pressure intraoperatively to reduce the incidence of POST (Ansari et al., 2014).

Video laryngoscopes

VL have been popularized due to enhanced glottic view and high rate of successful intubations (Hoshijima et al., 2018). Their introduction shifted the paradigm in airway management with enhanced intubation rates and most likely may soon become a standard of care (Najafi et al., 2014; Prekker et al., 2023). A trade-off for the superior glottic view with VL, the ETT must be curved to a considerably more acute angle to enable insertion and match the laryngoscope's angle of view. The manufacturers recommend using the stylet angled between 45° and 90° for optimal results (Shippey et al., 2007). Intubation with VL may occasionally be challenging, making intubation time significantly longer when compared to direct laryngoscopy (DL). In addition, insertion of the more

angulated stylet loaded ETT exerts more pressure of the tissue potentially predisposing to soft tissue trauma (Walls et al., 2010; Hoshijima et al., 2018). According to Najafi et al. (2014), sore throat seems a universal issue after VL intubations with an incidence of around 30% (Najafi et al., 2014; Prekker et al., 2023).

Lee et al. sought to determine the optimal angle of the stylet when utilizing McGrath VL comparing the time to intubation. The study showed that 60° angulation was associated with shorter intubation time when compared to 90° angulation (Lee et al., 2017). Given the fact that less force is needed to achieve a grade 1 -2 view with VL, one would expect less incidence of POST and tissue trauma. However, the above-mentioned study did not look at the incidence of POST. At present, there are no data on the optimal angulation of the stylet loaded ETT which could reduce the risk of POST.

Current evidence suggests that the use of malleable stylet with steep angulation is the potential mechanism of injury and POST. Yoon et al. reported that the use of a stylet during intubation with McGrath® MAC VL was associated with higer incidence of subglottic injury when compared to a group without stylet (Yoon et al., 2019). Two principal mechanisms play a role in airway trauma with intubation with a stylet loaded ETT. First, the rigid tip of stylet loaded ETT impinges on the anterior tracheal wall where it meets resistance and fails to advance resulting in subglottic injury. Second, the ETT curls anteriorly, when the stylet is removed, causing anterior subglottic trauma (Yoon et al., 2019).

Thus, the incidence of POST remains high despite the introduction of novel laryngoscopic devices and pharmacological interventions. Modifications in intubation technique allowing to address the above discussed mechanisms of injury could possibly reduce the airway trauma and, accordingly, the incidence of POST.

Rotation of the ETT 180° before removing the stylet (ETT 180°)

To decrease the trauma caused by the ETT pressure on the anterior wall in the upper airway, a novel maneuver has been suggested named ETT 180°: a clockwise rotation of the stylet loaded ETT 180 degrees on its axis, once the tip of ETT passes the patient's vocal cords (glottis) but before pulling the stylet out (Figure 1). This maneuverer allows for the stylet to match the posterior angulation of the trachea and thus minimizes the impact on the anterior wall. Once the rotation is completed, the stylet is gently removed and the ETT is advanced to the proper depth (Walls et al., 2010; Singh et al., 2013).

Unfortunately, there is scarce data regarding the incidence of POST and airway trauma related to the ETT 180° technique. In a single operator study, Seo et al. compared ETT 180° rotation of a double lumen tube (DLT) with the standard 90° rotation technique after passing the glottis. The authors reported a lower incidence of sore throat in the ETT 180 group on the first postoperative day (30/75 vs. 16/80, $p = 0.008$) and lower incidence of glottic trauma ($p = 0.032$) (Seo et al., 2013).

Additionally, this maneuver has been successfully described during selective blind endobronchial intubation in adults and children (Kubota et al., 1987).

The ETT 180° has the potential to reduce the incidence of POST and improve the quality of perioperative care. Taking this into account, our team has designed a prospective double-blinded randomized study to test the efficacy of the technique in reducing the incidence of POST. If the results of this and other studies prove the benefits of the novel technique, the ETT 180° may be introduced into clinical practice and become a new standard of care.

Conclusion

Despite advances in laryngoscopic devices, POST remains a common problem and is associated with poor patient satisfaction requiring additional pharmacological interventions. Modifications in intubation technic taking into account the possible mechanisms of POST are required to reduce its incidence and improve that perioperative patient care.

Author contributions

EM: Conceptualization, Writing–original draft, Writing–review and editing. SS: Conceptualization, Writing–original draft, Writing–review and editing. L-QH: Conceptualization, Writing–original draft, Writing–review and 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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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TYPE Review
PUBLISHED 15 December 2023
DOI 10.3389/fphar.2023.1297931

OPEN ACCESS

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RECEIVED 20 September 2023
ACCEPTED 04 December 2023
PUBLISHED 15 December 2023

CITATION
Echeverria-Villalobos M, Tortorici V, Brito BE, Ryskamp D, Uribe A and Weaver T (2023), The role of neuroinflammation in the transition of acute to chronic pain and the opioid-induced hyperalgesia and tolerance. *Front. Pharmacol.* 14:1297931. doi: 10.3389/fphar.2023.1297931

The role of neuroinflammation in the transition of acute to chronic pain and the opioid-induced hyperalgesia and tolerance

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Current evidence suggests that activation of glial and immune cells leads to increased production of proinflammatory mediators, creating a neuroinflammatory state. Neuroinflammation has been proven to be a fundamental mechanism in the genesis of acute pain and its transition to neuropathic and chronic pain. A noxious event that stimulates peripheral afferent nerve fibers may also activate pronociceptive receptors situated at the dorsal root ganglion and dorsal horn of the spinal cord, as well as peripheral glial cells, setting off the so-called peripheral sensitization and spreading neuroinflammation to the brain. Once activated, microglia produce cytokines, chemokines, and neuropeptides that can increase the sensitivity and firing properties of second-order neurons, upregulating the signaling of nociceptive information to the cerebral cortex. This process, known as central sensitization, is crucial for chronification of acute pain. Immune-neuronal interactions are also implicated in the lesser-known complex regulatory relationship between pain and opioids. Current evidence suggests that activated immune and glial cells can alter neuronal function, induce, and maintain pathological pain, and disrupt the analgesic effects of opioid drugs by contributing to the development of tolerance and dependence, even causing paradoxical hyperalgesia. Such alterations may occur when the neuronal environment is impacted by trauma, inflammation, and immune-derived molecules, or when opioids induce proinflammatory glial activation. Hence, understanding these intricate interactions may help in managing pain signaling and opioid efficacy beyond the classical pharmacological approach.

KEYWORDS

acute pain, chronic pain, neuroinflammation, dysbiosis, gliosis, inflammatory mediators, opioids

1 Introduction

According to the International Association for the Study of Pain (IASP), chronic pain persists or recurs for over 3 months and is a leading source of human suffering and disability (Treede et al., 2019). A cornucopia of etiological factors has been implicated in the genesis of chronic pain. It may be the primary symptom of a non-specific underlying disease (i.e., fibromyalgia), a sign of a progressive local/systemic disorder (i.e., rheumatic inflammatory diseases, Diabetes Mellitus), or secondary to direct nerve injury (Vergne-Salle and Bertin, 2021). More recently, a new pain mechanism identified as "nociplastic pain" has been proposed. It occurs in individuals with an abnormally elevated nociception sufficient to activate peripheral nociceptors without clear evidence of tissue damage, neural injury, or disease (Kosek et al., 2016). Although central sensitization is not included in the definition of nociplastic pain, patients with this condition frequently refer to signs of central sensitization, suggesting that nociceptive and neuroplastic pain may coexist (Kosek et al., 2016). Unlike acute pain, which functions as a defensive mechanism, chronic pain is considered maladaptive because it does not provide additional protective or recuperative benefits (Walters, 2019). Peripheral sensitization is the most common mechanism of pain initiation; nonetheless, the chronicity of pain is mainly determined by central sensitization. The neuroinflammatory response also gives rise to structural and functional maladaptive changes in the peripheral and central somatosensory pathways, modifying the pain-signaling process. The existing evidence suggests that activation of glial cells and other non-neuronal cells, such as immune cells (neutrophils, macrophages, T-cells, and mast cells), leads to increased production and release of proinflammatory mediators that play a crucial role in developing and maintaining neuropathic and chronic pain (Hains et al., 2006; Chiu et al., 2012; Du et al., 2023).

The main goal of this article is to review the current evidence on the molecular mechanisms that support the role of neuroinflammation as an important etiopathogenic factor in the transition from acute postoperative pain to chronic postoperative pain (CPSP). Similarly, the neuroimmune interactions associated with the decrease in the analgesic effect of opioid drugs are considered, including those involved in the development of opioid-induced inflammation, opioid tolerance, and paradoxical hyperalgesia.

2 The leading role of the immune response and glial activation in the transition from acute to neuropathic and chronic pain

Acute pain after surgery is almost a sine *qua non* condition; however, this kind of pain is ineffectively treated. It transitions to a state of chronic pain, often with neuropathic characteristics, that is refractory to treatment with opioids (Haroutiunian et al., 2013; Honkanen et al., 2021). The incidence of pain persisting beyond the period of wound healing after surgery is approximately 10%–85%, depending on the type of surgery. This has been typified as CPSP, with 5%–10% of cases rating the pain as severe, affecting patients quality of life and creating a significant economic burden for the health systems (Kehlet et al., 2006; Johansen et al., 2012; Jin et al., 2021; Jin et al., 2023). The most recent revision of the International Classification of Diseases (ICD-11) defines CPSP as "pain developing or increasing in intensity after a surgical procedure, in the area of the surgery, persisting beyond the healing process (i.e., at least 3 months) and not better explained by another cause such as infection, malignancy or a pre-existing pain condition". Similarly, the IASP defines it as "chronic pain that develops or increases in intensity after a surgical procedure or a tissue injury and persists beyond the healing process, i.e., at least 3 months after the surgery or tissue trauma" (Schug et al., 2019).

Currently, overwhelming evidence supports the fundamental role of neuroinflammation in pain; however, its etiopathogenic mechanisms are not yet fully elucidated. A neuroinflammatory state is characterized by the activation of glial cells, generation of proinflammatory mediators (cytokines and chemokines, among others), and changes in the vasculature, resulting in increased permeability and leukocytic infiltration, as well as alterations in gene expression (Ji et al., 2006; Ji et al., 2018; Donnelly et al., 2020). Increasing evidence shows that glial tissue activation (including microglia, astrocytes, oligodendrocytes, satellite glial cells, and ependymal cells) plays a pivotal role in developing peripheral and central sensitization (Figure 1).

2.1 Role of immune cells

In the perioperative period, harmful events, such as surgical incisions and organ manipulation, cause tissue and nerve damage, which triggers the activation of immune cells, glial cells, and nociceptive neurons. These cells then set forth the release of pro-inflammatory mediators causing a pervasive state of inflammation in the peripheral and central nervous system. If the inflammation is not adequately resolved and central sensitization is established, the nociceptive state may progress from acute postoperative pain to CPSP once (Ji et al., 2006; Ji et al., 2013; Ji et al., 2016; Pinho-Ribeiro et al., 2017; Ji et al., 2018; Ji, et al., 2019). Additionally, recent evidence from preclinical studies shows that epidermic resident cells, keratocytes, and dendritic cells (DCs) play an active role in inflammatory pain arising from surgical tissue injury as well as in the development of neuropathic pain and CPSP (Manjavachi et al., 2014; Hesselink et al., 2016; Guo et al., 2020; Silva et al., 2022). Keratocytes lie close to sensory afferent nerves and when stimulated by surgical incision initiate a nociceptive response mediated by the production and release of various neuroactivator agents such as cytokines (TNF-α and IL-1β), calcitonin gene-related peptide receptor (CGRP), acetylcholine, adenosine triphosphate (ATP), nerve growth factors, neuropeptides, and other neurotransmitters contributing to peripheral neuroinflammation (Guo et al., 2020). Studies in animal models have shown that activated keratocytes can also elicit afferent firing and sensitization, resulting in postsurgical incisional hypersensitivity (Hesselink et al., 2016; Ritter-Jones et al., 2016; Guo et al., 2020; Silva et al., 2022). DCs and Langerhans cells are another group of skin-resident cells that become upregulated after tissue injury and can directly activate peripheral nociceptive neurons (nociceptors), releasing chemokines CCL17 and CCL22 through the shared receptor CCR4, contributing to neuroinflammation and postoperative pain (Silva et al., 2022).

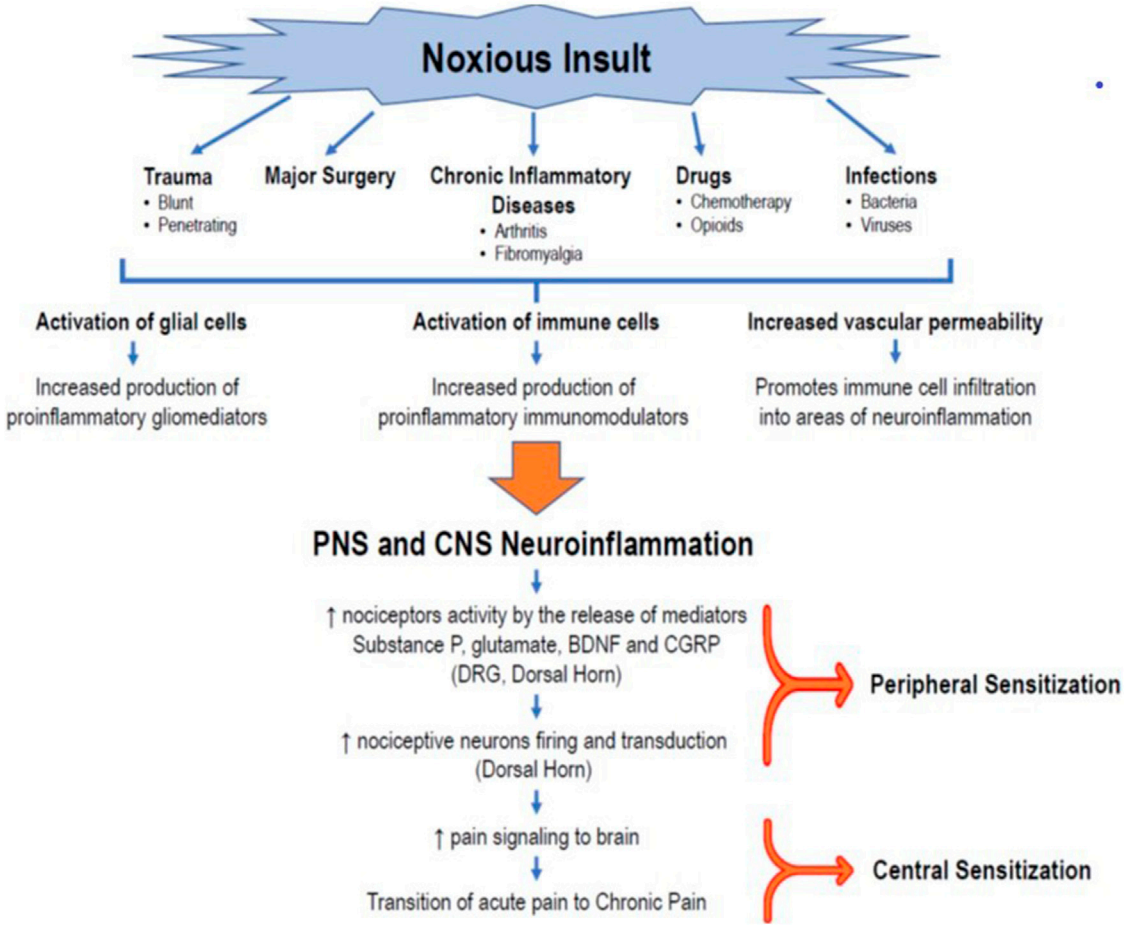

FIGURE 1
Role of neuroinflammation in the transition to CPSP. The occurrence of a noxious insult, such as trauma, major surgery, chronic inflammatory diseases, drugs (chemotherapy, opioids), or infections, triggers an initial immunoinflammatory response that, in turn, promotes the activation of glial cells (microglia, astrocytes, oligodendrocytes) in the peripheral sensory system, creating a state of peripheral neuroinflammation. At the same time, the production and release of inflammatory mediators produce changes in vascular permeability that facilitate the infiltration of immune cells that activate the glial cells of the CNS, generating the release of more proinflammatory mediators and a process of neuroinflammation in the CNS. This milieu of cytokines, chemokines, neuropeptides (substance P, CGRP), and neurotrophic factors leads to changes in the plasticity of second-order neurons in the posterior horn of the spinal cord. This results in an exaggerated firing activity and amplification of nociceptive signaling in the DRG and the posterior horn of the spinal cord, establishing the peripheral sensitization phenomenon. The transmission of painful signals to the brain, together with the process of neuroinflammation, keeps the nociceptor neurons of the brain's pain centers stimulated, giving rise to a state of central desensitization, and promoting the transition from acute pain to neuropathic or chronic pain. **BDNF** = brain-derived neurotrophic factor; **CGRP** = calcitonin gene-related peptide; **CNS** = central nervous system, **DRG** = dorsal root ganglion.

Activated immune cells (macrophages, neutrophils, T-cells, and mast cells) also produce and release pro-inflammatory mediators that interact with peripheral nerve terminals and their somas located in the dorsal root ganglia (DRG), which relay in laminae I and II of the dorsal horn of the spinal cord (Pinho-Ribeiro et al., 2017). DRG macrophages are critical contributors to the initiation and persistence of neuropathic pain in male and female mice, without the sexual dimorphism reported in microglial cells (Yu et al., 2020). It has been recently demonstrated that immediately after a nerve injury, there is a significant proliferation of resident macrophages in the DRG ipsilateral to the nerve lesion, which produces proinflammatory cytokines such as TNF-α, IL-1β, and HMGB1 (Hu and McLachlan, 2003; Guimarães et al., 2023). The proximity of macrophages to the cell bodies of primary nociceptors in the DRG facilitates the activation of primary sensory neurons by the proinflammatory cytokines (Chen et al., 2018)".

Macrophages are tissue immune cells that are stimulated early when nerve injury occurs. Until recently, macrophages were thought to be two polarized forms of immune cells (M1 and M2) with distinct phenotypic qualities and functional properties. Accordingly, M1 activity inhibited cell proliferation and caused tissue damage, whereas M2 activity promoted cell proliferation and tissue repair. However, recent evidence has shown that the expression of specific polarization markers for M1/M2 phenotypes *in vitro* observations can be influenced not only by a specific stimulus but even by a specific stimulation time sequence (Purcu Duygu et al., 2022).

In vivo, the situation is even more complex, as there is a wide range of different macrophages depending on the conditions of the microenvironment (Strizova et al., 2023). Moreover, most surface markers identified on macrophages generated *in vitro* do not translate to the situation *in vivo* (Orecchioni et al., 2020). These

facts suggest that macrophages exhibit phenotypic plasticity and can adopt different activation states in response to different conditions. Therefore, the current phenotypic status encompasses an expanded spectrum of possibilities that includes multiple subsets of macrophages identified by their different activation states, functional properties, and surface marker expression. To further complicate matters, certain subsets of macrophages may not be completely distinct from one another and may share common functional activities.

These dualistic implications also apply to microglia, the macrophages of the brain, whose phenotype is also influenced by the central nervous system microenvironment. The repertoire of microglial states and functions goes beyond the dichotomy of "resting vs activated," "M1 vs M2," or "good vs bad microglia," as demonstrated by the impressive work of Paolicelli et al. (2022), a group of multidisciplinary experts who advance the understanding of microglial states as a dynamic concept, emphasize the importance of considering microglial function, and provide a new conceptual framework for this type of dichotomy.

Therefore, the large phenotypic heterogeneity exhibited by macrophages might lead to oversimplification in light of recent observations. In the transitional phase, it might be appropriate, albeit risky, to describe macrophages as M1-like and M2-like to define their different roles rather than using the conventional M1 and M2 nomenclature (Strizova et al., 2023). However, the latter would be very helpful when referring to previous work reporting on the dichotomy.

It is normally accepted that M1-like macrophages liberate proinflammatory cytokines (TNFα, IL-1β, IL-6), chemokines (CCL2, CCL3, CCL4), and nitric oxide (NO). They also respond to damage-associated molecular patterns (DAMPs), and pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS). This results in further recruitment and activation of other immune cells (neutrophils, monocytes, mast cells, T-cells) and unmyelinated afferents, causing the sensitization of primary nociceptive neurons at the DRG (Nicol et al., 1997; Oh et al., 2001; Obreja et al., 2002; Zhang and An, 2007). In a rodent model of arthritis, a proinflammatory macrophage phenotype similar to the M1-like subtype was found in the rat DRG, and activation of these macrophages stimulated DRG neurons to release calcitonin gene-related peptide (CGRP), which plays an active role in the persistence of the pain state (Massier et al., 2015). Conversely, M2-like macrophages promote analgesia in response to IL-4, which stimulates the production of high levels of anti-inflammatory cytokines, such as IL-10 (Celik et al., 2020). IL-4 has also been shown to induce the M2-like subtype to produce endogenous opioid peptides that bind to peripheral opioid receptors, further contributing to pain relief by deactivating neuropathy-triggered mechanical hypersensitivity (Pannell et al., 2016; Celik et al., 2020). Furthermore, the action of the cytokine IL-4 also promotes the transcription of M2-like associated genes while reducing the transcription of M1-like associated genes (Kiguchi et al., 2015).

Neutrophils are polymorphonuclear leukocytes representing the first-line cells in the innate immune response to tissue damage or infections. However, their role in neuroimmune interactions has only recently been studied in greater detail (Chavan et al., 2017; Pavlov et al., 2018). Neutrophils are almost always absent around the intact nerves. However, when tissue damage occurs, they become activated by locally produced mediators such as proinflammatory cytokines, growth factors, leukotrienes B4 (LB4), DAMPs, and prostanoids such as prostaglandin E2 (PGE2). That milieu of mediators enhances neutrophil migration toward the sites of inflammation. Subsequent neutrophil infiltration of afferent nerve endings activates and sensitizes the terminals of the peripheral nociceptors and increases vascular permeability (Kalaczkowska and Kubes, 2013). Once activated, neutrophils continue releasing mediators, contributing to nociceptive amplification (Levine et al., 1984; Grace et al., 2014). Several studies have demonstrated that endoneural neutrophil invasion of peripheral nerves and DRGs occurs after induced chronic constriction injury of peripheral nerves. This neutrophil infiltration is correlated with an increase in the production of monocyte chemoattractant protein-1 (MCP-1, also known as CCL2) and neutrophil-derived elastase. Both are regarded as essential mediators in the development of hyperalgesia in animal models of neuropathic pain (Perkins and Tracey, 2000; Morin et al., 2007; Bali and Kuner, 2017). Contrarily, some researchers have questioned the role of cytokines in mechanical hyperalgesia while assigning a more important role to the release of bradykinin, PGE2, and sympathomimetic amines such as adrenaline, epinephrine, and norepinephrine (Green, 1974; Cunha et al., 2008). Neutrophils also participate in the process of neuroinflammation and post-incisional hypersensitivity through the production of other mediators such as metalloproteases, reactive oxygen species (ROS), hydrogen, and endothelins, which further increase nociceptors excitability (Steen et al., 1992; Wang et al., 2004; Woo et al., 2004; Mujenda et al., 2007). In the CNS, neutrophil infiltration occurs as a result of changes in the permeability of the blood-brain barrier (BBB) secondary to the neuroinflammation process, and the chemoattractant effect of chemokines CXCL2 and CXCL6, released by meningeal mast cells and astrocytes. This neutrophilic invasion causes demyelination and axonal damage (Simmons et al., 2014; Pierson et al., 2018).

T lymphocytes (T-cells) are part of the adaptive immune system. Studies have shown that mechanical allodynia after nerve injury is associated with infiltration of the DRG by T-cells (Vicuña et al., 2015). However, preclinical studies in mice demonstrated that the active involvement of T-cells in the pathogenesis of neuropathic pain depends on the subtype of T-cells and the mouses gender (Sorge et al., 2015). Interestingly, T-cells also actively participate in the pain resolution process. After a period of hypernociception, the PNS and CNS can enter into a state of apparent deactivation (remission), also called "latent sensitization" (Marvizon et al., 2015). In this state, any noxious or stressful event leading to the reactivation of nociceptors, including the use of naloxone, will trigger a prolonged hyperalgesic response with changes in the expression of pain-related genes (Parada et al., 2003; Rivat et al., 2007; Price and Ray, 2019). T-cells and macrophages generate endogenous opioid peptides such as β-endorphins and enkephalins, which play a key role in preventing the reappearance of pain during latent sensitization (Stein et al., 1990; Ritter-Jones et al., 2016). Likewise, the anti-inflammatory cytokine IL-4, produced by mast cells, granulocytes, and T helper 2 (Th2) cells, exerts a modulatory effect on proinflammatory mediators and induces M2-like macrophages to release opioid peptides that attenuate pain (Celik et al., 2020).

Mast cells are located very close to nociceptive neurons; once activated, they release neuroactive proinflammatory cytokines (TNF-α,

IL-1β, IL-6), chemokines, histamine, bradykinin, proteases, nerve growth factor (NGF), and substance P (SP). This release of proinflammatory cytokines generates the initial nociceptive signaling that modulates thermal and mechanical sensitivity through specific receptors (Chatterjee and Martinov, 2015). Crosstalk between mast cells and nociceptive neurons is established through their common receptor NK1. In addition, receptors located in the mast cells (S1P1, S1P2, and CRHR) interact with cytokines, chemokines, and NGF released by nociceptive neurons, sustaining the hyperactivation of nociceptors in the DRG and spinal dorsal horn and causing neurogenic inflammation (Kempuraj et al., 2019). Several authors have reported that substance P released from primary afferent nerve terminals not only interacts with its canonical receptor NK1 but can also activate the mast cell-specific receptor Mrgprb2 to promote the release of proinflammatory cytokines and chemokines, as well as facilitate the migration of immune cells to nociceptors (McNeil et al., 2015; Green et al., 2019). Additionally, NGF released by mast cells plays a primary role in peripheral sensitization by allowing the phosphorylation of transient receptor potential vanilloid 1 (TRPV1), which is a determinant factor in pain transduction. At the same time, TNF-α, IL-1β, and IL-6 also activate TRPV1 and other channel receptors like transient receptor potential ankyrin 1 (TRPA1), and sodium channels Nav1.7, Nav1.8, Nav1.9 in the nociceptor. Activation of these targets further contributes to peripheral sensitization and enhances signaling between nociceptor cell bodies in the DRG and the cerebral cortex where it will be processed as a pain sensation, subsequently resulting in central sensitization (Basbaum et al., 2009; Ji, et al., 2016; Pinho-Ribeiro et al., 2017; Locke et al., 2020).

Another determinant factor in the central sensitization process is the activation of Toll-Like Receptors (TLRs) in neurons and glial cells (Lacagnina et al., 2018; Zhang et al., 2020; Liu et al., 2022). Increased TLR signaling in macrophages, glial cells, and sensory neurons, accompanied by decreased action potential thresholds in nociceptive neurons, leads to increased nociceptive excitability and firing. The resulting exaggerated nociceptive response is a critical factor in the transition to persistent pain (Pinho-Ribeiro et al., 2017; Lacagnina et al., 2018; Locke et al., 2020). Furthermore, disruption of the BBB during the neuroinflammatory response allows for massive entry of immune cells into the CNS. The subsequent direct activation of nociceptive neurons and glial cells along the cerebral pathways in the brain worsens neuroinflammation and central sensitization, which perpetuates pain signaling, and facilitates the transition to chronic pain (Patel et al., 2015; Kempuraj et al., 2017; Gupta and IkkaHarvima, 2018; Mastrangelo et al., 2018).

In a rodent model, a proinflammatory phenotype similar to M1 in activated macrophages in the DRG was demonstrated, promoting the production of CGRP, which plays an active role in the persistence of the pain state (Massier et al., 2015).

2.2 Glial cell activation is essential in the transition from acute to chronic pain

Based on emerging evidence, the activation of glial cells is a phenomenon closely related to the origin and persistence of neuropathic and chronic pain, therefore it might be considered a "gliopathy" (Ji, Berta, and Nedergaard, 2013). Under normal conditions, the glial cells, especially microglia, provide microenvironmental conditions that promote neuronal development, synaptic pruning, and circuit formation, as well as the modulation of synaptic connectivity, neurotransmission, and neuroplasticity (Um, 2017). Microglial cells in the CNS emulate the phagocytic function of peripheral macrophages, helping in clearing the neural environment of damaged cells, microbial agents, and debris (Hanisch and Kettenmann, 2007). Astrocytes provide structural and metabolic support to glutamatergic synaptic transmission, regulating the extracellular concentration of glutamate (Vandenberg and Ryan, 2013; Ji et al., 2019). At the same time, oligodendrocytes speed up the synaptic transmission of the electrical impulse and are actively involved in pain in various ways. The production of IL-33 by oligodendrocytes in the spinal cord mediates the activation of microglial ST2 receptors in a mouse model of neuropathic pain (Malta et al., 2019). Glial cells also release anti-inflammatory cytokines that play an active role in repairing neurotoxic damage caused by neuroinflammation (Tiwari et al., 2014). Both in the DRG and in the trigeminal ganglion, satellite glial cells (SGCs) are located near the nuclei of nociceptive neurons, creating a neural structure unique to the PNS. Under normal conditions, this neuron-SGC coupling helps to maintain neuronal homeostasis, particularly by protecting axonic insulation and the integrity of the neural soma. Recent preclinical studies showed that SGCs have a key role in the neural repair process (Xiao et al., 2015; Hanani and Spray, 2020; Gazerani, 2021). Activation of SGCs after nerve damage leads to changes in K+ channels and increased release of cytokines and ATP (Mujenda et al., 2007). Immediately following nerve injury, there is an upregulation of the ATP receptor subtype P2X4 in spinal microglia, which influences microglial signaling to promote mechanical allodynia (Tsuda et al., 2003).

This functional relationship between neurons and SGCs contributes to the development of neuronal hyperactivity, and both peripheral, as well as the chronification of pain (Mujenda et al., 2007). After a peripheral nerve lesion, the degeneration produced by TNF-α and IL-1β release from the Schwann cells (SCs) significantly contributes to the progression to neuropathic pain (Fang et al., 2023).

Shortly after nerve damage, signs of microgliosis appear in the ipsilateral dorsal horn of the spinal cord within 2–3 days. It reaches peak levels in 4–7 days, before progressively declining weeks to months after the nerve lesion (Kohno et al., 2018). Spinal microglia activation originates from proinflammatory cytokines, chemokines, extracellular proteases, purines, excitatory neurotransmitters, and neuropeptides released by macrophages, natural killer cells (NK), and T-cells (Grace et al., 2014). T Helper 1 cells (Th1) also produce interferons (IFNs) that react with type 1FN receptors (IFNR) expressed by microglia, astrocytes, and neurons (Tan et al., 2021). IFNs vary in their effect when interacting with IFNR. IFNγ exhibits proinflammatory actions that activate glial cells and nociceptive neurons, contributing to the development of pain. IFNα and IFNβ promote the inactivation of microglia and astrocytes, as well as the inhibition of synaptic transmission in the spinal cord. In effect, they encourage restoration of the peripheral and central sensitization processes, leading to the resolution of neuropathic or chronic pain (Tsuda et al., 2009; Tan et al., 2021).

The complex array of inflammatory glial and immune mediators also includes other signaling molecules originating from the damaged nerve tissue, such as DAMPs and PAMPs (including

LPS) (Ji et al., 2019; Gong et al., 2020; Jurga et al., 2020). Neural damage results in the overexpression of peripheral and central neurotrophic factors generated by neural damage, such as NGF, brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF) (Salio et al., 2014), neurotransmitters and neuropeptides (substance P, glutamate, CGRP) (Gwak et al., 2017). Additionally, activated astrocytes located in the presynaptic sensory neurons of the DRG and dorsal horns generate chemokines that intervene in microglial and oligodendrocyte activation (Chen et al., 2014; Ji et al., 2018; Ji et al., 2019; Liu et al., 2019; Malta et al., 2019). Upregulation of ATP receptor subtype P2X2 in spinal microglia immediately after nerve injury is also involved in microglial signaling that leads to mechanical allodynia (Tsuda et al., 2003). As mentioned before, once the microglial cells are activated, a highly dynamic process begins that leads to the production of multivariate morphological, metabolic, and functional states (Paolicelli et al., 2022) with a unique role in maintaining or repairing the neuroinflammatory state. These include the classically activated proinflammatory M1-like phenotype, and the intermittently activated M2-like phenotype microglia with anti-inflammatory and reparative effects (Willemen et al., 2014; Chen et al., 2018). M2-like phenotype microglia produce inflammation, cytotoxicity, and vascular changes leading to increased BBB permeability, and prolongation of the immune response (Jurga et al., 2020).

The synthesis and release of all these inflammation by-products in the PNS and CNS significantly affect synaptic transmission and interneuronal networking excitability, influencing the initiation and maintenance of pain (Coull et al., 2005; Ji et al., 2006; Pezet and McMahon, 2006; Kawasaki et al., 2008; Vezzani and Viviani, 2015). The resulting neuroinflammatory state creates an exaggerated afferent input that promotes changes in plasticity in nociceptive neurons and synaptic transmission at the spinal cord level, increasing hyperexcitability of nociceptors, enhancement of signaling transduction to the brain and facilitating the development of central sensitization, which perpetuates the pain state and the transition to neuropathic or chronic pain (von Banchet et al., 2009).

2.3 The resolution phase of the neuroinflammatory damage

After peripheral nerve injury, transected axons elicit degeneration of the distal nerve endings and in the axotomized nociceptors bodies in the DRG. The post-injury neuroinflammation state that occurs can originate deleterious consequences (neuropathic and/or chronic pain) and beneficial effects triggering reparative processes in the injured peripheral nerve as well as in the DRGs nociceptive neurons. The axonal regeneration and neuron functional recovery is not an autonomous process and depends on immune cells, especially macrophages, and glial cells (Schwann cells). On day 3 after nerve injury, macrophages accumulate, most at the distal end and less proximal to the lesion (Taskinen and Roytta, 1997). Almost at the same time (day 4), macrophage accumulation can be detected at the DRG (Lu and Richardson, 1993). This noxious event activates chemokines CCL2 in the nerve injury region, Schwann cells, and in the DRG, which binds to CCR2, G-protein-coupled receptors located in the macrophages, attracting them to the distal nerve cell body area as well as to the DRG (Ransohoff, 2009). Macrophages and Schwann cells facilitate the removal of axon debris, myelin phagocytosis, and the clearance of molecules from degenerating axons that inhibit neural regeneration and axonal outgrowth in the nerve endings and the DRG (Zigmond and Echevarria, 2019). Post-traumatic neural regeneration is almost an exclusive property of the PNS, however, not all injured axons achieve complete regeneration (Gordon et al., 2009) since the neural repair mechanism in the PNS is not only slow but often incomplete. Resident macrophages are cells found in peripheral nerves and ganglia while infiltrating macrophages access the neural tissue after a nerve injury or infection, outnumbering the resident macrophages. Although resident macrophages are the "first responder cells" after nerve injury, later, infiltrating macrophages outnumber them (Mueller et al., 2003). Unlike peripheral axonal damage or transection, there is no macrophage accumulation with crushing damage to the dorsal root neurons, in which regeneration of centrally projecting axons does not occur (Kwon et al., 2013).

During the resolution phase that follows the initial post-injury activation, M1-like macrophages can transition into M2-like macrophages (Van der Bossche et al., 2016). Several recent studies showed that infiltrating macrophages attracted to the nerve injury and to the DRG express M2-like subtype which not only release antiinflammatory cytokines (IL-4, IL-10, IL-13, and TGF-β) depending upon the pathologic state (Willemen et al., 2014). M2-like macrophages also release other mediators that promote repair of the axonal and neuron damage such as neurotrophic factors, growth factors, colony-stimulating 1 (CSF-1), and progranulin (Kwon et al., 2013; Martinez and Gordon, 2014; Wynn and Vannella, 2016; Jurga et al., 2020). Oncomodulin, secreted by macrophages and granulocytes, promotes neuron outgrowth in axotomized sensory neurons in the DRG (DeFrancesco-Lisowitz et al., 2015; Kwon et al., 2013). *In vitro* studies demonstrated that cytokine IL-1β secreted by macrophages stimulates the production of NGF and other neurotrophins such as BNDF, NT3, and NT4/5, which enhances regeneration at the distal nerve stump (Barrette et al., 2008). A recent study conducted by Feng et al. reported that the self-renovation of resident macrophages in the DRG is a contributing factor to axonal regeneration very similar to the self-renewal of glial cells in the brain (Feng et al., 2023).

Microglial polarization into the M2-like phenotype is also stimulated by the presence of IL-4 and IL-13 cytokines produced by T-cells (Th2) (). After activation, the M2-like microglial phenotype releases antiinflammatory cytokines (IL-10 and TGFβ), (Saijo et al., 2013; Jurga et al., 2020).

M2-like phenotype microglia plays a decisive role in repairing neural damage by inhibiting neuroinflammation, restoring neuronal homeostasis, removing cellular debris through phagocytosis, and protecting the extracellular matrix (Jurga et al., 2020).

Other components involved in the resolution phase of neuroinflammation are resolvins and protectins, which are a group of molecules derived from omega-3 fatty acids. Resolvins and protectins represent one part of a biochemical arsenal that functions to restore homeostasis once the initial inflammatory response is over (Sommer and Frank, 2011). New data suggest these substances might have future applications as analgesic drugs

that reduce inflammatory pain by blocking TRP channels and NMDA receptors in somatosensory neurons located in the dorsal horn of the spinal cord (Ji et al., 2011; Sommer and Frank, 2011). Additionally, resolvins and protectines exhibit a neuromodulator-like profile that affects only pathological pain sensations, but not normal sensations evoked by painful stimuli (Ji et al., 2016; Roh et al., 2020).

The transition from acute to chronic pain can start shortly after the event that triggered the onset of the acute pain (2–3 weeks) (Price and Ray, 2019). Effective modulation of the neuroinflammation and initiation of the restorative process requires a balanced expression of M1-like and M2-like microglial phenotypes. A recent preclinical study by Li et al. in rats revealed that activated microglia mediate the transformation of spinal cord astrocytes predominantly into the A1 phenotype, which promotes neuroinflammation and neurotoxicity, and favors the appearance of CPSP, and to a lesser extent into the A2 phenotype, which provides neuroprotection and restoration (Li et al., 2020). The existing preclinical and clinical evidence suggests that after this transitional process, the maintenance of the chronic pain state is mainly attributed to central sensitization; however, recent clinical studies using neuroimaging have shown that peripheral nerve blocks in patients with neuropathic pain provide pain relief. This suggests that sustained primary afferent output from nociceptors and altered neuroplasticity, characterized by hyperexcitability and over-signaling in the synaptic relays at the spinal cord play a crucial role in the development of chronic and neuropathic pain after surgery (Haroutiunian et al., 2013; Haroutiunian et al., 2014; Vaso et al., 2014; Ratte and Prescott, 2016).

3 Importance of the enteric nervous system in acute and chronic pain

Increasing evidence supports the role of continuous functional interdependence of the microbiota, enteric nervous system (ENS), PNS, and CNS. The so-called microbiota-gut-brain axis is composed of the colonic myenteric plexuses, the dorsal root ganglion, the nucleus solitary tract (NST), and the periaqueductal grey. It constitutes an important factor in the pathogenesis of acute visceral, nociplastic, neuropathic, and chronic pain; however, most studies remain in the realm of research in animal models of pain (Harotounian et al., 2014; Vaso et al., 2014; Ratte and Prescott, 2016). The intrinsic structure of the ENS consists of a neural network of resident neurons and glial cells located in the intestinal mucosa and the inner muscularis propria. The ENS integrates and transduces immune, inflammatory, and neuroendocrine signals that reach the brain tissue through the vagus nerve and the BBB, producing alterations in its permeability and allowing the translocation of immune and inflammatory mediators to the brain tissue. Current evidence also suggests that enteric neuronal plasticity and glial activation are fundamental players in the development of neuropathic and chronic pain (Morales-Soto and Gulbransen, 2019). The alleged mechanisms proposed to activate enteric neurons and glial cells include the production of immune and inflammatory mediators and neuromodulatory by-products of bacterial metabolism (Grubišić and Gulbransen, 2017). Enteric neuronal plasticity is directly involved in sensitizing visceral afferent sensory nerve fibers, augmenting neural sensitivity, and increasing firing patterns in the peripheral pain neural networking, spinal cord, and brain, which are all regulated by glial cell hyperactivity (Grubišić and Gulbransen, 2017; Morales-Soto and Gulbransen, 2019). Subtle differences in microbiota composition, amino acid levels, and neurotransmitters have been detected in individuals suffering from several chronic pain syndromes, such as fibromyalgia (Clos-Garcia et al., 2019; Ji et al., 2019; Minerbi et al., 2019; Bistoletti et al., 2020). Qualitative and quantitative alterations in the microbiota, or dysbiosis, stimulate the production and release of proinflammatory substances by enteric immune and glial cells. Some noxious events, including surgical trauma and bowel surgery, produce dysbiosis and activation of IL-1 receptor type I (IL-1R1), which induces a reactive phenotype of enteric glial cells (EGCs) called enteric gliosis (Schneider et al., 2021). Once activated, EGCs release cytokines, chemokines, and colony-stimulating factors 1 and 3 (CSF1, CSF3) which are key elements modulating macrophage activation (Grubišić and Gulbransen, 2017; Schneider et al., 2022). The bidirectional communication between EGCs and macrophages is crucial to enteric neuroinflammation and visceral afferent nerve hypersensitivity (Schneider et al., 2022). Vagal afferent neurons (VAN) are the enteric primary nociceptive neurons that integrate gut signaling and connect VAN via the vagus nerve to the NST in the brainstem. In this way, dysbiosis modulates inflammation in the afferent vagal nerve and the transmission of noxious information from the gut to the brain (Kim et al., 2020). The visceral nociceptor neurons and VAN hyperactivity also induce nociceptor sensitivity in the PNS, which is substantive in generating chronic visceral pain and transitioning from acute to chronic pain. Schneider et al. recently identified another potential pathway for enteric gliosis and neuroinflammation following intestinal surgery. According to them, surgical trauma triggers ATP release that binds to purinergic receptors (P2X receptors), drives enteric gliosis and intestinal inflammation, and is mainly responsible for visceral hypersensitivity and abdominal pain (Schneider et al., 2021) Although not wholly studied, enteric gliosis and gliotransmitter release have been suggested to be closely associated with the activation of enteric nociceptive neurons and TRVP1 sensory neurons in the mesenteric plexus, contributing to the development of prolonged visceral pain (Figure 2). However, the mechanisms involved in the changes in sensitivity in the PNS and CNS resulting from the interaction of gliotransmitters with enteric nociceptors remain largely unknown (Xu et al., 2008; Morales-Soto and Gulbransen, 2019). After the neuroinflammatory response accompanying the initial neural injury, the healing process begins and promotes tissue restoration, neutrophil apoptosis, and scarification. However, nociceptor activation and the release of immunoinflammatory mediators may persist elevated for weeks or months, leading to the transition to chronic or neuropathic pain (Chavan et al., 2017).

4 Neuroinflammation associated with opioids

The belief that opioids exert their effects solely by binding to their receptors does not adequately support the pharmacological basis of their use as pain control agents in clinical practice. The appearance of

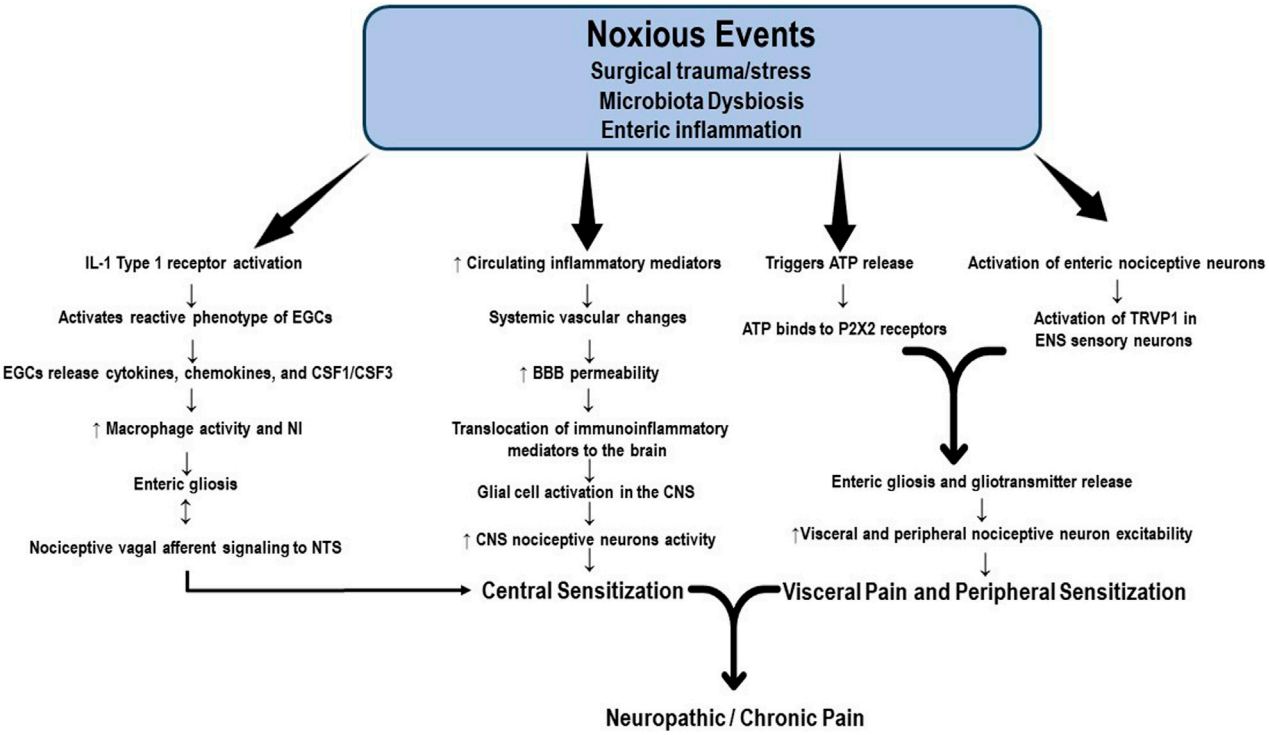

FIGURE 2
Potential mechanisms of enteric gliosis. Noxious events, including surgical trauma and bowel surgery, produce enteric dysbiosis and activation of the IL-1 receptor, which induces a reactive phenotype of enteric glial cells (EGCs), a process called enteric gliosis. EGCs release cytokines, chemokines, and colony-stimulating factors 1 and 3 (CSF1, CSF3), key elements modulating macrophage activation. The crosstalk between EGCs and macrophages is crucial to enteric neuroinflammation and visceral afferent nerve hyperactivity. Vagal afferent neurons (VAN) are the primary enteric nociceptive neurons that integrate gut signaling and connect VAN via the vagus nerve to the NST in the brainstem. Enteric dysbiosis modulates inflammation in the afferent vagal nerve and the transmission of noxious information from the gut to the brain, contributing to central sensitization. The visceral nociceptive neurons and VAN hyperactivity also induce nociceptor sensitivity in the peripheral nervous system. Surgical trauma triggers the release of ATP, which ultimately binds to purinergic receptors (P2XR). This signaling pathway represents another factor responsible for the visceral hypersensitivity and chronic abdominal pain associated with enteric gliosis. Gliotransmitter release activates the mesenteric plexus enteric nociceptive neurons and TRVP1 sensory neurons. Nociceptor activation and the release of immunoinflammatory mediators may persistently elevate for weeks or months, leading to the transition to chronic or neuropathic pain. **BBB:** brain blood barrier; **CSF1:** colony-stimulating factor 1; **CSF3:** colony-stimulating factor 3; **EGCs:** enteric glial cells; **NST:** nucleus solitary tract; **P2X2:** purinergic 2 × 2 receptor; TRVP1: transient receptor potential vanilloid receptor.

undesirable effects that compromise analgesic efficacy, such as hyperalgesia, allodynia, tolerance, and increased opportunistic infections, particularly in prolonged use scenarios, suggests the involvement of other mechanisms. This section considers some aspects of the immune response as elements of the opioid-analgesic equation. It is important to note that interactions between the nervous and immune systems are not exclusively limited to inflammatory conditions. Communication between these systems also occurs as a consequence of signaling crosstalk between immunocompetent cells, glia, endothelial cells, and neuronal cells in peripheral and central locations, and ultimately alters neuronal function (Watkins et al., 2007; Shah and Choi, 2017; Morioka et al., 2019). It is also important to recognize that pain processing is not simply the result of signals traveling from a damaged zone to the brain cortex but the confluence of multiple dynamic influences that can enhance or suppress nociceptive messages (Milligan and Watkins, 2009). Before unraveling the complex relationship between opioids and neuroinflammation, the beneficial analgesic actions of opioids must be separated from the detrimental interactions that underlie their undesirable effects. Additionally, it must be remembered that drugs currently used to treat clinical pain conditions were developed to target neurons before the discovery of these complex interactions that compromise opioid efficacy (Watkins et al., 2007).

The seminal work of Goldstein et al. brought to the forefront that opioids could also nonselective bind to non-opioid receptors (Goldstein et al., 1971). Years after, Wybran et al. reported that morphine possessed an immunosuppressive effect that could be modulated by naloxone, a classic antagonist of opioid activity (Wybran et al., 1979). Later, Watkins et al. published an elegant paper reporting that morphine administration caused glial activation in the spinal cord. As a result, it led to the release of substances that antagonize opioid action while causing pro-inflammatory effects and inducing a central immune response (Watkins et al., 2005). The participation of non-neuronal cells in these mechanisms further complicates the pharmacology of opioids.

Research aimed at clarifying this less-known opioid action identified TLR4 as a critical element of this "atypical" signaling (Figure 3). This transmembrane receptor belongs to the Toll-like receptor (TLR) family, which activates the innate immune response by recognizing PAMPs (from viruses, bacteria, protozoa, and fungi) or DAMPs as a consequence of tissue damage or cell death (Moresco et al., 2011; Zhang et al., 2020). In an interesting study, Grace et al. suggested that morphine administration leads to the persistent

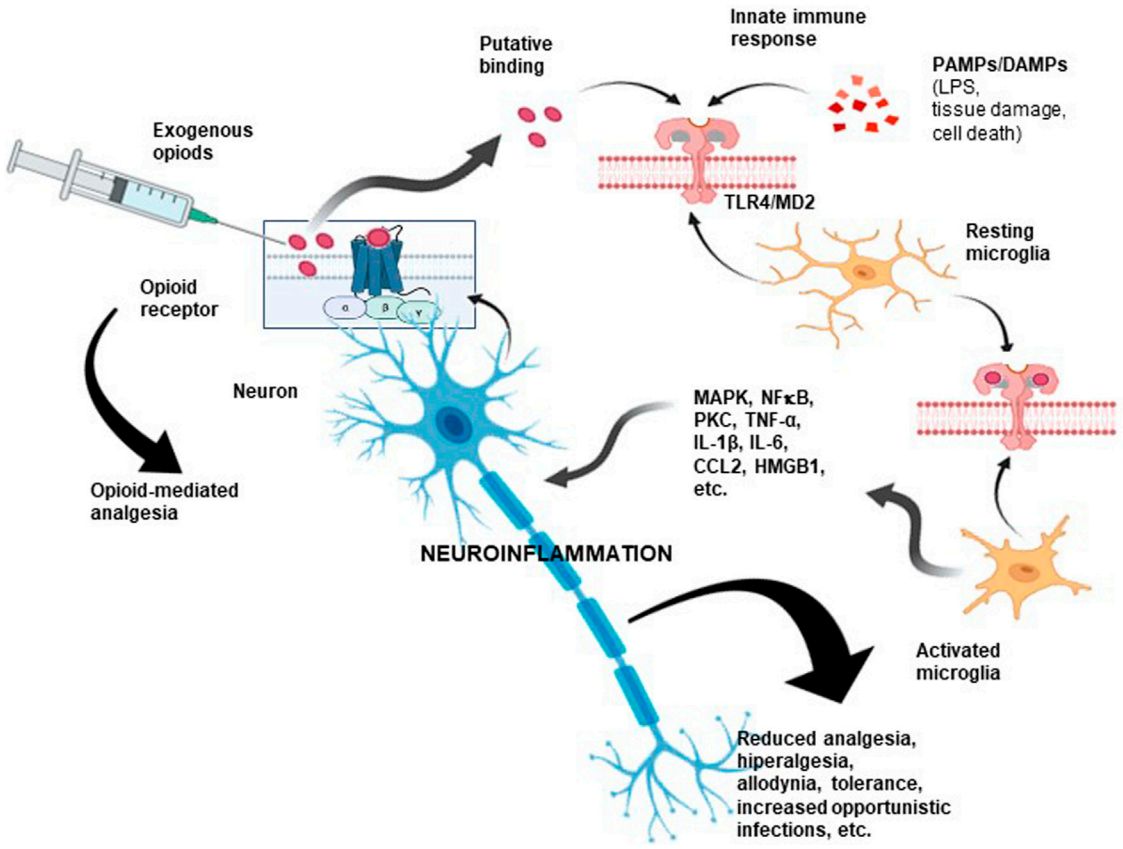

FIGURE 3
Opioid-associated neuroinflammation. As a consequence of opioid administration, proinflammatory scenarios become activated via TLR4/MD-2. As shown, opioids could also bind nonselectively to a non-opioid receptor due to interactions with critical sites shared by LPS, some PAMPs, and DAMPs, inducing downstream signaling. These interactions may compromise analgesic efficacy and cause unwanted opioid side effects. Hence, an opioid could be considered a proinflammatory molecule. This type of neuroimmune interaction could partly explain the unwanted side effects observed after prolonged administration of opioids, including the development of tolerance, allodynia, paradoxical hyperalgesic effects, and even the induction of a proinflammatory response. **TLR4**: toll-like receptor 4; **MD-2**: myeloid differentiation factor 2; **PAMPs**: pathogen-associated molecular pattern molecules; **DAMPs**: damage-associated molecular pattern molecules.

release of DAMPs with actions mediated by TLR4 and the purinergic receptor P2X7R (Grace et al., 2016).

LPS, a component of the cell wall of Gram-negative bacteria, is a classic exogenous TLR4 agonist. However, a comprehensive review by Zhang et al. showed evidence that opioid receptor agonists directly activate TLR4, even in the absence of LPS (Zhang et al., 2020). Of note, this property is also shared with endogenous opioids, which, by the way, can be derived from immune cells. Unlike the interaction between opioid and opioid receptors, the binding of opioids to TLR4 is not stereoselective. Interestingly, morphine-3-glucuronic acid (M3G), an inactive metabolite without affinity for opioid receptors, also activates TLR4 (Wu et al., 2007; Hutchinson et al., 2010).

The high mobility group box 1 protein (HMGB1), an endogenous TLR4 agonist, is an alarmin that acts in synergy with endogenous and exogenous danger signals to promote inflammation. HMGB1 is secreted not only by reactive immunocompetent cells but also by neurons and glial cells (Takeuchi and Akira, 2010; Shah and Choi, 2017). It is important to note that TLR4 has been associated with morphine-induced HMGB1 production (Qian et al., 2020) and that HMGB1 is associated with abnormal pain processing and development of tolerance, hyperalgesia, and allodynia (Zhang et al., 2020).

Myeloid differentiation factor 2 (MD2), is an essential component of the TLR4 signaling receptor complex that recognizes and initiates an innate immune response to bacterial LPS. Opioid binding to MD2 activates signaling processes that lead to increased expression of the nuclear factor kappa-light-chain enhancer of activated B cells (NF-kB) and the production of pro-inflammatory cytokines such as TNF-a, IL-1β, and IL-6 (Takeuchi and Akira, 2010; Liu et al., 2022). Furthermore, opioid and TLR4 signaling activates the mitogen-activated protein kinase (MAPK) pathway, leading to neuroinflammation (Zhang et al., 2020). These pieces of evidence suggest that opioids may function as proinflammatory-like cytokines causing neuroinflammatory and immunosuppressive effects. It also highlights potential intracellular crosstalk mechanisms between immune cells, glial products, and neurons (Wang et al., 2012; Grace et al., 2014; Grace et al., 2015).

As suggested above, the interaction between opioids and the TLR4 receptor may also explain the hyperalgesia, allodynia, and tolerance observed after morphine administration, which has been associated with opioid-induced proinflammatory glial activation (Hutchinson et al., 2010). Evidence indicates that opioid-induced immune effects could explain the drugs decreased efficacy, including

the critical role that non-neuronal immunocompetent cells, such as astrocytes and microglia, could play (Shah and Choi, 2017). As discussed earlier, the endogenous TLR4 agonist HMGB1 can translocate from the nucleus to the cytoplasm or the extracellular space. The binding of transmembrane TLR4 initiates the innate immune response, which activates NF-κB and mediates the transcription of pro-inflammatory cytokines in macrophages, monocytes, and glial cells. HMGB1 binds to several receptor systems, including TLR2, TLR4-5, and the receptor for advanced glycosylation end products (RAGE). All these receptors are implicated in the antianalgesic effects of opioids (He et al., 2013; Das et al., 2016; Morioka et al., 2019). Prior work has demonstrated that morphine administration increases HMGB1 expression and release. Additionally, it has been shown to promote mechanical allodynia, which may be sustained for months after the discontinuation of morphine treatment. In this setting, investigators noted an increase in IL-1β release from activated spinal microglia and the NOD-like receptor protein 3 (NLRP3) inflammasome (Grace et al., 2016), a cytosolic multiprotein oligomer of the innate immune system responsible for activating inflammatory responses. Interestingly, this multiprotein complex activates IL-1β through proteolytic cleavage by caspase-1. TLR4 has also been associated with opioid-induced hyperalgesia via protein kinase C (Araldi et al., 2019). It should be noted that the involvement of TLR4 in the antianalgesic effects of opioids has also been demonstrated in TLR4 mutant and knockout mice (Mattioli et al., 2014), suggesting that perhaps anti-opioid activity does not depend exclusively on TLR4 but can be complemented and facilitated by this receptor.

As we already know, pain induced by a stimulus or pathological damage sets in motion multiple interactions in the neuronal environment. The appropriate knowledge of these multipartite interactions might help avoid vicious cycles that cause pain persistence and counteract the analgesic effect of opioids. Such interactions may also be triggered by opioid administration alone, disrupting the innate response to infections and tissue damage. Therefore, we must expand our knowledge of analgesic pharmacology and the related neuroimmune responses. This might help us to understand that the apparent pronociceptive incongruities observed after sustained opioid administration have a reason to exist. These discrepancies become an interesting paradox when selecting the most appropriate analgesic for pain management. Fortunately, the contributions of recognized research teams are opening new avenues for deciphering these entangled concepts. They are also expanding frontiers in pain management. Specifically, they beckon the future development of therapeutic agents that target immune-neuronal-glial interactions during pain processing without inhibiting these interactions restorative and protective properties. Additionally, they reveal opportunities to design new analgesic molecules that may avoid non-neuronal sites while retaining their original neuronal binding properties. Perhaps the solution to these problems lies in maintaining an adequate homeostatic balance among the cellular constituents that inhabit the same neighborhood in which neurons exist. Most undesirable effects of opioids are not evident under basal conditions in glial and immunocompetent cells.

5 Summary and conclusion

This narrative review was undertaken to address the complex cellular mechanisms involved in the genesis of neuroinflammation as a fundamental factor contributing to the progression and chronicity of pain as well as the immunoinflammatory response resulting from the activation of glial cells by opioids, which aggravates the neuroinflammatory process and causes the development of tolerance, dependence, or paradoxical hyperalgesia that interferes with the analgesic effects of opioid drugs. We also sought to identify the most recent evidence supporting the usefulness and effectiveness of alternative non-pharmacological interventions, such as regulation of the microbiota-gut-brain axis, which can also modulate glial cell activation and create more effective multimodal synergistic therapies for patients with chronic pain syndromes, improving their clinical and functional outcomes.

Author contributions

ME-V: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing–original draft, Writing–review and editing. VT: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Writing–original draft, Writing–review and editing. BEB: Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Writing–original draft, Writing–review and editing. DR: Formal Analysis, Investigation, Writing–original draft, Writing–review and editing. AU: Conceptualization, Formal Analysis, Methodology, Resources, Validation, Writing–review and editing. TW: Conceptualization, Formal Analysis, Resources, Supervision, Validation, Writing–review and editing.

Funding

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

Acknowledgments

The authors acknowledge McKenna Carr, BSc, from the Department of Anesthesiology, The Ohio State University, Wexner Medical Center, Columbus, OH, for her contribution during the final editing process.

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 Pharmacology

TYPE Case Report
PUBLISHED 08 March 2024
DOI 10.3389/fphar.2024.1335345

OPEN ACCESS

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RECEIVED 08 November 2023
ACCEPTED 08 February 2024
PUBLISHED 08 March 2024

CITATION
Shelton T, Nama S, Hall O and Williams M (2024), Case report: Successful induction of buprenorphine in medically complex patients concurrently on opioids: a case series at a tertiary care center.
Front. Pharmacol. 15:1335345.
doi: 10.3389/fphar.2024.1335345

Case report: Successful induction of buprenorphine in medically complex patients concurrently on opioids: a case series at a tertiary care center

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Effective pain management is essential for optimal surgical outcomes; however, it can be challenging in patients with a history of opioid use disorder (OUD). Buprenorphine, a partial opioid agonist, is a valuable treatment option for patients with OUD. Initiating buprenorphine treatment in patients concurrently taking opioids can be complex due to potential adverse outcomes like precipitated withdrawal. Evolving guidelines suggest there are benefits to continuing buprenorphine for surgical patients throughout the perioperative period, however situations do arise when buprenorphine has been discontinued. Typically, in this scenario patients would be restarted on buprenorphine after they have fully recovered from post-surgical pain and no longer require opioids for pain control. Unfortunately, holding MOUD may expose the patient to risks such as opioid induced respiratory depression or addiction relapse. In this case series, we discuss a novel method to restart buprenorphine in small incremental doses, known as micro-dosing, while the patient is still taking opioids for pain. We will present two complex clinical cases when this method was used successfully at a tertiary care hospital system.

KEYWORDS

MOUD, OUD, micro-dosing, Belbuca, buprenophine

Introduction

The opioid epidemic is one of the most pressing public health crises facing the United States today. In the 12 month period ending in December 2022, an estimated 82,310 people died from opioid overdose (CDC, 2023). This statistic marks a worrying continuation in the rise of drug overdoses seen since the onset of the COVID-19 pandemic (Centers for Disease Control and Prevention, 2020). Contributing to the increasing scale of the epidemic is the rise in prevalence of synthetic opioids such as fentanyl (CDC, 2022). The true scale of the opioid epidemic becomes clear through studies that show the true prevalence of people living with OUD is between 6–7 million (Keyes et al., 2022).

Medication treatment of Opioid Use Disorder (MOUD) has been shown to be highly effective in reducing the overall rates of mortality and relapse in patients (Sordo et al., 2017). However, there are certain circumstances when patients on MOUD are at risk for relapse. These include the

induction period, the cessation of MOUD due to medical care, and the time period after hospital discharge prior to following up with outpatient addiction clinic (White et al., 2015; Sordo et al., 2017; Kohan et al., 2021). Newer research and guidelines advocate for the continuation of buprenorphine postoperatively given these risks (American Society of Addiction Medicine, 2020; Kohan et al., 2021). Additionally, it has been shown that buprenorphine may improve mortality in hospitalized patients with a history of OUD even in patients who had not been taking buprenorphine prior to hospitalization (Evans et al., 2015; Kohan et al., 2021; Button et al., 2022). Furthermore, buprenorphine treatment likely increases patient quality of life across a range of metrics (Golan et al., 2022). Unfortunately, hurdles to addiction treatment exist as many patients are hesitant to start or continue buprenorphine perioperatively due to fears of precipitated withdrawal, inadequate pain control, or limited time in the hospital (Button et al., 2022).

Historically it was recommended that buprenorphine be discontinued prior to surgery due to fears of inadequate pain control. MOUD would then be restarted once the patient no longer needed opioids for pain control. Unfortunately, perioperative discontinuation of MOUD put these patients at higher risk of OUD relapse as well as other complications such as respiratory depression (Kohan et al., 2021; Komatsu et al., 2021). To avoid these risks, micro-dosing protocols have been attempted as a way to initiate MOUD while continuing opioid medications. These protocols could allow patients to restart MOUD earlier while avoiding withdrawal symptoms, thereby reducing the risks associated with stopping buprenorphine in the perioperative period. Despite the early promise of micro induction, there is still a lack of consensus surrounding ideal dosing, time frame, and patient selection (Ahmed et al., 2021). In this case series we summarize current literature on the micro-induction of buprenorphine in the postoperative period. We also present our institution's successful experience using patient tailored micro-induction protocols. Here, two patient cases demonstrate how micro-dosing protocols can be best applied and adapted to the individual patient.

Current state of perioperative buprenorphine management

Buprenorphine is a highly effective drug treatment of OUD but concerns about its initiation (also known as induction) have traditionally limited its use in practice. Buprenorphine binds the μ-opioid receptor with a high affinity and thus outcompetes other opioids at the opioid receptor. When a patient has opioids in their system and has developed a tolerance to opioids, buprenorphine induction could lead to "precipitated withdrawal." Precipitated withdrawal is the development of intense and sudden withdrawal symptoms. To avoid this, buprenorphine is typically initiated while patients are already in clinical withdrawal and have abstained from opioids (American Society of Addiction Medicine, 2020).

Though guidelines have evolved to now recommend continuation of buprenorphine in the perioperative period, variations in clinical practice still exist (Acampora et al., 2020; Wyse et al., 2022). One retrospective cohort study using Veterans Affairs Corporate Data Warehouse found that 66% of patients experienced a perioperative buprenorphine dose hold and that a year after surgery, 33% of patients lacked an active buprenorphine prescription (Wyse et al., 2022).

Patients with OUD may face more challenges with their postoperative care, like increased severity of pain following surgery and may require higher doses of opioids for adequate pain control (Cleary and Rood, 2022). In addition, nearly half of patients on MOUD may also suffer from chronic pain. (Delorme et al., 2023). Pain control perioperatively and prompt initiation of MOUD is of particular concern in this patient population. Studies have found that for patients taking MOUD, momentary pain can create cravings and may be linked to relapse (Mun et al., 2021).

Micro-induction techniques can help patients start buprenorphine perioperatively while minimizing the risks of precipitated withdrawal and effects on pain control. Such protocols are used to decrease the risk of precipitated withdrawal and allow for timely treatment of acute pain (Ahmed et al., 2021). Low doses of buprenorphine activate a few mu opioid receptors at a time minimizing symptoms of precipitated withdrawal. Furthermore, introducing small doses of buprenorphine enables clinicians to start or re-start OUD treatment earlier, therefore preventing relapse in patients whose MOUD was stopped for surgery. However, given the multifactorial nature of OUD and the lack of consensus regarding MOUD micro-induction, it is important to work with patients and tailor induction to their unique situations. This is echoed by the 2020 ASAM National Practice Guideline for the Treatment of Opioid Use Disorder which recommends that "decisions related to discontinuing or adjusting the dose of buprenorphine prior to a planned surgery should be made on an individual basis, through consultation between the surgical and anesthesia teams and the addiction treatment provider when possible" (American Society of Addiction Medicine, 2020).

Current micro-induction strategies

The micro-induction technique is versatile and can be used to start buprenorphine for the first time, to convert MOUD from methadone to buprenophine, and in cliical scenarios with an increased risk of precipitated withdrawal. De Aquino, et al. describes success in the outpatient setting using buprenorphine transdermal patches for rapid micro-induction (De Aquino et al., 2020). Similar success was described by Silva, et al. in using the FOOT STEP protocol for outpatient micro-induction (Jasmine Silva et al., 2022). Of note, considerable variation existed among all these protocols further emphasizing the importance of adapting treatments to individual patients. Hammig, et al. describes multiple micro-dosing protocols for the re-induction of buprenorphine (Hämmig et al., 2016). Similar protocols have since been adapted in several other case studies to successfully induce and transition patients on methadone to buprenorphine (De Aquino et al., 2020; Jasmine Silva et al., 2022).

More recent studies have also explored micro-induction in the inpatient setting. DeWeese et al., reported a successful experience using an accelerated schedule in hospitalized patients. They were able to administer sizable doses over the course of 3 days and even a fully therapeutic dose of 8 mg TID over the subsequent 6 days (DeWeese et al., 2021). Another retrospective cohort study described three different micro-induction protocols. The most common method utilized in that study started buprenorphine at 0.5 mg and titrated to 4 mg BID over 6 days. A rapid-micro induction technique was also trialed which started at 0.5 mg q3-q4h. It was found that most of the patients who elected to discontinue buprenorphine initiation due to side effects were undergoing rapid-micro induction (Nunn et al.,

2023). This suggests that hospital based micro-induction is feasible and effective, however careful attention to side effects is required. One characteristic that was shared by these studies was that the majority of patients on micro-induction of buprenorphine were titrated to a lower dose of 8 mg daily while on full-agonist opioids and then increased to doses between 12 and 16 mg daily once opioids were discontinued (DeWeese et al., 2021; Kohan et al., 2021).

Despite the success of micro-inductions in the literature, there remains significant variability in accepted protocol. Hjelmstrom et al.'s review of buprenorphine efficacy data could not reach any firm conclusions on dosage, or protocol, from the existing data. They recommended buprenorphine should be largely "individualized based on a continuous benefit-risk assessment" (Hjelmström et al., 2020). Together these studies show that micro-induction can be an effective tool despite the lack of consensus on protocol.

Patient selection

Patient selection is important for successful induction of buprenorphine using micro-dosing protocol. Patients who can undergo micro-induction are those who have used illicit opioids in the preceding 5 days. Another group includes patients with OUD who are hospitalized with injury or infection causing acute pain and are receiving short acting opioids to manage pain. Using a micro-induction protocol in this circumstance decreases the 12-h waiting period after the last dose of opioid and enables quicker pain treatment. Additionally, patients who are currently on buprenorphine which has been discontinued or held for longer than 24 h over the course of treatment are also good candidates.

Micro-induction of buprenorphine is not recommended for patients who necessitate standard induction protocol. These include patients whose last illicit opioid use was more than 5 days ago and those in severe withdrawal. Patients must consent to any form of MOUD induction, and patients who have an allergy to buprenorphine buccal film or patch are also not candidates for micro-induction.

Variable dosing schedules

The Ohio State University Medical Center (OSUMC) addiction service has utilized various micro-dosing schedules. Patient can be initially started on buprenorphine buccal film (Belbuca™) and then transitioned to sublingual buprenorphine formulations (Suboxone™, Subutex™). Alternatively, patients can be started on a buprenorphine transdermal patch (Butrans™), then transitioned to buprenorphine buccal and then ultimately switched to sublingual buprenorphine formulations. Examples of the most commonly used dosing schedules are outlined in Figure 1.

Case series

Case 1

Patient information and clinical findings

Patient 1 is a critically ill female in her thirties transferred to our institution from an outside facility for management of sepsis and respiratory failure due to pneumonia. Upon arrival she was mechanically ventilated and in septic shock requiring vasopressor support and broad-spectrum antibiotics. Pertinent medical history includes OUD treated with maintenance buprenorphine-naloxone which was discontinued. She was sedated with fentanyl and midazolam infusions. Later in the hospitalization, the addiction service was consulted for recommendations on restarting MOUD. Review of her prescription drug monitoring program history revealed that she had consistently been on buprenorphine-naloxone 8–2 mg daily. After discussion with immediate family, it was determined that restarting MOUD was in line with the patient's treatment goals. A micro-dosing protocol was tailored for this specific clinical circumstances and is outlined in Figure 2. While the patient was on the micro-dosing protocol, breakthrough pain was controlled with short acting full agonist opioids (ex. hydromorphone) and medications for the treatment of opioid withdrawal were administered when needed.

Outcomes and follow-up

Patient was discharged home on HD17 on buprenorphine sublingual tab 4 mg TID with outpatient follow up schedule with addiction clinic.

Case 2

Patient information and clinical findings

Patient 2 is a male in his late thirties, with unknown past medical history upon admission to an outside hospital sustaining injuries after a motor vehicle accident. The patient presented obtunded with a Glasgow Coma Scale 5 and was intubated. Workup revealed facial, ankle and rib fractures, a left sided pneumothorax, and a subarachnoid hemorrhage. In addition, he sustained injury to the right iliac artery and was transferred to our institution for further management.

He underwent multiple procedures including:

HD1: IR embolization of iliac artery. External fixation of left ankle and closed reduction of right hip with traction pinning.

HD6: Tracheostomy, ORIF of Le Fort facial fractures, dental extractions, and PEG tube placement.

HD7: Hip acetabular fracture repair.

HD15: Exploratory laparotomy and splenectomy after development of acute abdomen and hemorrhagic shock.

HD16: Abdominal wound closure.

HD18: ORIF ankle fracture.

The addiction service was consulted on day 24 and the patient discussed history of substance use disorder and consented to buprenorphine initiation. A buprenorphine micro-dosing schedule was initiated as outlined in Figure 3. The patient's pain was managed initially with hydromorphone and ketamine infusions along with oral methadone 25 mg TID. He was then transitioned to intermittent doses of intravenous hydromorphone and scheduled oral oxycodone which was tapered and discontinued prior to discharge.

Outcomes and follow-up

Patient discharged home on day 43 with prescription for buprenorphine-naloxone sublingual strip 8 mg TID with follow up planned at a local addiction clinic.

A

Day 1: Belbuca 300 mcg BID	**Day 1:** Belbuca 300 mcg TID
Day 2: Belbuca 600 mcg BID	**Day 2:** Subutex 2 mg BID
Day 3: Belbuca 900 mcg BID	**Day 3:** Subutex 4 mg BID
Day 4: Suboxone 2 mg BID	**Day 4:** Subutex 4 mg TID
Day 5: Suboxone 4 mg BID	
Day 6: Suboxone 4 mg TID	

B

Day 1: Butrans 20 mcg /24h
Day 2: Belbuca 600 mcg BID
Day 3: Belbuca 900 mcg BID
Day 4: Suboxone 2 mg BID
Day 5: Suboxone 4 mg BID
Day 6: Suboxone 4 mg TID

FIGURE 1
The Ohio State University variable dosing schedules. **(A)** Example dosing schedule utilizing buccal film. **(B)** Example dosing schedule utilizing buccal film and transdermal patch.

Day	Intervention
Day 1	Buprenorphine buccal film 150 mcg at bedtime
Day 2	Buprenorphine buccal film 300 mcg at 9AM, 600 mcg at 9PM. Fentanyl infusion decreased and improved ventilator parameters
Day 3	Buprenorphine buccal film 900 mcg at 9AM, buprenorphine sublingual tab 2 mg at 2pm & 10 pm
Day 4 -5	Patient was exhibiting tachypnea and agitation on the ventilator Fentanyl infusion was increased and dexmedetomidine infusion started. Buprenorphine sublingual tab was decreased to 2 mg BID.
Day 6	Dexmedetomidine infusion was discontinued Buprenorphine sublingual tab increased to 2 mg sublingual tab in the AM 900 mcg buccal film in afternoon and 2 mg sublingual tab at night.
Day 7	Patient was extubated and Fentanyl infusion discontinued Buprenorphine sublingual tab increased to 2 mg QID after mild withdrawal symptoms.
Day 8	Regimen changed buprenorphine sublingual tab 4 mg BID
Day 9	Dose increased to buprenorphine sublingual tab to 4 mg TID due to irritability

FIGURE 2
Timeline and Therapeutic Intervention—Micro-dosing regimen Case 1.

Discussion/conclusion

The current literature supports continuing buprenorphine during episodes of acute pain as it offers distinct advantages (Kohan et al., 2021). By capitalizing on buprenorphine's unique pharmacological properties, clinicians can achieve effective pain control while minimizing the risk of opioid withdrawal, and potentially use buprenorphine as a bridge between analgesia and addiction management (Ahmed et al., 2021; Edinoff et al., 2023). This approach aligns with the overarching shift towards individualized pain management paradigms and reinforces the importance of personalized care plans.

Specific to micro-induction, the existing body of literature is conflicted on its utility. A recent systematic review of buprenorphine micro-induction by Spreen et al., concluded that micro-induction protocols were comparable to traditional initiation protocols, and effectively reduce withdrawal symptoms (Spreen et al., 2022). However, a separate review and pharmacological model suggests that micro-induction protocols may have limited use, and that traditional induction may be a more effective method of induction in many settings (Greenwald et al., 2022). Given the ongoing controversy in the field, case series like this one offer additional value in contributing to this rapidly evolving literature.

Our case series provides a tangible example of the successful micro-dosing of buprenorphine in patients on concurrent full opioid agonists. The seamless integration of buprenorphine within a multimodal analgesic regimen resulted in optimal pain relief, mitigated opioid cravings, and facilitated a smoother recovery process. However, the case also highlights the significance of meticulous patient selection, interdisciplinary collaboration, and judicious dose adjustment to ensure patient safety and favorable outcomes. This is consistent with literature reviews, which

Day	Intervention
Day 1	buprenorphine buccal film 300 mcg BID
Day 2	buprenorphine buccal film 600 mcg BID
Day 3	buprenorphine buccal film 900 mcg BID
Day 4	buprenorphine-naloxone sublingual strip 2 mg BID
Day 5	buprenorphine-naloxone sublingual strip 4 mg BID
Day 6	buprenorphine-naloxone sublingual strip 4 mg TID
Day 8	methadone decreased from 25 mg TID to 20 mg TID
Day 10	methadone decreased to 15 mg TID
Day 11	methadone decreased to 15 mg BID
Day 12	methadone 15 mg once daily buprenorphine-naloxone sublingual strip increased to 6 mg TID oxycodone decreased to 10 mg Q6H
Day 13	methadone discontinued
Day 14	buprenorphine-naloxone sublingual strip increased to 8 mg TID oxycodone discontinued

FIGURE 3
Timeline and Therapeutic Intervention—Micro-dosing regimen.

emphasize the importance of protocol flexibility to treat patients most effectively across wide ranges of settings (Ahmed et al., 2021).

While the reviewed evidence and case studies underscore the potential benefits, it is crucial to acknowledge the complexities associated with continuing buprenorphine in the setting of acute pain. Challenges such as individual variability in response, potential drug interactions, and the need for clear communication among clinicians is paramount (Spreen et al., 2022; Edinoff et al., 2023). Further research is warranted to delve into the nuances of dosing strategies, patient selection criteria, and the long-term impact of this approach on pain trajectories and addiction management. As the medical community continues to advance in its understanding addiction treatment, collaborative efforts will play a pivotal role in shaping its integration strategies like micro-induction, thereby optimizing outcomes for patients facing the intersection of acute pain and opioid use disorder.

Data availability statement

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

Ethics statement

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

TS: Writing–original draft. SN: Conceptualization, Supervision, Writing–original draft, Writing–review and editing. OH: Writing–review and editing, Methodology. MW: Data curation, Writing–original draft, Writing–review and 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.

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 05 April 2024
DOI 10.3389/fmed.2024.1345144

OPEN ACCESS

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RECEIVED 21 December 2023
ACCEPTED 07 March 2024
PUBLISHED 05 April 2024

CITATION
Tsige AW, Beyene DA, Wondmkun YT, Endalifer BL, Habteweld HA, Gebretadik FA, Gebeyehu AA, Azene BA, Alamneh MA, Tesfaye DZ, Fered MA, Girma MT, Mekonen MB, Dessie TY and Ayele SG (2024) Assessment of the appropriateness of stress ulcer prophylaxis use and its determinants among admitted surgical patients at Debre Berhan University Hakim Gizaw Hospital, Ethiopia. A hospital-based cross-sectional study.
Front. Med. 11:1345144.
doi: 10.3389/fmed.2024.1345144

Assessment of the appropriateness of stress ulcer prophylaxis use and its determinants among admitted surgical patients at Debre Berhan University Hakim Gizaw Hospital, Ethiopia. A hospital-based cross-sectional study

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Introduction: Pharmacological stress ulcer prophylaxis (SUP) has been recommended for many years to reduce the risk of clinically significant upper gastrointestinal (GI) bleeding caused by stress ulcers (SUs). Stress-related ulcer bleeding in surgical patients significantly increases morbidity and mortality. Therefore, preventing stress-induced hemorrhage is the most appropriate measure for patients who are at increased risk. However, the inappropriate use of SUP has increased in recent years, and its use in Ethiopian surgical patients has not been well studied.

Objective: The aim of this study was to assess the appropriateness of SUP use and its determinants among admitted surgical patients at Debre Berhan University Hakim Gizaw Hospital (DBUHGH), Ethiopia.

Methods: We randomly selected 230 patients from the whole cross-sectional group of all surgical patients at DBUHGH from 1 February to 30 June 2023. The risk of stress ulcer (SU) development was assessed using the modified American Society of Health-System Pharmacists (ASHP) guidelines. For data analysis, we used SPSS version 25.

Results: The mean age of study participants was 47.2 years (SD ± 20.4), and out of the total of 230, 130 (56.5%) were women. Approximately 66% of study participants took inappropriate SUP based on ASHP guidelines criteria. The most

commonly used drug class for SUP was histamine-2 receptor blockers 115 (50%). Study participants who have a Charlson Comorbidity Index Score of moderate and GI bleeding have been significantly associated with the inappropriate use of SUP.

Conclusion: In our study, inappropriate SUP use was common in the surgical ward of DBUHGH. This may be an area that requires further and more focused working together among clinical pharmacists and medical professionals in an institution-specific SUP protocol that aids clinicians in identifying appropriate candidates for SUP medication.

KEYWORDS

stress ulcer prophylaxis, stress ulcer, American Society of Health-System Pharmacists, surgical patients, Ethiopia

Introduction

Stress ulcer (SU) is a type of hemorrhagic gastritis that can occur in critically ill patients who have experienced a moderate to severe physiological stress event (1–3). The regional bleeding associated with SUs that are accompanied by mucosal obstruction also affects the upper gastrointestinal (GI) system (4). The development of this condition is influenced by several factors, such as increased acid production, changes in the gastric mucosa's epithelial turnover, and abnormal secretion of mucus and bicarbonate (5). Stress-related mucosal damage (SRMD) is classified into two distinct categories: broad, surface epithelial damage and deep, localized SUs that penetrate the sub-mucosa. These ulcers typically affect the GI system and fundal regions of the intestines (6, 7).

Mucosal damage and ulceration are significantly influenced by decreased blood circulation, mucosal ischemia, inadequate perfusion, and circulatory disturbances (8, 9). In addition, a variety of components, including hyper-secretion of acids, alterations in routine defense mechanisms including mucosal and bicarbonate fluids, the release of arachidonic acid, cytokines, and free radicals from oxygen, and ischemia of the GI system, contribute to the development of SUs (9–11). This damage can develop immediately (usually only 24 h after ingestion) or gradually (throughout more than 10–14 days) (10).

In critically ill people, stress-related ulcer bleeding significantly increases morbidity and mortality (12), and the mortality rate ranges from 37 to 77% (13–15). Bleeding from the upper GI tract is one of the most common symptoms of stress-related ulceration (12). Prevention of stress-induced hemorrhage is the most appropriate measure for patients who are at increased risk for SRMD (9, 11, 16). Although excessive acidity is not the main cause of SRMD, regulation of acid release seems to be preventive against bleeding episodes in vulnerable individuals (17, 18). The use of pharmacological stress ulcer prophylactics (SUP) has been encouraged for many years to reduce the risk of clinically serious upper GI bleeding caused by SUs (19, 20).

Proton pump inhibitors (PPIs), histamine-2 receptor blockers (H2RBs), and sucralfate are available as prophylactic alternatives. The choice of the type of prophylaxis can be influenced by a variety of parameters, including the presence of risk factors, the possibility of hospital-acquired pneumonia, and cost (19, 21–23).

In terms of reducing the risk of clinically significant bleeding from the GI tract, a meta-analysis reported that PPIs are significantly more beneficial than H2RB, sucralfate, and placebo (24). However, the scientific studies and recommendations for the critically ill group recommend the administration of PPIs or H2RB as SUP (25, 26). In the literature, inappropriate SUP medication use (drugs given without indication) in surgery patients was common (27). The study conducted by Maz, Chen, and Chu et al. concluded that 22–97% of SUP was administered to surgical inpatients without a clear indication (27–29).

There are no prior studies to evaluate the appropriateness of SUP among surgical patients admitted to DBUHGH. Moreover, there is a limited study examining the suitability of SUP among admitted surgical patients in Ethiopia. Therefore, the objective of this study was to assess the appropriateness of SUP use and its determinants among surgical patients admitted to DBUHGH. The findings of the study will help researchers and decision-makers thoroughly understand how clinicians use SUP and offer practical solutions for SUP management.

Materials and methods

The STROBE checklist was followed for this cross-sectional study.

Study area, design, and period

A hospital-based study was conducted in DBUHGH from 1 February to 30 June 2023, among surgical ward admitted patients. Debre Berhan is the administrative city of North Shoa Zone, Amhara regional state, Ethiopia (30, 31–34).

Population

All surgical ward admitted patients in DBUHGH during the study period were the source population, while patients who fulfilled our inclusion criteria, who took up SUP, and who had been admitted during the study period were the study population.

Eligibility criteria

We randomly selected 230 patients from the whole cross-sectional group of all surgical patients aged ≥18 years who underwent surgical operations in the surgical department, had at least a hospital stay length of 2 days, had risk factors for stress-induced ulcers according to ASHP guidelines criteria, and had taken acid-suppressive therapy. Whereas, study participants who had a history of peptic ulcers,

acid-suppressive medication prescriptions for the treatment of GI diseases such as ulcers, esophagitis, dyspepsia, gastroesophageal reflux disease, or epigastric pain within 1 month before admission, or a new onset of GI disease during hospitalization confirmed by endoscopy, were excluded from the study.

Variables

Appropriateness of SUP was the dependent variable, while study participant demographics (occupation, age, social drug use, educational status, living status, and marital status) and clinical characteristics (number of comorbidities, type of diagnosis, type of acid suppressant therapy used, duration of hospital admission, presence of hospital admission history, and concomitant drug use) were predictor variables.

Sample size determination and sampling technique

The sample size was computed using a single population proportion formula. Considering the 50% prevalence of SUP in Ethiopia (35, 36), since there were no previous studies performed in the current study area. Using a margin of error of 5% at a 95% confidence level resulted in 384.

The expected number of individuals in the source population during the study period (N), based on the average number of patients admitted to the surgical ward who received surgical services within the total 6-month study period, was 463. The corrected sample size, using the following correction formula, was $209.9 \approx 209$,

$$\text{Corrected sample size} = \frac{n \times N}{n + N.}$$

Then 10% contingency of non-response rate is added on 209;

$209 \times 10\% = 21$

$209 + \text{contingency} = Nf = 230$

A simple random selection was employed to select study participants from the electronic medical record (EMR) system of the DBUHGH surgical ward who met the eligibility criteria.

Data quality assurance, collection instrument, and collection process

The data were collected using pre-tested structured data abstraction tools from the EMR of surgical ward admitted patients, which contains all relevant variables based on the objectives of the study. The first part of the structured data abstraction tool contained socio-demographic data, and the second part was the clinical characteristics of the study participants.

Assessment of SUP appropriateness

The appropriateness of SUP was determined using modified American Society of Health-System Pharmacists (ASHP) guidelines with various SUP protocols summarized in Table 1 (10, 37–39). The appropriateness of SUP was identified by clinical pharmacists who were trained on the study protocol in a special workshop that was held by the principal investigator of the study. The inappropriateness of SUP was identified from the collected data using the above guidelines, reviewed literature, drugs.com, Micromedex, and up-to-date resources. The identified inappropriate SUPs were recorded using the data abstraction format, which is taken from ASHP guidelines.

TABLE 1 Major and minor risk factors for stress ulcers used in our study based on ASHP guidelines.

At least one major risk factor from the following
Populations having general surgery
Coagulation related problem (a platelet count <50,000 or INR > 1.5 or a PTT > two times the control value)
Failure of respiration (mechanical ventilation greater than 48 h)
Multiple traumas with an injury severity score greater than or equal to 16
Liver and kidney failure
Head injury with a Glasgow Coma Score of ≤10 or an inability to obey simple commands
History of gastric ulceration or bleeding during the year before admission
Thermal injury involving >35% of body surface area
The presence of at least two of the following minor risk factor
History of NSAIDs >3 months of use
Current high-dose NSAID therapy (ibuprofen >1,200 mg/day, naproxen >1,000 mg/day, all scheduled ketorolac regimens)
Prolong NPO status lasting >5 days with GI pathology or after major surgery
Use of heparin with the therapeutic dose
Corticosteroid therapy (>250 mg hydrocortisone or equivalent)
Sepsis
Occult or overt bleeding for ≥6 days
Use of two antiplatelet agents (i.e., clopidogrel, aspirin, cilostazol, ticagrelor, and dipyridamole)
Use of warfarin

Data processing, analysis, and interpretations

The hand-gathered data were coded, cleaned, and imported into Epi-data 4.2.0 after being carefully validated for completeness. Data analysis made use of SPSS version 25.0. To determine the relationship between the occurrence of inappropriate SUP use and independent variables, binary logistic regression analysis was used. The multivariable binary logistic regression analysis was conducted to identify potential determinants of the inappropriateness of SUP, and all factors having a p-value of 0.2 in the univariable binary logistic regression analysis were included. Statistical significance was defined as a p-value of 0.05.

Results

Socio-demographic characteristics of the patients

As shown in Table 2, a total of 230 study participants took part in this study, of which more than half, 130 (56.5%), were women. Regarding age distribution, the mean age of study participants with

TABLE 2 Socio-demographic characteristics of patients receiving stress ulcer prophylaxis in the surgical ward of DBUHGH.

Variables		Frequency	Percentage
Sex	Female	130	56.5
	Male	100	43.5
Age	<40 years	109	47.4
	40–64 years	57	24.8
	≥65 years	64	27.8
Religion	Orthodox	204	88.7
	Muslim	18	7.8
	Protestant	8	3.5
Marital Status	Single	46	20.0
	Married	181	78.7
	Divorced/widowed	3	1.3
Educational Status	Unable to read and write	26	11.3
	Able to read and write	129	56.1
	Elementary school	8	3.5
	Secondary school	10	4.3
	Diploma and above	57	24.8
Occupation	Farmer	40	17.4
	Merchant	24	10.4
	Employed	37	16.1
	Unemployed	30	13.0
	Housewife	50	21.7
	Student	17	7.4
	Retried	21	9.1
	Others*	11	4.8
Residency	Rural	94	40.9
	Urban	136	59.1

Others*; Daily worker, Garage.

standard deviation was 47.2 ± 20.4 years, and most 109 (47.4%) participants were in the age group of <40 years. Majority 204 (88.7%) of study participants followed Orthodox Christian. Married 181 (78.7%) made up the largest proportion. Approximately half 129 (56.1%) of the study participants could only read and write, and 50 (21.7%) were housewives. More than half of the study participants 136 (59.1%) of them lived in the city (near the hospital).

Clinical characteristics of patients taking stress-induced ulcer prophylaxis

In this study, 128 (55.7%) of the study participants have a comorbidity, with 96 (41.7%) having a Charlson comorbidity index of 1–2 (mild), as indicated in Table 3. In addition, 75 (32.6%) of the study participants were taking medication for SUP at discharge. As for the degree of prescribing SUP medications, half of 117(50.9%) of them were general practitioners.

At Hakim Gizaw Hospital, out of all the patients who were evaluated surgically, 30 (13.04%) had suffered from stroke (ischemic

TABLE 3 Clinical characteristics of patients taking stress ulcer prophylaxis treatment in the surgical ward of DBUHGH.

Variables		Frequency	Percentage
Comorbidities	Yes	128	55.7
	No	102	44.3
Social drug use	Alcohol consumption	3	1.3
	Do not use	227	98.7
Level of SUP prescribers	Intern	47	20.4
	General Practitioner	117	50.9
	Specialist	66	28.7
Charlson Comorbidity	1–2 (Mild)	96	41.7
Index Score	3–4 (Moderate)	12	5.2
	≥5 (Severe)	5	2.2
History of drug allergy	Yes	2	0.9
	No	228	99.1
Stress ulcer drugs during	Yes	75	32.6
discharge	No	155	67.4

and hemorrhagic), 30 (13.04%) had heart failure (congestive heart failure, ischemic heart disease, and hypertensive heart disease), followed by 29 (12.61%) with pneumonia (community-acquired, hospital-acquired, and ventilator-associated), 21 (9.13%) with gastric ulcers, and 19 (8.26%) with fractures of the head, rib, and femur, as stated in Figure 1.

Treatment-related characteristics of study participants

As for the patients taking SUP treatment, 115 (50.0%) of the study participants were taking H2RBs, followed by 67 (29.1%) PPIs. As for the type of PPIs taken for SUP, 52 (22.6%) were taking omeprazole 40 mg daily IV. On the other hand, for H2RBs, 120 (52.2%) took cimetidine 200 mg IV BID. In addition, patients were taking other medications concurrently with SUP; in this study, 68 (29.6%) of study participants were taking NSAIDs, followed by 41 (17.8%) anticoagulants and 30 (13%) systemic corticosteroids + NSAIDs (Table 4).

Prevalence of inappropriate use of SUP

According to the ASHP Guidelines, 151 (66%) of study participants had inappropriate use of SUP (Figure 2).

Duration of stress ulcer prophylaxis taking in days

Among the study participants, the mean duration of taking SUP with standard deviation was 5.18 ± 4.07 days, and the median duration

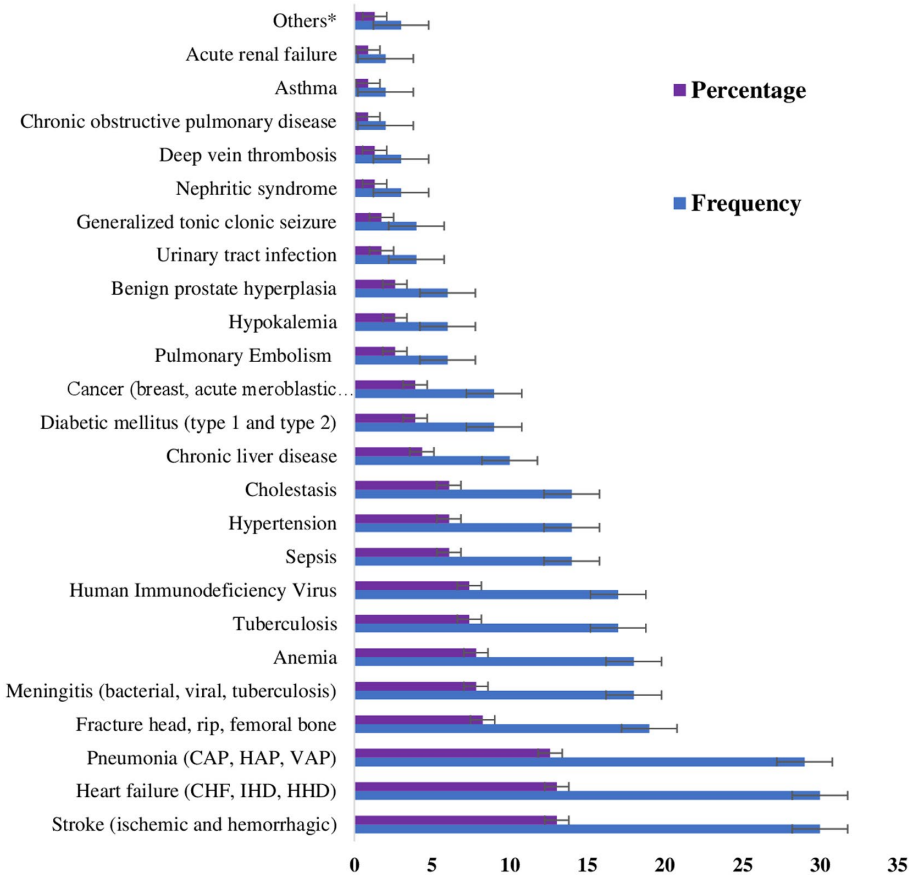

FIGURE 1
Patients' assessments in the surgical ward of DBUHGH throughout their hospital stay. Others* Pelvic inflammatory disease, gout, and Crohn's disease. CHF, congestive heart failure; IHD, ischemic heart disease; HHD, hypertensive heart disease; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

of taking SUP in days was 4 days, ranging from a minimum of 1 day to a maximum of 23 days (Figure 3).

Based on the data shown in Figure 4, among the study participants who were admitted to the HGH, the median length of hospital stay for patients who received SUP was 11.5 days, with a range of 2–60 days. The mean length of hospital stay, along with its standard deviation, was 14.49 ± 10.57 days. In addition to that, the highest mode of length of hospital stay for patients who received SUP was 1 week (7 days).

Factors associated with the inappropriate use of stress-induced ulcer prophylaxis

In univariate analysis, six of the variables studied showed an association with inappropriate use of SUP treatment. Of these candidate variables, all were categorical variables, of which five were multi-categorical variables (age, religion, Charlson Comorbidity Index score, level of SUP prescribers, and reason for taking SUP), and the remaining one variable was binary (sex). Of the six variables used for multivariate binary regression analysis, only two were identified as associated with inappropriate use of SUP treatment by multivariate binary logistic regression methods entered and cross-validated by the hierarchical regression method.

The study found that the odds of inappropriate use of SUP were 59% lower in surgical ward admitted patients whose Charlson Comorbidity Index Score was moderate (ranging from 3 to 4) (AOR = 0.41, 95% CI: 0.20–0.86, $p = 0.02$), as compared to those with mild scores ranging from 1 to 4. In addition, the odds of inappropriate use of SUP were increased 2.99-fold in patients with GI bleeding in the surgical ward (AOR =2.99, 95% CI: 1.18–7.56, $p = 0.02$), compared with patients who had not taken acid-suppressive therapy before admission (Table 5).

Discussion

In the current study, SUP was prescribed to more than two-thirds (79.1%) of surgical ward admitted patients. This is higher than the study conducted in the USA (which included 963 participant data with a retrospective chart review), which reported the use of SUP (32%) of admitted patients (28). This might be due to differences in the study setting, study participant characteristics, and level of prescribers.

The data observed in our study indicated that the mean age of study participants was 47.2 years (SD ± 20.4), and more than half, 130 (56.5%), were women. This finding is higher than the USA the mean

TABLE 4 Treatment-related characteristics of patients receiving stress ulcer prophylaxis treatment in the surgical ward of DBUHGH.

Variables		Frequency	Percentage
Type of acid suppressant	Proton Pump Inhibitors	67	29.1
	Histamin-2 Receptor Blockers	115	50.0
	Histamin-2 Receptor Blockers followed by Proton pump inhibitors	48	20.9
Proton Pump Inhibitors	Omeprazole 40 mg IV daily	52	22.6
	Omeprazole 20 mg po BID	33	14.3
	Omeprazole 40 mg IV BID	29	12.6
Histamin-2 Receptor Blockers	Cimetidine 200 mg IV BID	120	52.2
	Cimetidine 400 mg IV state	42	18.3
Other concomitant drugs used	NSAIDS	68	29.6
	Anticoagulant	41	17.8
	Systemic corticosteroids + NSAIDs	30	13
	systemic corticosteroids	21	9.1
	Anticoagulants + Systemic corticosteroids + NSAIDs	18	7.8
	Anticoagulants + NSAIDs	13	5.7
	Antiplatelet	10	4.3
	Anticoagulants + Antiplatelet ± Systemic corticosteroids/NSAIDs	6	2.6
	Anticoagulants + Systemic corticosteroids	5	2.2
	Anticoagulants + Antiplatelet	4	1.7
	Others*	4	1.7

NSAIDs, non-steroidal anti-inflammatory drugs; IV, intravenous; BID, two times a day. Others*, Anticoagulants + Antiplatelet + Systemic corticosteroids + NSAIDs, Antiplatelet + Systemic corticosteroids, Antiplatelet + NSAIDs, Antiplatelet + Systemic corticosteroids + NSAIDs.

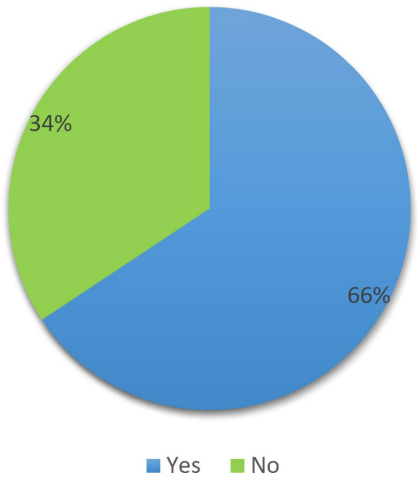

FIGURE 2
Rates of inappropriate use of SUP.

age of the study participants was 53.2 years (±17.4) and the majority of participants were men 74 (56.9%) (35).

Our study showed that surgical ward admitted patients frequently used appropriate SUP medications. Approximately 66% of study participants did not meet SUP criteria based on ASHP guidelines, which was interpreted as inappropriate use of SUP. This finding was higher than the study reported in the USA (22%) (28), China % (1), and Gondar, Ethiopia (63.4%) (36), and lower than the study conducted in University Malaya Medical Centre Malaysia (96.4%) (37) and Jordan (86%) (38). A possible justification might be the study was performed in Malaysia in a tertiary hospital medical ward, and study participants might have had multiple co-morbidities, stayed longer periods in the hospital, and took polypharmacy, resulting in a higher rate of inappropriate prescription of SUP. Initiatives to reduce the use of improper SUPs are thus very important and urgently needed. For SUP, Ethiopia currently lacks its own set of nationally prepared clinical guidelines. As a result, a national agreement or recommendation is necessary to advise clinicians, as well as clinical and community pharmacists, on how to prescribe SUP. Onward visits and a specialized clinical pharmacist can be assigned to track the daily prescription of SUP. Fear of SU syndrome developing in patients outside of intensive care units who were not receiving SUP therapy was one of the factors that led practitioners to unnecessarily prescribe SUP (39). Clinical pharmacist intervention could significantly reduce the inappropriate utilization of acid-suppressive medications (ASMs), drug costs, and the risk of side effects (40–42).

Of the study participants, 75 (32.6%) were taking medication for SUP at discharge. This is lower than the published study done by USA (37.2%) (35). The study conducted in the USA indicated that 75% of the study participants continued on a PPI at the time of discharge (28).

Sixty-seven (29.1%) of PPIs were prescribed as SUP. This is higher than Malaysia (23.9%) (43) and lower than the study performed in Gonder, Ethiopia 76/82 (92.7%) (36), USA (70.9%) (35), Jordan 56% (38), China 96.1% (1), USA (70.0%) (44), Singapore (46.5%) (45), and Ireland (79.0%) (46). Furthermore, the literature reported that 48% (47), 61.6% (48), and 69% (49) of inpatients in the surgery department were found to be inappropriately prescribed PPIs for SUP. Based on recent published studies, PPIs seem to be more effective than H2RAs for SUP (50).

As for the type of PPIs taken for SUP, the prevalence of intravenous omeprazole 40 mg daily was 52 (22.6%). This is lower

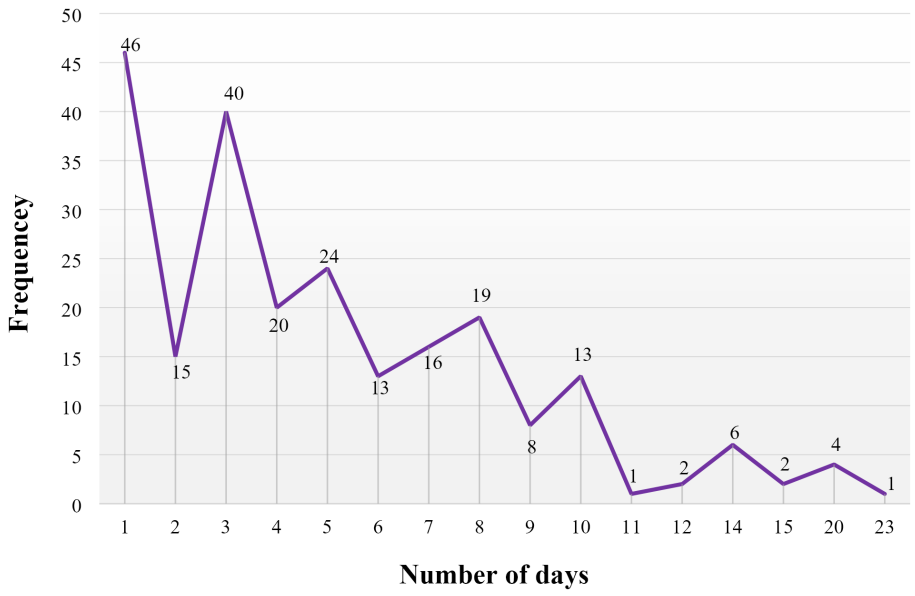

FIGURE 3
Duration of stress ulcer prophylaxis treatment, measured in days, administered in the surgical ward of DBUHGH.

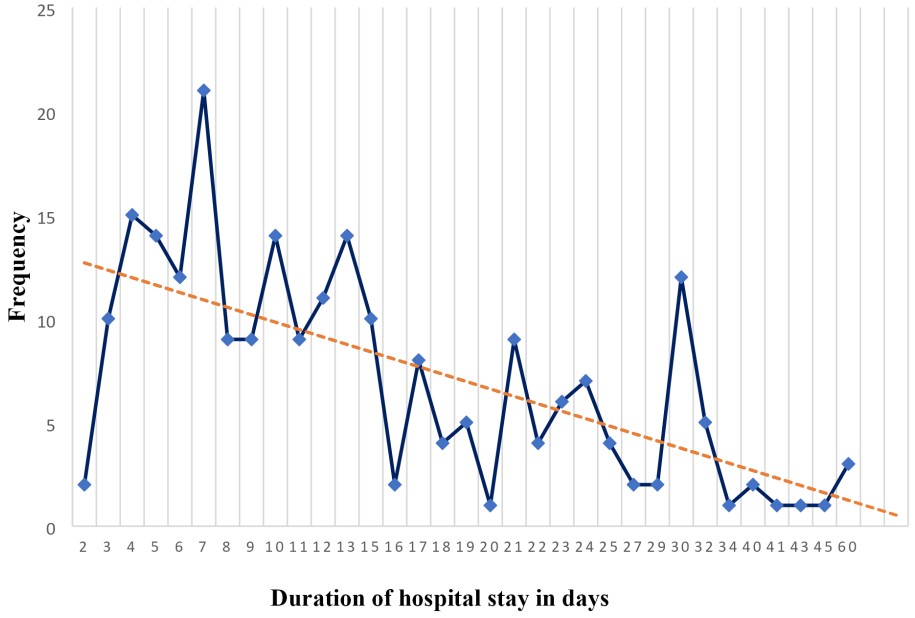

FIGURE 4
Length of hospital stay in days for patients receiving stress ulcer prophylaxis in the surgical ward of DBUHGH.

than a study in China (95.3%) (1). The study conducted in the USA indicated that 75% of the study participants took omeprazole 20 mg capsule daily as SUP (28). In our observation, omeprazole was the only prescribed PPI for SUP. The possible explanation is that, in our study setting, out of all PPIs', only omeprazole is available in IV and PO dosage forms during the study period. However, Ethiopia does not have any PPI lists for SU prevention. According to the literature, injections administered to inpatients with nil-by-mouth situations or who encounter severe motility difficulties have been deemed suitable (49). Oral PPIs' effectiveness was comparable to injectable formulations at comparable doses, but they were more affordable and had fewer difficulties than intravenous administration (47, 49). This highlights the need for clinical pharmacists to intervene and recommend appropriate drug delivery routes for hospital patients.

The mean duration of taking SUP was 5.18 ± 4.07 days. Based on the study conducted in China, the mean duration of SUP was 3.65 ± 3.24 days (1), which appears to be shorter than our finding in our study. However, the USA reported that most patients received SUP for a mean duration of 6.3 ± 4.5 (SD) days (47), which was longer than our finding. This might be explained by the fact that physicians did not reassess the need for PPI use regularly (48).

TABLE 5 Factors associated with the inappropriate use of stress-induced ulcer prophylaxis treatment in patients of the surgical ward of DBUHGH.

Variables	Category	Inappropriate use of SUP		AOR of 95% CI	*P*-value
		Yes	No		
Age	<40 years	44	65	1	0.55
	40–64 years	17	40	1.35 (0.59–3.05)	0.47
	≥65 years	30	34	0.81 (0.35–1.87)	0.63
Sex	Male	52	78	1	
	Female	39	61	0.58 (0.27–1.23)	0.16
Religion	Orthodox	80	124	1	0.15
	Muslim	10	8	0.51 (0.17–1.56)	0.24
	protestant	1	7	5.60 (0.55–56.79)	0.15
Charlson	1–2 (Mild)	43	53	1	0.08
Comorbidity Index Score	3–4 (Moderate)	6	6	0.41 (0.20–0.86)	0.02*
	≥5 (Severe)	1	4	0.37 (0.09–1.53)	0.17
Reason for acid-suppressive medication prescribing	On AST before admission	64	66	1	0.03*
	GI bleeding	14	41	2.99 (1.18–7.56)	0.02*
	Dyspepsia	3	1	0.248 (0.02–3.24)	0.29
	Upper GI tract bleeding	5	8	2.40 (0.61–9.34)	0.21
Level of SUP prescriber	Intern	22	25	1	0.72
	General Practitioner	47	70	0.91 (0.40–2.07)	0.82
	Specialist	22	44	1.24 (0.49–3.07)	0.65

*Indicates statistical significance. AST, acid suppression therapy; SUP, stress ulcer prophylaxis; GI, gastrointestinal; COR, crude odds ratio; AOR, adjusted odds ration.

Study participants who have the Charlson comorbidity index score of moderate (3–4) and GI bleeding had been significantly associated with inappropriate use of SUP in surgical ward admitted patients. On the other hand, studies conducted in Lebanon (51), USA (52), and Iran (53) indicate that increasing age, being male, PPI indications not documented in the chart, and concomitant use of NSAIDs and anticoagulants were associated with inappropriate use of SUP. The possible justification is that participants who have comorbidity and GI bleeding may have an increased likelihood of receiving an incorrect SUP prescription.

5 Study limitations

Due to the small size of the inpatient population and the single location of this study, it was not possible to extrapolate the findings to all hospitals in Ethiopia.

Incomplete electronic records may also be another potential limitation. Patients using acid-suppressive therapy for whom there was no indication on the computerized record were assumed to be taking it as SUP.

6 Conclusion

In our study, inappropriate SUP use was common in the surgical ward of DBUHGH. As a result, our institution does not strictly follow the SUP criteria of the ASHP guidelines. With this finding, it is evident that specialized efforts are needed to prevent prescribing inappropriate SUP to surgical patients, and institution-specific SUP protocols are required to aid clinicians in identifying appropriate candidates for SUP.

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 From Debre Berhan University Asrate Woldeyes Health Sciences Campus Institutional Review Board (ERB), ethical clearance of the study was obtained. 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

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

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Funding

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

Acknowledgments

The authors truly thank all the study participants who volunteered for this 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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