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Cannabinoid products for pain management



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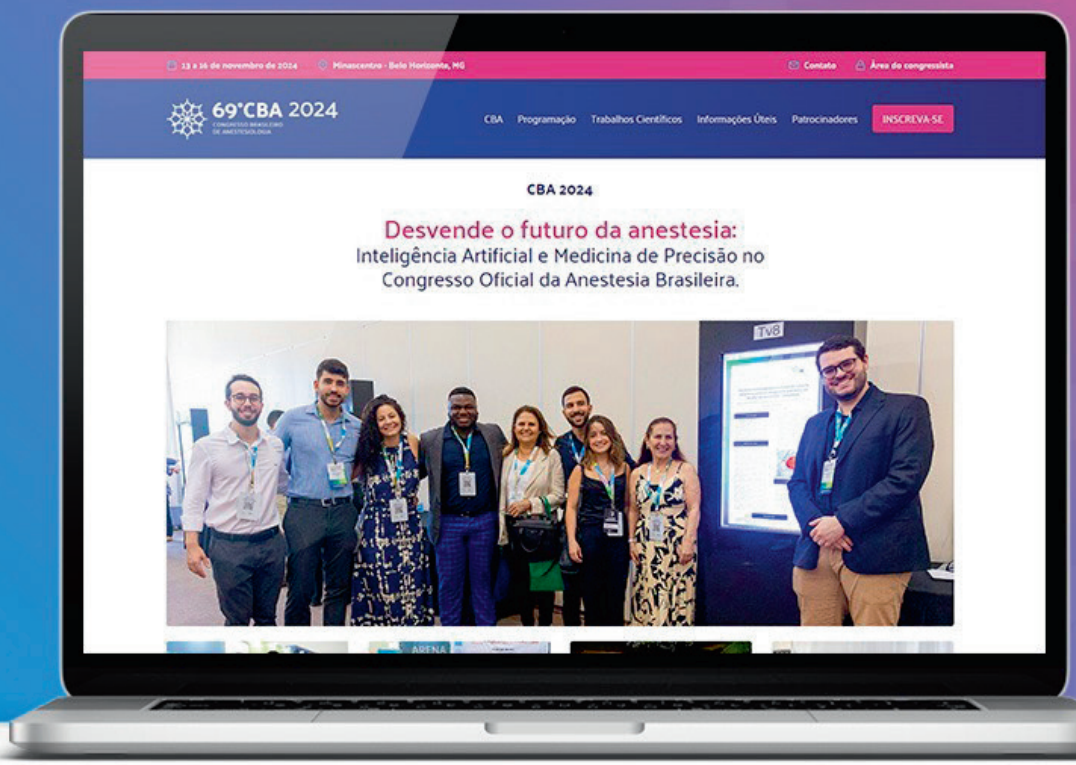

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EDITORIAL

The role of cannabinoids in chronic pain management: clinical insights and challenges

Cannabinoid-based therapies have garnered significant attention as potential treatments for various types of pain, including chronic pain, neuropathic pain, and pain associated with cancer and neurological diseases. Phytocannabinoids, the active compounds found in cannabis plants, interact with the endocannabinoid system in the human body, playing a crucial role in modulating pain and inflammation.[1] The most well-known phytocannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD). The discovery of phytocannabinoids and their effects enabled the design of a myriad of synthetic cannabimimetic compounds that served as the basis for several groundbreaking studies in the last few years.[2,3]

Cannabinoids exert their analgesic effects primarily by activating cannabinoid receptors (CB1 and CB2) in the endocannabinoid system. CB1 receptors, predominantly located in the central nervous system, display critical roles in numerous functions and are associated with the well-known psychotropic effects of THC. Notably, CB1 receptors are located on neuronal circuits along the pain pathways, especially in the dorsal horn of the spinal cord.[4] In contrast, CB2 receptors, mainly found in peripheral tissues and immune cells, are highly induced in microglia following injury and associated with anti-inflammatory and antinociceptive effects.[5]

The elucidation of the roles of the endocannabinoid system in pain modulation has been facilitated by animal models that employed a variety of sophisticated methodologies, including genetic knockout techniques and comprehensive pharmacological investigations.[2,6,7] In a previous systematic review and meta-analysis of animal studies using inflammatory and neuropathic pain paradigms, CB1 and CB2 receptor agonists consistently decreased pain behaviors in inflammatory and nerve-injury models.[8] Importantly, considering the complexity of multidimensional clinical pain, there is indeed a significant discordance between the apparent robust effect of cannabinoids in animal models compared with mixed evidence from human studies of cannabis.[9]

Several clinical trials and meta-analyses have investigated the efficacy of cannabinoids in pain management.[10,11] Studies have shown that cannabinoids can provide moderate pain relief in chronic conditions, but these reports have provided mixed results on efficacy for chronic pain. A previous consensus from the National Academies of Sciences, Engineering, and Medicine has shown evidence of a significant reduction in chronic pain with the use of cannabis or cannabinoids.[12] In a 2018 systematic review of clinical trials, there was moderate evidence that cannabis reduced chronic pain by 30%, but the rate of adverse events was relatively high; the number needed to treat was 24, and the number needed to harm was 6.[13] A 2022 systematic review has investigated the effects of various doses and concentrations of synthetic and plant-extracted cannabinoids.[10] This study found small and short-term improvements in neuropathic chronic pain, however conclusions from this review are limited by the heterogeneity of various cannabis products and the lack of adequate studies on specific preparations and patient populations. Of note, cannabis was used as an adjunct to other pain therapies in most studies.

While numerous studies have examined the utility of medical cannabis for managing chronic pain, most published data are of low to moderate quality due to small sample sizes, short follow-up periods, and non-blinded or non-randomized study designs. Additionally, most studies do not use a standardized dose or route of administration, and the chronic pain populations studied vary by the etiology of the pain. Given the complexity of the plant, lack of product quality control, and numerous routes of administration, conclusive statements on the actual analgesic benefits of cannabinoids still cannot be made.

While cannabinoids offer potential analgesic benefits, their use is associated with various side effects, including dizziness, dry mouth, fatigue, nausea, vomiting, drowsiness, and psychoactive effects, primarily due to THC.[14] The risk of dependence and cognitive impairment also raises concerns, particularly with long-term use.[15] CBD, a non-psychoactive cannabinoid, presents a more favorable safety

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profile and is being investigated for its anti-inflammatory and analgesic properties without the psychoactive effects.[13,14]

Importantly, the legal status of cannabinoid products varies globally, affecting their accessibility and clinical use. In some regions, cannabinoids are available only through special access schemes or clinical trials. Regulatory hurdles and variability in product quality and potency also pose significant challenges to their widespread adoption in pain management.

Ongoing research aims to better understand the mechanisms of cannabinoids and optimize their therapeutic use. This includes exploring the synergistic effects of different cannabinoids, developing formulations with improved safety profiles, and identifying patient populations that may benefit the most from cannabinoid therapy. Additionally, more high-quality randomized controlled trials are needed to establish standardized dosing guidelines and long-term safety data.

In this issue of the *Brazilian Journal of Anesthesiology*, a task force from the São Paulo State Society of Anesthesiology (SAESP) shares its general recommendations for using cannabinoid products for pain management.[16] The authors conducted a narrative review using the Delphi method and requiring a minimum agreement of 60% among panelists. Overall, the document reinforced the potential of cannabinoids in some types of chronic pain management but underlined the importance of cautious prescription. Patients exhibiting poor therapeutic responses to established protocols or demonstrating intolerance to recommended management may be considered as potential candidates for cannabinoids, which should be prescribed by physicians experienced in handling these substances. Of note, the SAESP task force concluded that the use of cannabinoids for treating acute pain or cancer-related pain is still not supported by current scientific evidence.

By further analyzing the present literature review, we observe that there is a need for more systematic and rigorous research on cannabinoids for the management of pain to determine their safety and efficacy. Research on dosing procedures and product characteristics, as well as how these factors may impact other clinical outcomes, is crucial. More consistent evidence is needed to inform policy changes and patient/physician education, aiming to minimize potential risks and optimize benefits for patients seeking cannabinoids as an alternative treatment.

In summary, cannabinoid-based therapies hold promise for pain management, particularly in conditions where conventional treatments have displayed limited efficacy. However, balancing the benefits with potential risks and navigating regulatory landscapes remain key challenges. Continued research and well-designed clinical trials will be essential to fully integrate cannabinoids into mainstream pain management practices.

Declaration of competing interest

The author declares no conflicts of interest.

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EDITORIAL

Anesthesia and perioperative care management in patients with Dengue Fever: considerations and challenges

Dengue is an arbovirus infection transmitted through *Aedes aegypti* mosquitoes that annually impacts millions worldwide. Its causative agent is the Dengue virus (DENV), with four serotypes in humans (DENV 1-4).[1-6] The pathogenesis of Dengue initiates upon viral entry into the bloodstream, targeting and infecting key cells such as endothelial cells, macrophages, and monocytes. This provokes an immune response and release of a variety of inflammatory mediators. While aimed at controlling viral replication, the response significantly influences the clinical spectrum of the disease, from mild to severe presentations.[1]

Dengue exhibits widespread distribution in over 100 countries, mostly in tropical and subtropical regions, including Brazil. Approximately half of the world's population is at risk of Dengue infection, underscoring its status as a critical public health issue.[2,6]

This editorial aims to update clinical manifestations, diagnosis, and classification of Dengue Fever, and clarify anesthesia and critical care management in the perioperative period. Briefly, the search strategy was published literature until April 13, 2024 in PubMed, Scopus, Lilacs and Google Scholar databases, and keywords were: (("dengue") OR ("dengue infections")) AND (("anesthesia") OR ("surgery") OR ("surgical complication") OR ("management") OR ("perioperative period") OR ("postoperative") OR ("pregnancy") OR ("intensive care")). We included articles in English, Portuguese, and Spanish and evaluated the full text of the most relevant records. The authors' opinions were considered for doubtful topics and in the lack of specific literature, but do not represent formal guideline recommendations.

Clinical manifestations

Dengue virus infection can manifest as asymptomatic or as a systemic and dynamic disease with a wide clinical spectrum, which can progress to death. Clinically, it unfolds into three phases: febrile, critical, and recovery (Fig. 1).

The febrile phase is characterized by sudden high fever (39–40°C), severe headache, asthenia, myalgias, arthralgias, retro-orbital pain, and rash (occurring in 50% of the cases, predominantly maculopapular, affecting face, trunk, and limbs). Typically, it lasts 2–7 days. This phase may be mistaken for other febrile illnesses, and in most patients, there is a gradual improvement, with a return to general well-being.[2,7]

The critical phase begins after fever resolution and is marked by plasma leakage, fluid accumulation, respiratory distress, and severe bleeding. Close monitoring for warning signs is required in this phase, indicating potential progression to Severe Dengue and warranting immediate medical intervention. Warning signs include severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums, fatigue, and blood in vomit or stools. Additional severe manifestations include hemorrhage and dysfunction of critical organs, including heart, lungs, kidneys, liver, and central nervous system.[2,6] Patients who have gone through the critical phase experience gradual reabsorption of the extravasated content, leading to progressive clinical improvement over the following 48 to 72 hours (recovery phase).[2,3,6]

The most recent Dengue severity classification (WHO, 2009) divides cases into 3 groups: A) Dengue Fever without warning signs; B) Dengue Fever with warning signs; C) Severe Dengue.[6] Severe Dengue is defined by one or more of the findings: 1) shock or respiratory distress, 2) bleeding, and 3) severe organ damage.[2,3,5,6] Patients with secondary infections are at risk of severity. Several co-existing conditions increase the risk of Severe Dengue: pregnancy, diabetes, hypertension, extremes of age (< 1 year and > 60 years), hemolytic anemia, chronic renal or hepatic failure, asthma, chronic obstructive pulmonary disease, and use of anticoagulants.[2,6,8]

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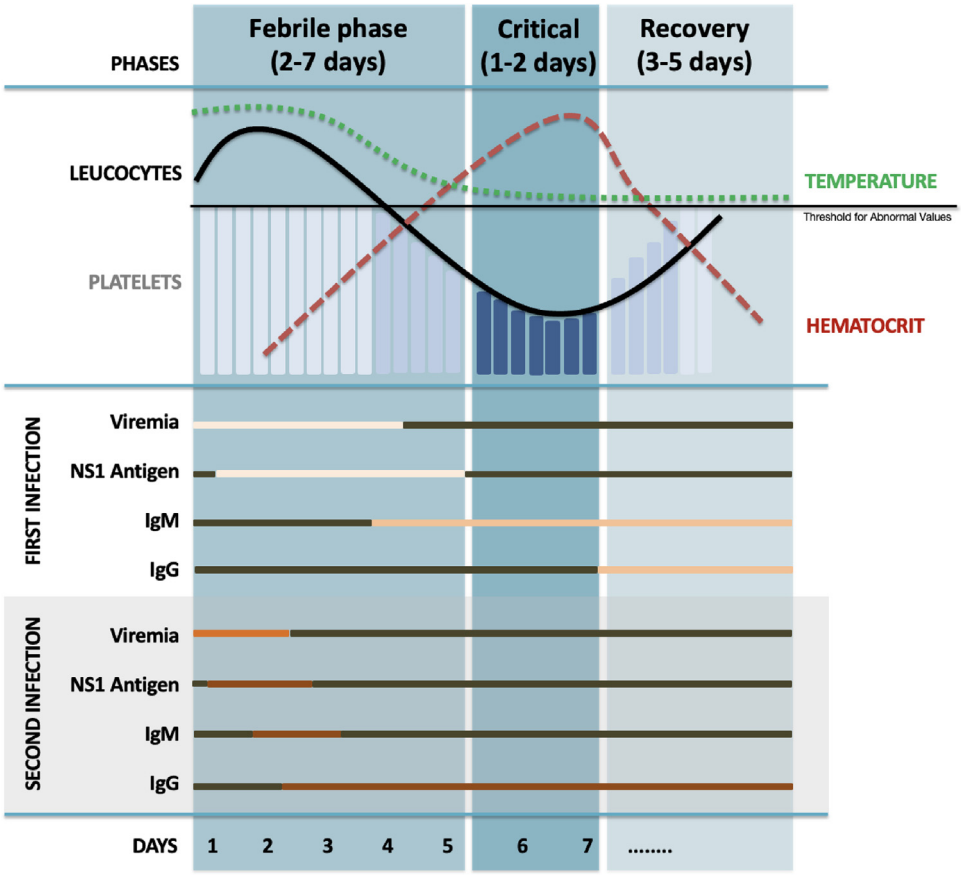

Figure 1 **Correlation between clinical phases of Dengue infection and associated clinical and laboratory findings.** Adapted from: Tejo AM, Hamasaki DT, Menezes LM, Ho YL. Severe dengue in the intensive care unit. J Intensive Med. 2024;4(1):16-33.

Differential diagnoses for Dengue include other infectious diseases, such as Malaria, Leptospirosis, Typhoid Fever, and Zika and Chikungunya viral infections, due to overlapping symptomatology. Dengue, Zika, and Chikungunya share the same vector and some clinical features. Serological assays and polymerase chain reaction (PCR) testing for Dengue virus infection confirm the diagnosis.[1,9,10]

Dengue Fever can generate major organ dysfunction, mainly affecting coagulation, cardiovascular, pulmonary, central nervous system, and others (Fig. 2).

Hematological system and coagulopathy

Coagulopathy, vasculopathy, platelet dysfunction (qualitative and quantitative), and imbalance between clotting and fibrinolytic systems are present.[11] Low fibrinogen levels and prolonged activated partial thromboplastin time (aPTT) are the culprits for coagulopathy. Mild to moderate thrombocytopenia (considered a severity marker) occurs 3 to 7 days after infection and returns to normal levels on day 8 or 9 of infections in adults without Severe Dengue.[12,13]

Cardiovascular

Cardiac manifestations of Dengue Fever can present with a mildly raised cardiac enzyme to severe myocarditis leading to congestive heart failure, arrhythmias, cardiogenic shock, and death.[14] Myocarditis occurs in approximately 21% of Dengue Fever cases.[15]

Central nervous system

Neurological involvement includes encephalopathy, intracranial hemorrhage,[16] cerebellar infarction, and obstructive hydrocephalus.[17,18] Encephalopathy affects from 0.5 to 6.2% of patients. Coagulopathy may cause cerebellar infarct, obstructive hydrocephalus, and spontaneous intracranial hemorrhage with spinal cord hematoma. Dengue patients have a slightly increased risk of non-vascular dementia.[19]

Others

Hepatitis and elevated liver enzymes are frequent. Acute liver failure, encephalitis, myocarditis, and acute kidney injury (AKI) are less frequent but can occur.[15] Among hospitalized patients with Severe Dengue, 3.3 to 4.8% develop AKI, with 14.1% requiring dialysis.[20,21] Dengue Fever can also trigger malignant hyperthermia in susceptible patients.[22]

Dengue fever and pregnancy

The Dengue virus is related to major consequences on pregnancy, ranging from abortion in the first trimester to severe

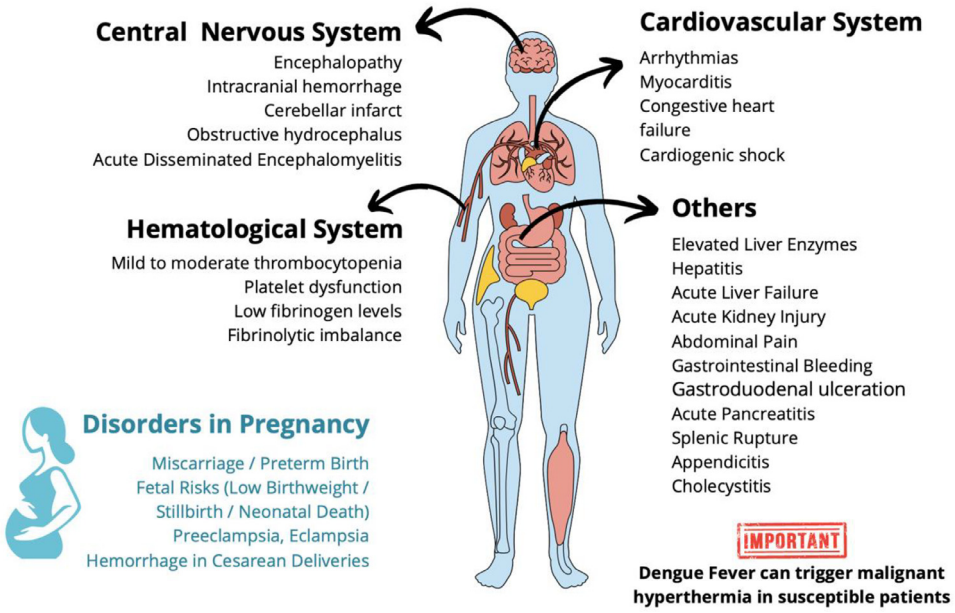

Figure 2 **Clinical manifestations of Dengue Fever across various systems** (original).

maternal illness in the second and third trimesters. Cesarean deliveries are more frequent and adverse outcomes include hemorrhage, preeclampsia, and eclampsia.[12] Dengue is also hazardous to the fetus (increased risk of miscarriage, stillbirth, and neonatal death), but no fetal malformations have been identified.[23] Maternal-fetal transmission has been described. Preterm birth (< 37 weeks) and low birth weight were the most common adverse pregnancy outcomes.[24]

Perioperative implications of Dengue Fever and anesthetic management

Severe Dengue causes fluid leakage, microvascular changes, and coagulopathy.[13] Moreover, the immunological imbalance of Dengue Fever superimposes surgical trauma, leading to surgical complications and major postoperative adverse events, including hemorrhage, systemic inflammation, and shock.[13,21]

Generalized abdominal pain can be a true or apparent cause of acute abdomen in Dengue.[25] Gastrointestinal bleeding, acute pancreatitis, and splenic rupture have been described.[25] Acute appendicitis and cholecystitis can occur, due to direct viral invasion or extravascular leakage and serous edema.[25,26] Neurosurgical emergencies are further challenges.[16,17]

Preoperative evaluation

Preoperative evaluation of the Dengue Fever patient involves a detailed history comprising: 1) days of symptoms; 2) clinical phase; 3) warning signs; 4) severity and organic dysfunction, focusing on hemodynamic instability, plasma leakage, and bleeding potential; and 5) urgency of the case.[27] In surgical patients, suspected Dengue cases must be confirmed by direct or indirect laboratory methods (Fig. 1), depending on clinical manifestations and local resources.

For hypertensive patients, discontinuation of diuretics and other antihypertensives in case of plasma leakage and shock is recommended. Vigilance of glycemic levels and discontinuation of oral hypoglycemic agents are warranted in diabetic patients.[5] Statins should be interrupted during Dengue infection due to their potential to increase transaminases and creatine kinase levels.[5]

Preoperative exams

Main preoperative exams in Dengue Fever and their respective findings include full blood count (baseline hematocrit and platelet counts), serum glucose and electrolytes, renal, hepatic and coagulation tests, thorax radiograph, point-of-care ultrasound (pleural effusion, B-lines in pulmonary edema, ascites, pericardial effusion), electrocardiogram (bradycardia, atrioventricular block, T-wave and ST-segment abnormalities), echocardiogram (ventricular dysfunction and myocarditis).[5,25,27] Outcome and mortality markers are useful in high-risk and critical patients (admission APACHE II and SOFA scores, lactate, serum albumin, and procalcitonin levels).[7]

Perioperative vaccination

Currently, there are two licensed Dengue vaccines: Dengvaxia (Dengvaxia, Sanofi Pasteur Inc., France) and Qdenga (TAK-003, Takeda, Japan).[1] Both are tetravalent live attenuated vaccines targeting all four Dengue serotypes and approved for 9 years and older individuals from endemic areas, with previously confirmed Dengue infection.[1,9,28] The Brazilian Ministry of Health has incorporated Qdenga as a public health policy since December 2023.[29] Adverse effects in vaccinated patients during the perioperative period remain controversial, but there is an isolated recommendation to postpone elective procedures for 3 weeks after attenuated virus immunization and wait 7 days following

surgery for vaccination.[30,31] Yet, this is not a formal guideline, and surgery is not a barrier to immunization programs.

Criteria to undergo elective surgery

Postponing elective surgery after Dengue Fever infection is a relevant but neglected topic. Limited evidence from case reports suggests significant postoperative complications due to Dengue, mainly hemorrhage and respiratory distress.[11,13,21,32-35] Hence, it is strictly advised to avoid surgery during acute Dengue infection, even in mild cases. This recommendation is supported by the existing literature and experience with perioperative Dengue Fever patients. Some experts recommend postponing elective surgery based on the anticipated progression and severity of the disease. Following a confirmed case of Dengue, with day 1 being the onset of symptoms, the suggested waiting periods are as follows: 14 days for group A patients (mild disease), 21 days for group B (patients with warning signs or co-existing conditions), and no specific recommendation for group C (Severe Dengue). However, clinical judgment is paramount, particularly when considering major or time-sensitive surgeries and the vulnerability of the patient.

Additionally, all health-care discharge criteria must be fulfilled: 1) clinical — no fever for the past 48 hours without antipyretics use and improvement in clinical status (general well-being, appetite, normal hemodynamic status, urine output and respiratory function, and absence of bleeding); and 2) laboratory - increasing trend in platelet count and stable hematocrit without the need for intravenous fluids.[6]

Patients on anticoagulant or antiplatelet medication

The main concerns in managing antiplatelet and anticoagulant therapy in Dengue Fever are: 1) risk of thrombotic events, particularly in patients with coronary stents under dual antiplatelet therapy (DAPT); 2) acute bleeding and shock; and 3) low platelet count or rapidly declining trend.[36]

In cases of bleeding, it is imperative to discontinue antiplatelet and/or anticoagulant therapy promptly. Platelet transfusion or fresh frozen plasma may be necessary depending on the severity of bleeding. Hospitalization is recommended for close monitoring of thrombocytopenia in patients at high risk of thrombosis or with platelet counts $< 50 \times 10^3$ cells.μL^{-1}.[3]

The Brazilian Ministry of Health offers specific recommendations for managing antiplatelet and anticoagulant therapy in Dengue Fever:[3]

DAPT: 1) It is generally advised to maintain DAPT in patients with conventional coronary stents implanted within the past month or drug-eluting stents implanted within the past 6 months. 2) If platelets $< 30 \times 10^3$ cells.μL^{-1}, withholding DAPT is recommended.[3] Some experts suggest considering discontinuation of DAPT at higher platelet counts (50×10^3 cells.μL^{-1}).[36]

Anticoagulants: 1) warfarin: if platelet count below 30×10^3 cells.μL^{-1} - withhold; if between 30 and 50×10^3 cells.μL^{-1} - initiate bridging therapy with unfractionated heparin (UFH); and if $> 50 \times 10^3$ cells.μL^{-1} — maintain warfarin therapy with regular monitoring of activated prothrombin time.[3]

Direct thrombin inhibitors (DTIs) and direct factor Xa inhibitors (xabans): if platelets $< 50 \times 10^3$ cells.μL^{-1}, discontinue therapy, followed by hospitalization for bridging therapy with UFH. Bridging therapy should commence after 24 h from the last dose of dabigatran, rivaroxaban, apixaban, or edoxaban, or two times the half-life of the medication.

Intraoperative anesthetic management

Airway management

Plasma leakage in Dengue Fever can lead to airway edema and an increased risk of bleeding during manipulation and intubation, requiring careful attention to airway management.[27] Additionally, patients may experience compromised pulmonary function, hypoxia, and respiratory distress. The risk of aspiration during induction is heightened in cases of persistent vomiting.[6]

Anesthetic agents

In Severe Dengue, plasma leakage and increased capillary permeability are the key mechanisms of hypovolemic shock.[5] Pharmacological repercussions of shock are: 1) reduced central compartment volume and clearance;[37] 2) increased concentration and effect of intravenous anesthetics (propofol with the highest potency in shock, and etomidate the most stable);[37] and 3) decreased minimum alveolar concentration of inhaled anesthetics.[38] In Severe Dengue, rational anesthetics use is recommended; if possible, guided by processed electroencephalogram monitors, such as bispectral index. Baseline neurological assessment is paramount.

Hypoalbuminemia in Dengue Fever leads to an increased unbound fraction and higher plasmatic concentration of local anesthetics, resulting in a lower threshold for local anesthetic systemic toxicity (LAST), particularly in extreme age, comorbidities, and critically ill patients.[39] Cardiovascular and neurological manifestations of Dengue Fever may complicate the diagnosis of LAST. Therefore, the use of local anesthetics requires caution, adhering to toxicity dose limits, and avoiding continuous blocks.

Neuraxial anesthesia and invasive procedures

Neuraxial anesthesia is contraindicated in cases of active bleeding due to the risk of spinal or epidural hematoma. Special precautions are also necessary for invasive procedures: nasogastric tube insertion, bladder catheterization, airway manipulation, and the placement of central venous and arterial lines, which should be guided by ultrasound.[6]

A platelet count $< 50 \times 10^3$ cells.μL^{-1} is a formal contraindication for neuraxial anesthesia, gastrointestinal endoscopy, and major surgery (exceptions: neurological and ocular surgeries [100×10^3 cells.μL^{-1}], and central line placement [20×10^3 cells.μL^{-1}]).[40] For epidural catheter placement or removal, a minimum of 75×10^3 cells.μL^{-1} platelets is

recommended.[40] The risk of spinal epidural hematoma associated with a platelet count $\geq 70 \times 10^3$ cells.μL^{-1} is likely to be very low in obstetric patients with thrombocytopenia.[41] This reference may be applied to obstetric patients with Dengue Fever, but decisions regarding most cases are made on an individual basis.[42,43] Moreover, functional platelet impairment is an additional hazard.[12]

Hemodynamic and fluid management

The cornerstone to reduce morbidity and mortality lies in the early recognition of plasma leakage and supportive management.[1,2] Severe Dengue patients must be admitted to the intensive care unit (ICU) and receive vigorous fluid expansion. Current evidence shows no significant difference between crystalloids and colloids for Dengue Fever; therefore, initial fluid expansion with crystalloids is recommended. Colloids, primarily 5% albumin, may be considered for cases of persistent shock, for instance, after three crystalloid boluses of 10-20 mL.kg^{-1}.h^{-1} over 30 min to 1 h each.[5,7,9,29,44] Clinical parameters indicating response to expansion include decreased tachycardia, improvement of blood pressure or pulse volume, return of capillary refill to < 3 s, level of consciousness, urine output ≥ 0.5 mL.kg^{-1}.h^{-1}, resolution of acidosis, and most importantly, decreased hematocrit.[2,5] It is important to constantly reassess fluid response to mitigate fluid overload, especially in the early recovery period.[6]

Patient blood management (PBM)

PBM is a well-established practice grounded in three major goals: optimizing erythropoiesis, minimizing blood loss, and managing anemia.[45] PBM has been previously applied in the context of Zika virus infection[45] and can be similarly employed for Dengue Fever to optimize patient care and reduce unnecessary transfusions.

In a randomized controlled trial in adult patients with Dengue Fever and $\leq 20 \times 10^3$ platelets.μL^{-1}, prophylactic platelet transfusion was not superior to supportive care in preventing bleeding and was associated with more adverse events (circulatory overload and allergic reactions).[46]

Bleeding in Dengue Fever is multifactorial and cannot be solely attributed to thrombocytopenia.[36] It affects 20–60% of hospitalized Dengue patients[36] and it is an indicator of disease severity. Hematocrit levels and curves are inverse to platelet counts in the critical phase (Fig. 1), and offer a practical guide for the optimal moment for procedures.[5] Thus, the selection of blood components should directly address the underlying cause of coagulopathy: FFP (10 mL.kg^{-1}), cryoprecipitate (1 unit per 10 kg), and vitamin K.[5] Individualized transfusion strategies should be employed, guided by specific goals and using tools such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) when available.[45]

Analgesia and adjuvants

Analgesia plays a crucial role in perioperative care, and a multimodal approach is currently the standard practice. However, it is important to tailor analgesic strategies to accommodate the specific limitations posed by Dengue Fever during invasive procedures. Even minor punctures can lead to significant hematomas in Dengue patients, making peripheral nerve blocks and neuraxial blocks challenging.[32,40] Nonsteroidal anti-inflammatory drugs (NSAIDS) and acetylsalicylic acids should be avoided due to the risk of gastrointestinal bleeding and Reye's Syndrome.[2,6] Similarly, intramuscular injections are discouraged in Dengue patients.[6] Furthermore, corticosteroids lack evidence for efficacy in treating Dengue Fever.[5]

Conclusions

The management of Dengue patients involves timely acknowledgment of risk predictors, warning signs, and laboratory markers to guide rapid interventions. Despite being a worldwide epidemic disease, Dengue Fever remains neglected in many aspects, including anesthetic and perioperative care management. Future research and evidenced-based guidelines are of foremost importance to better understand the implications of Dengue in anesthetic practice and improve outcomes.

Conflicts of interest

The authors declare no conflicts of interest.

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ORIGINAL INVESTIGATION

Neuroligins facilitate the development of bone cancer pain via regulating synaptic transmission: an experimental study



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Abstract
Background: The underlying mechanism of chronic pain involves the plasticity in synaptic receptors and neurotransmitters. This study aimed to investigate potential roles of Neuroligins (NLs) within the spinal dorsal horn of rats in a newly established Bone Cancer Pain (BCP) model. The objective was to explore the mechanism of neuroligin involved in the occurrence and development of bone cancer pain.
Methods: Using our rat BCP model, we assessed pain hypersensitivity over time. Quantitative real-time polymerase chain reaction and Western blot analysis were performed to investigate NL expression, and NLs were overexpressed in the rat spinal cord using lentiviral vectors. Immunofluorescence staining and whole-cell patch-clamp recordings were deployed to investigate the role of NLs in the development of BCP.
Results: We observed reduced expression levels of NL1 and NL2, but not of NL3, within the rat spinal cord, which were found to be associated with and essential for the development of BCP in

Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; AP, action potential; BCP, bone cancer pain; ChE, cholinesterase-homology; DRG, dorsal root ganglion; EGTA, ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid; GABA, γ-aminobutyric acid; GAD, glutamic acid decarboxylase; gcGFP, lentiviral vectors containing green fluorescent protein; GO, Gene Ontology; HEPES, 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid; LG, laminin G-like; NL, neuroligin; NRXN, neurexin; PBS, phosphate-buffered saline; NMDAR, N-methyl-D-aspartate receptor; PSD-95, postsynaptic density protein-95; PWT, paw withdrawal threshold; qRT-PCR, quantitative real-time polymerase chain reaction; sEPSCs, spontaneous excitatory postsynaptic currents; sIPSCs, spontaneous inhibitory postsynaptic currents; sPSCs, spontaneous postsynaptic currents; vGlut2, vesicular glutamate transporter 2.

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our model. Accordingly, NL1 or NL2 overexpression in the spinal cord alleviated mechanical hypersensitivity of rats. Electrophysiological experiments indicated that NL1 and NL2 are involved in BCP via regulating γ-aminobutyric acid-ergic interneuronal synapses and the activity of glutamatergic interneuronal synapses, respectively.

Conclusions: Our observations unravel the role of NLs in cancer-related chronic pain and further suggest that inhibitory mechanisms are central features of BCP in the spinal dorsal horn. These results provide a new perspective and basis for subsequent studies elucidating the onset and progression of BCP.

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Introduction

Bone Cancer Pain (BCP) is a major complication affecting cancer patients' quality of life substantially. Current treatments for pain control are largely ineffective due to the poor understanding of the underlying mechanisms.

Neuroligins (NLs) are type I postsynaptic transmembrane proteins of the central nervous system that are encoded by four genes in rodents (NL1, 2, 3, and 4) and by five in higher primates and humans (NLGN4Y in addition).[1] Neurexins (NRXNs) are presynaptic transmembrane proteins associated with the release of presynaptic transmitters. The Extracellular Cholinesterase-homology (ChE) domain of NLs interacts with the repeats of laminin G-Like (LG) domains of NRXNs.[2] NL-NRXN complexes further establish trans-synaptic connections. Intracellularly, NLs interact with several Postsynaptic Density Protein (PSD)-95/disks large/zonula occludens-1 domains of scaffolding proteins, which directly interact with postsynaptic receptors, ion channels, and other signaling proteins.[3]

Different isoforms of NLs exhibit synapse-specific localization and functions. NL1 is localized to glutamatergic and some cholinergic synapses, whereas NL2 is found predominantly at γ-Aminobutyric Acid (GABA)ergic and glycinergic synapses; NL3 has been observed at both glutamatergic and GABAergic synapses.[4] Conversely, NL4 is poorly conserved among NLs and has been detected at GABAergic synapses in the central nervous system and glycinergic synapses in the retina.[5] At glutamatergic synapses, NL1 couples to PSD-95, which assembles glutamate receptors and binds to presynaptic NRXNs to cluster glutamate.[6-8] At GABAergic synapses, NL2 couples to postsynaptic gephyrin via its intracellular cytoplasmic tail, and in turn recruits GABA receptors[9] and binds to presynaptic NRXNs to regulate the release of GABA.[10] Consistent with its localization, NL3 can modulate both glutamatergic and GABAergic post synapses.[11] Although NL4 is reportedly restricted to inhibitory glycinergic synapses in mice,[5] NL4-R704C complexes have been found to induce an excitatory synaptic phenotype in human stem cell-derived neurons.[12] Besides the studies on the localization and basal synaptic transmission of NLs in synapses, there are numerous studies that focused on how NLs participate in the pathophysiology of diseases, especially in relation to pain. The interaction between NL2 and PSD-95 may contribute to postoperative pain upon an increase in NL2 expression in the spinal dorsal horn.[13,14] NL1 is involved in pain hypersensitivity by facilitating the synaptic incorporation of N-Methyl-D-Aspartate Receptors (NMDARs).[15] However, the level of expression and the role of NLs in different pain models remain controversial.[6,15]

In the present study, we show that modifications in the protein expression levels of NLs were involved in the excitation/inhibition equilibrium of the spinal dorsal horn, thus contributing to chronic pain in cancer-bearing rats. By confocal imaging and whole-cell patch-clamp recordings combined with behavioral analyses, we demonstrate that NL1 regulated hyperactivity of dorsal horn superficial projection neurons and mitigated mechanical allodynia through modulating the activity of GABAergic interneurons, and NL2 alleviated bone cancer-induced pain via decreasing the activity of glutamatergic neurons, which reduced the excitability of spinal cord interneurons.

Methods

Animals

All experimental procedures and protocols used in this study were approved by the Animal Use and Care Committee of Hubei University of Medicine (Hubei, China) and were conducted in accordance with the National Institutes of Health (NIH) guide for the care and use of laboratory animals and with the ethics guidelines of the International Association for the Study of Pain. Adult female Sprague-Dawley (SD) rats weighing 180—220g and newborn rats within 24h were provided by the Institute of Laboratory Animal Science, Hubei University of Medicine (Hubei, China). Rats were housed at 22±2°C with a 12h light-dark cycle and free access to food and water.

Preparation of Walker 256 carcinoma cells

We injected 0.5—1 mL (3×10^7 cells/mL) of Walker 256 rat mammary gland carcinoma cells into the abdominal cavity of a female SD rat weighing 80—100g. Walker 256 rat mammary gland carcinoma cells proliferated in the peritoneal cavity of rats and led to the formation of ascites. Ascitic fluid containing a large number of tumor cells was extracted and cells were harvested by differential centrifugation from ascitic fluid 6—7 days later, diluted to achieve a final concentration of 10^6 cells/mL and kept on ice until surgery. For the sham group, Walker 256 cells were prepared in the same way but were boiled for 20 min prior to injection.

BCP model establishment

The rat BCP model was established by injection of Walker 256 rat mammary gland carcinoma cells into the bone marrow cavity of the right tibia of SD rats according to a previous report.[16]

Lentivirus construction and microinjection

A lentiviral vector containing Green Fluorescent Protein (gcGFP) was employed in this study to stably overexpress NL1 or NL3. To this end, vector GV492 (Ubi-MCS-3FLAG-CBh-gcGFP-IRES-puromycin; Shanghai GeneChem Co. LTD, Shanghai, China) was recombined with the gene sequences of NL1 (NM_053868; NL1-LV) or NL3 (NM_134336; NL3-LV). The same vector framework, carrying gcGFP without the target gene sequences, was used as a negative lentivirus control (NC1-LV or NC3-LV). The lentiviral vector GV320 (Ubi-MCS-3FLAG-SV40-Cherry; Shanghai GeneChem Co. LTD, Shanghai, China) containing Cherry was recombined with the NL2 gene sequence (NM_053512; NL2-LV) to stably overexpress this NL. The same vector backbone carrying Cherry only was used as a negative control (NC2-LV). The viral titers of NL1-LV, NL2-LV, and NL3-LV were 1.0×10^9 TU/mL, 1.0×10^9 TU/mL, and 2.0×10^9 TU/mL, respectively. Following carcinoma implantation, the L4–L6 lumbar spinal cord was exposed carefully by laminectomy. A glass capillary (35±5 mm diameter) containing a viral suspension (5 μM) was injected into the right spinal dorsal horn. The injection point was at 0.4 mm from the midline in the right dorsal horn, and the glass capillary was lowered into the parenchyma to 0.5 mm below the pia mater to reach the dorsal horn. Finally, the incision was dusted with penicillin powder and the skin was sutured.

Pain behavior assessment

Mechanical allodynia of rats was assessed by means of the paw withdrawal threshold (PWT) using a dynamic plantar esthesiometer (Ugo Basile, Stoelting, IL, USA) on days 0 (before surgery), 3, 6, 9, 12, 15, 18, and 21. The measurements were conducted from 8:30 to 11:30 a.m. Rats were placed in separate transparent boxes on an elevated wire mesh platform. After 20 min of acclimation, mechanical allodynia was measured using the hind paw withdrawal response to von Frey filament stimulation. The filament (0.5 mm diameter) was placed beneath the hind paw until it touched the plantar surface of the paw and began to exert an upward force. The forces were recorded in grams when the withdrawal response was elicited, up to a maximum of 50g. Each rat was assessed at least three times at intervals of 3 min.

Real-time polymerase chain reaction analysis

RNA isolation, cDNA synthesis, and Real-Time Polymerase Chain Reaction (RT-PCR) were performed as previously described.[17] The gene names and Forward (F) and Reverse (R) primers are listed in the Supplementary material 1.

Protein extraction and Western blot analysis

Proteins from rat L4 to L6 lumbar spinal cord were extracted using radioimmune precipitation lysis buffer (CST, America). Total protein concentrations were assayed using a bicinchoninic acid protein assay kit (N3219; TIAN GEN, China). Samples were calibrated to 30 μg/μL with loading buffer solution and Phosphate-Buffered Saline (PBS) and heated for 10 min at 95°C. Following sodium dodecyl sulfate-polyacrylamide gel electrophoresis, the proteins were transferred to a polyvinylidene fluoride membrane. Membranes were blocked with 5% skim milk in Tris-Buffered Saline (TBS) containing 0.1% Tween (TBST) for 1 hour at room temperature and incubated with primary antibodies at 4°C overnight. After three washes in TBST, they were incubated with horseradish peroxidase-linked secondary antibodies for 40 min at room temperature. Finally, the membranes were washed in TBST three times, processed using the ECL Plus kit and exposed to MP-ECL film.

Immunohistochemistry

For Immunohistochemical (IHC) staining, rats were deeply anesthetized with 3% isoflurane and transcardially perfused with cold PBS followed by 4% Paraformaldehyde (PFA). After perfusion, the Lumbar (L4–L6) spinal cord was harvested, post-fixed in 4% PFA at 4°C for 2h, and cryoprotected in 30% sucrose in PBS at 4°C for 24h. Indoor temperature of the frozen slicer (Leica, America) was adhyted to -20°C, the specimen wrapping agent placed on the specimen table and frozen for 30 minutes, adjust the slice thickness of the frozen slicer to 15 μm and then slice, and adsorb the frozen slices on the glass slide. The frozen sections were blocked using 10% donkey serum at room temperature for 10 min and then incubated with primary antibodies diluted in blocking solution at 4°C overnight. For immunofluorescence detection, the slices were incubated with corresponding fluorescent secondary antibodies at room temperature in the dark for 1h. Following washes with PBS, the stained sections were mounted by coverslips with 50% glycerinum. The sections were examined, and immunostaining images were obtained with a laser scanning confocal microscope Leica TCS SP8 (Leica, Wetzlar, Germany). The primary antibodies used are listed in the Supplementary material.

Electrophysiology

Primary cortex neurons were cultured as described previously.[18,19] Briefly, the neocortex tissue of newborn rats was harvested from postnatal pups and cut into small pieces within 1 mm^3, papain-digested (10 min, 37°C), and then filtered through a 400 μm mesh strainer. The dissociated neurons were plated on poly-L-lysine (P7405; Sigma, America)-coated glass coverslips in 12-well plates (1.5×10^5 cells/well). The cultures were maintained in Dulbecco's Minimum Essential Medium (Gibco, America) supplemented with 10% fetal calf serum (Gibco). After 4–6h, the culture medium was changed to Neurobasal A medium (10888-022; Gibco) supplemented with 2% B27 (17504044; Gibco) and 1% GlutaMAX (Gibco) and incubated at 37°C in 5% CO_2. Neurons were transfected with lentivirus and recorded on day 10.

In vitro whole-cell patch-clamp recordings in cultured primary neurons were performed at room temperature. The extracellular solution contained the following (in mM): 140 NaCl, 3 KCl, 2 $MgCl_2$, 2 $CaCl_2$, 10 glucose, and 10 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid (HEPES; pH 7.4, 300 mOsm). Borosilicate glass recording pipettes (resistance: 5–8 MΩ) were filled with intracellular solution, which contained the following (in mM): 135 K-gluconate, 2

$MgCl_2$, 10 HEPES, 1 ethylene glycol-bis (β-aminoethyl ether) -N, N, N', N'-tetraacetic acid (EGTA), and 5 MgATP, Na_3GTP (pH 7.3, 290 mOsm). Data was collected using a Multiclamp 700B (Molecular Devices, Sunnyvale, CA, USA), filtered at 2 kHz and digitized at 10 kHz by a Digidata 1550A and Clampex 10.5 software (Molecular Devices). To elicit Action Potentials (APs), increasing amounts of depolarizing currents from 0 pA to 220 pA with 20 pA increments were used. The parameters of the first evoked AP were used for analysis. The evoked spontaneous Excitatory Postsynaptic Currents (sEPSCs) and spontaneous Inhibitory Postsynaptic Currents (sIPSCs) were recorded by holding a potential of -70 mV and 0 mV, respectively.

In vivo whole-cell patch-clamp recordings were made in superficial spinal dorsal horn neurons from adult rats. Briefly, rats were deeply anesthetized and transcardially perfused with 60 mL ice-cold cutting solution containing the following (in mM): 93 N-methyl-D-glucamine, 93 HCl, 2.5 KCl, 1.2 NaH_2PO_4, 30 $NaHCO_3$, 25 glucose, 20 HEPES, 5 Na-ascorbat, 3 Na-pyruvate, 2 thiourea, 10 $MgSO_4$, and 0.5 $CaCl_2$. Laminectomy was performed, and the lumbar enlargement was quickly removed to ice-cold cutting solution with 95% O_2 and 5% CO_2. Sagittal slices (400 μm) were prepared with a Leica VT1000S vibratome. Subsequently, the slices were transferred into artificial cerebrospinal fluid (containing, in mM: 126 NaCl, 2.5 KCl, 1.25 NaH_2PO_4, 26 $NaHCO_3$, 10 glucose, 2 $MgSO_4$, and 2 $CaCl_2$) and incubated for 30 min at room temperature. Under a dissecting microscope with transmitted illumination, the *substantia gelatinosa* was clearly visible as a relatively translucent band across the dorsal horn. Patch pipettes (3−5 MΩ) were filled with internal solution, which contained (in mM): 135 potassium gluconate, 0.5 $CaCl_2$, 2 $MgCl_2$, 10 EGTA, 10 HEPES, 0.5 Na_3GTP, and 5 MgATP. All experiments were performed at room temperature. Series resistance was 10−30 MΩ and was monitored during the process. Data was collected as described above. To elicit APs, increasing amounts of depolarizing currents were injected for 20 ms in a stepwise manner from -60 Pa to 220 pA in 20 pA increments. The parameters of APs were determined from the first AP evoked at threshold. To identify the firing pattern, a 150 pA current was applied for 150 ms. The membrane potential was held at -70 mV for sEPSCs and 0 mV for sIPSCs. APs were analyzed using Clampfit 10.5 and Spontaneous Postsynaptic Currents (sPSCs) were analyzed with Mini Analysis (Synaptosoft, America).

High throughput sequencing

RNA was collected from spinal dorsal horn and Dorsal Root Ganglia (DRGs) of carcinoma-bearing rats and sham controls, and all subsequent analyses were entrusted with Novogene (https://www.novogene.com/amea-en/). Additional details about RNA isolation, sample preparation and data analysis are available in Supplementary material 2.

Statistical analysis

Data was analyzed by SPSS 22.0 software (IBM, Armonk, NY, USA) and results were presented as mean ± SEM. Comparisons among groups were analyzed using one-way analysis of variance (ANOVA) and, where appropriate, followed by the Student-Newman-Keuls test. A value of $p < 0.05$ was considered statistically significant.

Results

Illumina HiSeq™ revealed BCP-related genes in lumbar spinal cord and dorsal root ganglia of BCP rats

In order to identify altered genes that might relate to the formation and maintenance of BCP in the Dorsal Root Ganglion (DRG) and spinal cord, we conducted high throughput sequencing (Illumina HiSeq™) experiments on rats with carcinoma tibia implantation and sham controls. The ipsilateral L4−L6 lumbar spinal cord and DRGs were harvested and the mRNA was sequenced using the Agilent 2100 Bioanalyzer platform (Agilent Technologies, Palo Alto, CA). The gene expression profiles in carcinoma rats were compared with those in sham controls. In DRGs, we identified 1274 differentially expressed genes, of which 684 were upregulated and 590 were downregulated (Fig. 1 A–B). In the spinal cord, we identified 2098 differentially expressed genes, of which 1632 genes were upregulated, and 466 genes were downregulated (Fig. 1 A–C). These genes are likely to be involved in the peripheral and central mechanisms of the development and/or maintenance of BCP. Gene Ontology (GO) is the international standard classification system of gene functions, which directly reflects the differentially expressed genes on GO terms enriched in biological processes, cell components, and molecular functions.[20] Unexpectedly, the GO analysis demonstrated that the differentially expressed genes involved in bone cancer-induced pain in spinal dorsal horn and DRGs were immune-related genes (Fig. 1 D–E).

Decreased NL expression facilitates the development of BCP

Next, to investigate whether NLs were involved in the development of BCP, we used our newly established rat model; BCP was induced by injection of carcinoma cells into the tibia of animals and the PWT was measured to assess mechanical allodynia using a dynamic plantar esthesiometer. Lentiviruses were injected into the ipsilateral dorsal horn to overexpress NLs (NL-LV), and the expression of NLs in the spinal cord was examined by IHC, Western blot analysis, and RT-PCR. The results showed that NL1 was dispersedly distributed from the spinal dorsal horn to the ventral horn and was located mainly in the lamina I and II of the dorsal horn (Fig. 2A). Similarly, NL2 and NL3 were found predominantly in lamina I and II of the dorsal horn (Fig. 2 B−C). Quantitative analysis by RT-PCR and Western blot indicated that the expression of NLs was decreased in the carcinoma-bearing rats compared with sham controls, which was reversed by NL overexpression (Fig. 2 D–E). The behavioral tests showed that carcinoma inoculation resulted in significant changes in pain behaviors on the ipsilateral paw, which were attenuated by the overexpression of NL1 or NL2, but not of NL3 (Fig. 2F). These results indicate that the diminished endogenous expression of either NL1 or NL2 might be in part responsible for the development of BCP.

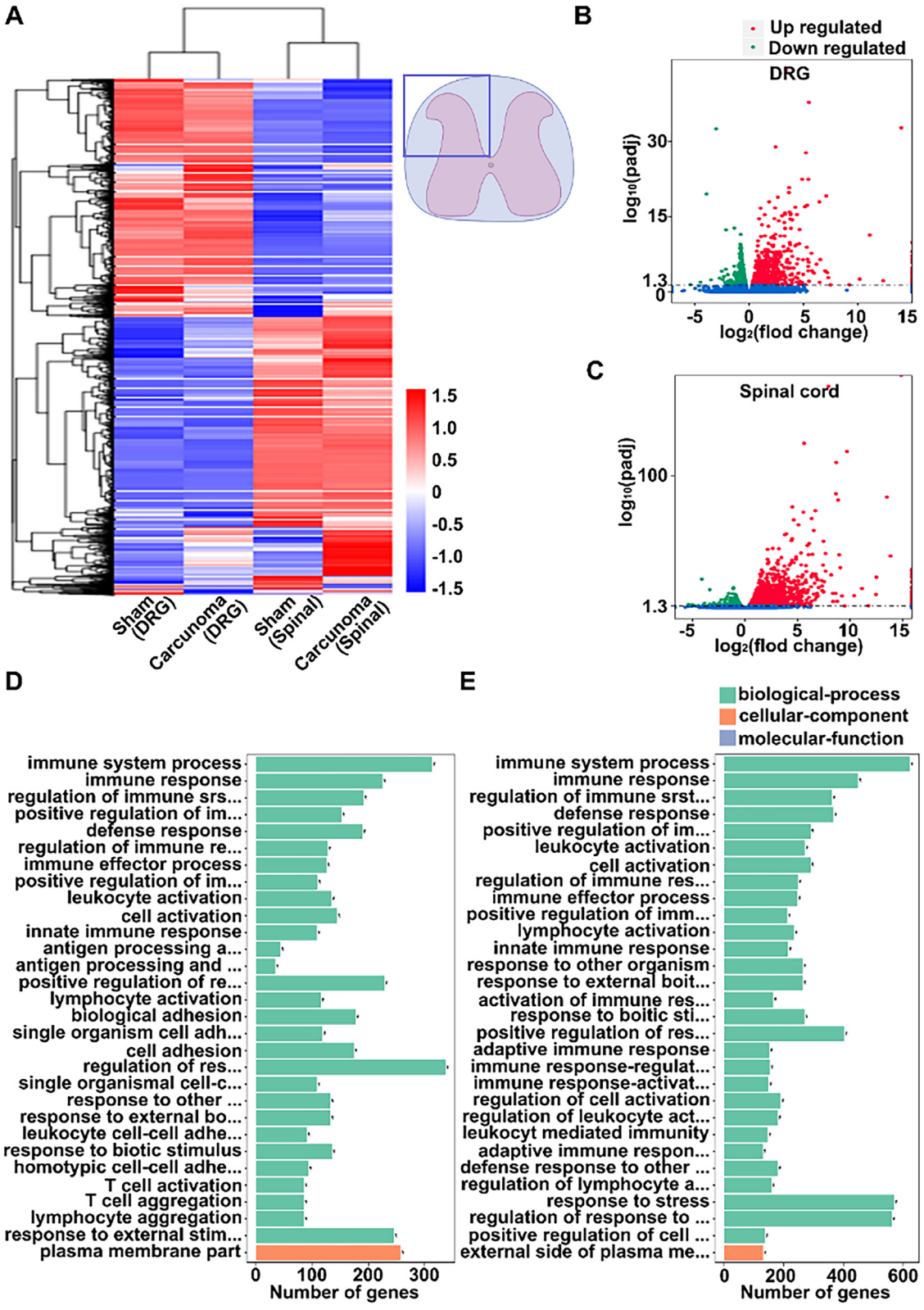

Figure 1 Illumina HiSeqTM analysis revealing pain-related genes in spinal dorsal horn and dorsal root ganglia of carcinoma-bearing rats. (A) Cluster heat map of differentially expressed genes in spinal dorsal horn and Dorsal Root Ganglia (DRGs) of carcinoma-bearing rats and sham controls. Expression values are scaled by rows with values greater than the mean displayed in red and those smaller than the mean in blue, and the intensity of color corresponding to the relative level of expression. Top right: illustration of the harvested spinal cord and DRGs from carcinoma-bearing rats and sham controls. (B–C) Volcano plot of differentially expressed genes in DRGs (B) and spinal dorsal horn (C) in carcinoma-bearing rats compared with sham controls. The red spots represent significantly

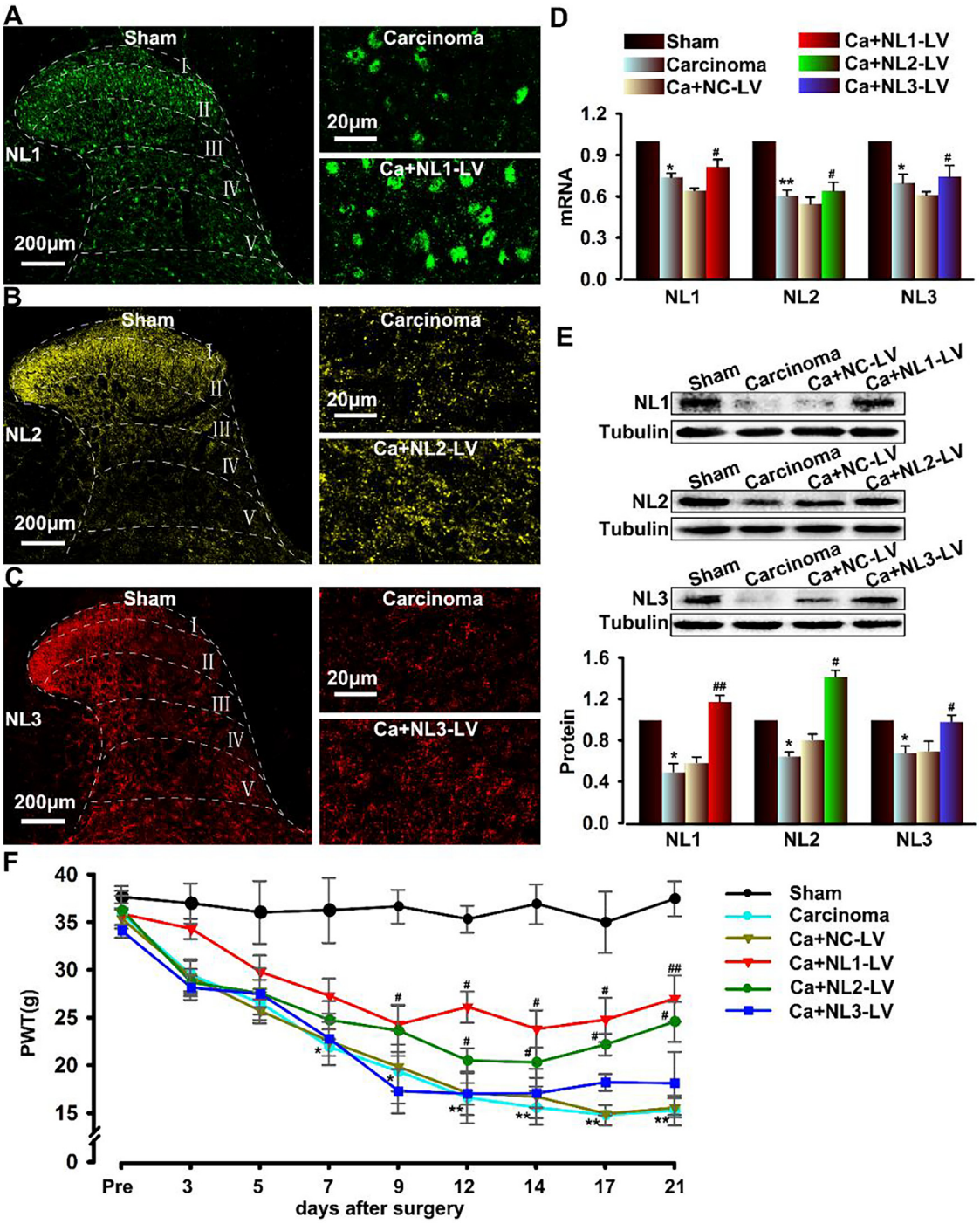

Figure 2 Diminished expression of NL1 and NL2 associated with bone cancer pain. (A–C) Immunofluorescent labeling of NL1 (green), NL2 (yellow), and NL3 (red) in the spinal dorsal horn of sham and cancer-bearing rats with lentivirus-mediated NL1 overexpression (A), NL2 (B), and NL3 (C). (D) Quantitative analysis of NL1, NL2, and NL3 using RT-PCR of spinal cord. Values represent the mean ± SEM, (n = 4; $^{*}p < 0.05$). (E) Quantification and representative image of NL1, NL2, and NL3 using Western blot analysis of spinal cord. Values represent the mean ± SEM, (n = 4. $^{*}p < 0.05$). (F) Mechanical allodynia was measured by Paw Withdrawal Threshold (PWT). $^{*}p < 0.05$ compared with sham rats, $^{**}p < 0.01$; $^{\#}p < 0.05$ compared with carcinoma + NC-LV group, $^{\#\#}p < 0.01$; n = 12 rats/group. All data shown as mean ± SEM.

upregulated genes, the green ones significantly downregulated genes, and the blue spots indicate unaltered genes. (D–E) Gene Ontology analysis indicating enrichment of differentially expressed genes according to biological processes in DRGs (D) and spinal dorsal horn (E) of carcinoma-bearing rats versus sham controls.

Cellular localization of NL1 and NL2 in spinal dorsal horn interneurons

Given the potential mechanism of NLs involved in the development of BCP, the distribution of NLs in neuronal cells was examined using triple immunofluorescence staining and analyzed by confocal microscopy imaging. Our results revealed that NL1 was co-expressed with the glutamate receptor GluR1 on GABAergic neurons (Fig. 3A), indicating that it may contribute to the excitability of GABAergic neurons. NL2 was co-localized with GABAR-γ2 in glutamatergic neurons (vesicular Glutamate transporter 2 [Glut2]), pointing towards a role in the regulation of inhibitory synaptic transmission in glutamatergic neurons (Fig. 3B). Taken together, the distinct expression of NLs in interneurons may have resulted in an imbalance of excitatory and inhibitory synaptic transmission in the spinal cord and could thus have induced the development of BCP.

Decreased expression of NL1 and/or NL2 inhibits synaptic transmission in spinal cord interneurons of BCP rats

To further investigate the role of NLs in synaptic transmission, we performed whole-cell patch-clamp recordings of acute spinal slices from sham, carcinoma, and carcinoma +NL1/2-LV or NC1/2-LV (respective negative control) rats, and the APs and sPSCs were recorded. We found that overexpression of NL2 increased the latency of the first AP and that of the AP evoked by a current of 200 pA (Fig. 4 A–C), whereas NL1 overexpression decreased the threshold of the first AP and that of the AP stimulated by 200 pA (Fig. 4 D–E). Both the frequency and amplitude of sEPSCs decreased significantly in spinal slices of carcinoma-bearing rats compared with those of sham counterparts, which was reversed by the overexpression of NL1 in spinal cord (Fig. 4 F–H). Thus, it appears that diminished NL1 levels dominate the inhibitory neuronal excitability in the spinal cords of cancer-

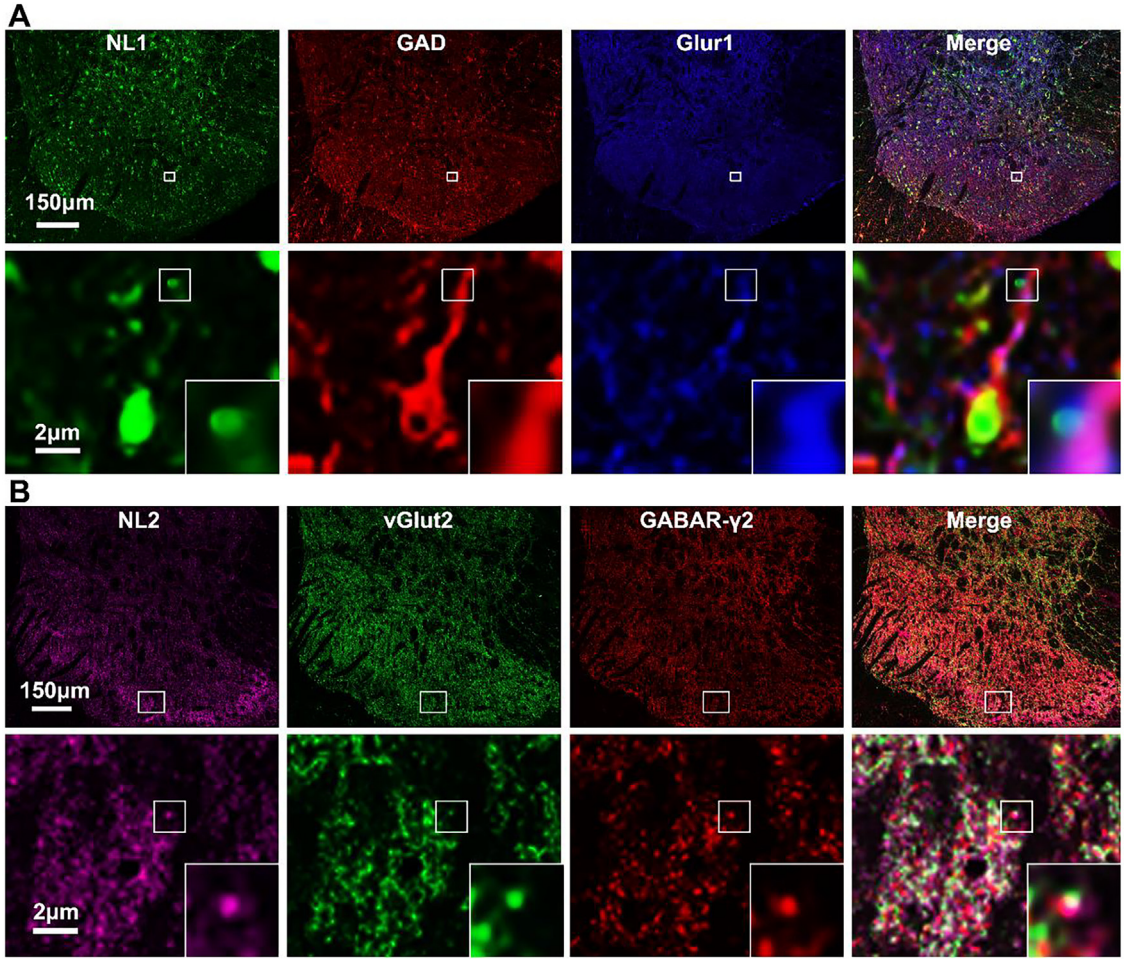

Figure 3 NL1 and NL2 localized at GABAergic and glutamatergic neurons, respectively, in the spinal cord of rats. (A) Multiple immunostainings showing that NL1 (green) co-localized with Glutamic Acid Decarboxylase (GAD; red) and glutamate receptor-1 (blue) in the spinal dorsal horn. Magnified images (bottom) depicting that NL1 was localized on excitatory synapses of GAD-positive neurons. Scale bar = 150 μm. (B) Immunofluorescence images showing that NL2 (magenta) co-localized with vesicular glutamate transporter-2 (vGlut2; green) and γ-aminobutyric acid receptor-γ2 (GABAR-γ2; red) in the spinal dorsal horn. Magnified images (bottom) indicating that NL2 was localized at inhibitory synapses in vGlut2-positive neurons. Scale bar = 150 μm.

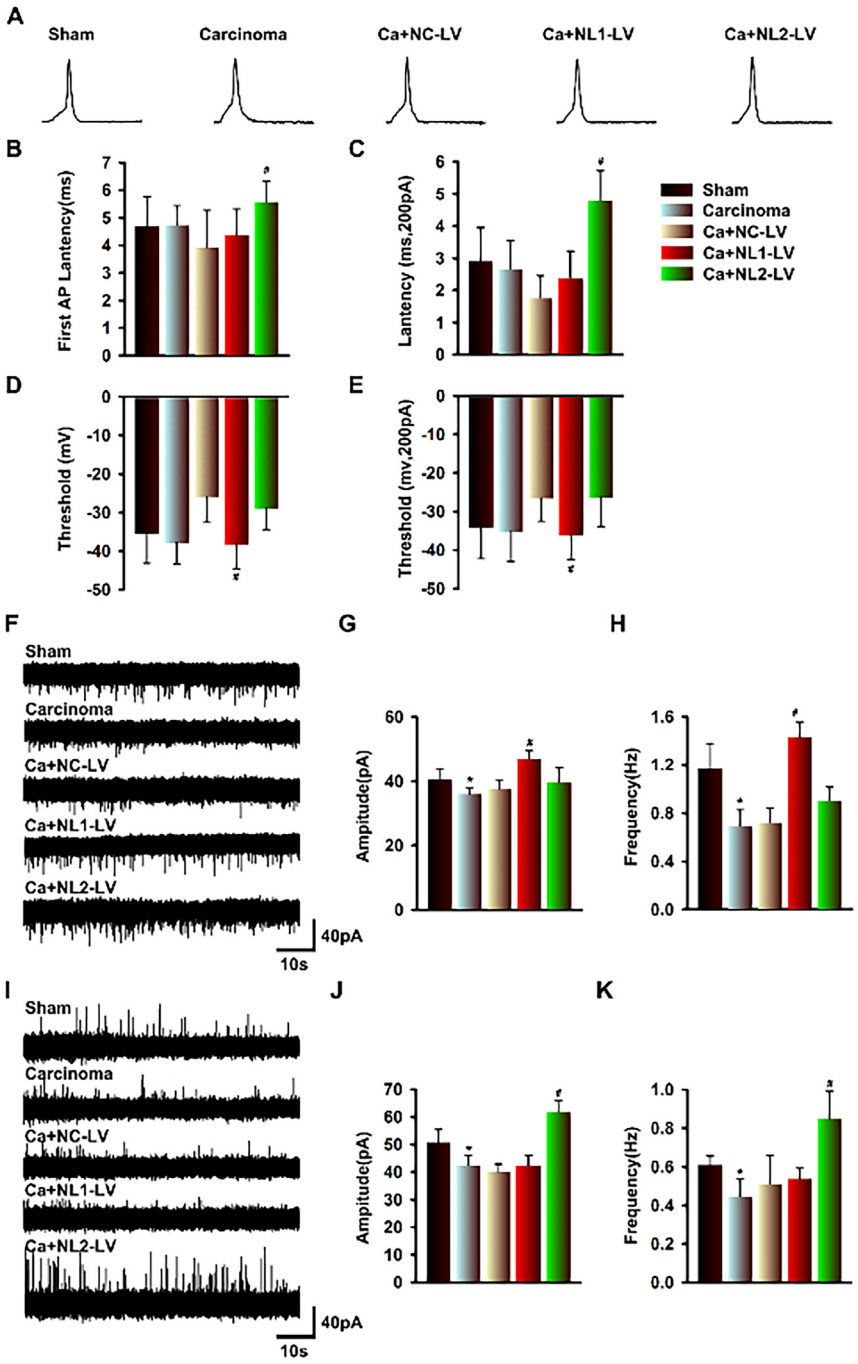

Figure 4 Electrophysiological properties of spinal cord interneurons expressing NL1 and NL2 in BCP rats. (A) Representative traces of evoked Action Potentials (APs) in acute spinal slices of sham, carcinoma, carcinoma+NC-LV, carcinoma+NL1-LV, and carcinoma +NL2-LV rats. (B–C) Overexpression of NL2 increased the latency of the first AP and that of the AP stimulated by 200 pA. (D–E) NL1 overexpression decreased the threshold of the first AP and that of the AP stimulated by 200 pA. (F) Traces of spontaneous EPSCs of acute spinal slices of sham, carcinoma, carcinoma+NC-LV, carcinoma+NL1-LV, and carcinoma+NL2-LV rats. (G–H) Frequency (G) and amplitude (H) of spontaneous EPSCs (n = 46 for sham, n = 23 for carcinoma, n = 7 for carcinoma+NC-LV, n = 32 for carcinoma+NL1-LV, and n = 7 for carcinoma+NL2-LV; $^{*}p < 0.05$ compared with sham; $^{\#}p < 0.05$ compared with carcinoma + NC-LV group.). (I) Traces of spontaneous IPSCs of acute spinal slices of sham, carcinoma, carcinoma + NC-LV, carcinoma + NL1-LV, and carcinoma + NL2-LV rats. (J–K) Frequency (G) and amplitude (H) of spontaneous IPSCs (n = 46 for sham, n = 23 for carcinoma, n = 7 for carcinoma + NC-LV, n = 32 for carcinoma+NL1-LV, and n = 7 for carcinoma+NL2-LV; $^{*}p < 0.05$ compared with sham; $^{\#}p < 0.05$ compared with carcinoma +NC-LV group).

bearing rats via decreasing excitatory synaptic transmission on GABAergic neurons and therefore cause the development of BCP.

The frequency and amplitude of sIPSCs also decreased in carcinoma-bearing rats compared with sham controls, which could be reversed by overexpression of NL2 in spinal cord (Fig. 4 I–K). This suggests that low levels of NL2 in cancer-bearing rats inhibit the inhibitory synaptic transmission of glutamatergic neurons and therefore cause an increase in their excitability. These results demonstrate that low expression of NL1 and NL2 reduced the excitatory and inhibitory synaptic transmission in BCP, respectively, which suggests that an underlying inhibitory mechanism may be a central feature of BCP in the spinal dorsal horn.

Overexpression of NL1 and/or NL2 changes electrophysiological properties of primary cultured rat cortical neurons

To further confirm the roles of NL1 and NL2 in synaptic transmission, whole-cell patch-clamp recording was used to identify electrophysiological properties of cultured neurons treated with NC-LV, NL1-LV, or NL2-LV. The results showed that neurons infected with NL1-overexpressing lentivirus exhibited a significantly higher input resistance (Fig. 5 A–B), suggesting that upregulation of NL1 altered the membrane characteristics (such as permeability and integrity) of neurons. NL2 overexpression decreased the latency of the first AP, rise time, decay time, and increased the rise slope of evoked APs. Additionally, overexpression of NL2 decreased the depolarization time and increased the threshold of APs evoked by a current of 200 pA (Fig. 5 C–H). The overexpression of NL1, but not of NL2, increased the amplitude of sEPSCs, whilst their frequency remained unchanged. Conversely, NL2 overexpression, but not NL1, caused a profound increase in the amplitude and frequency of sIPSCs (Fig. 5 I–N). In summary, NL1 and NL2 played different roles in excitatory and inhibitory synaptic transmission.

Discussion

In this study, the expression patterns and functions of NL1 and NL2 were analyzed using different approaches in carcinoma-bearing and sham rats. Based on our *in vitro* and *in vivo* experiments, NL1 and NL2, but not NL3, are involved in the development and/or maintenance of BCP.

Previous studies have shown that NL1 is associated with pain. Recruitment of NL1 in the spinal dorsal horn contributes to inflammatory pain,[6] and NL1 knockdown in this region alleviates pain hypersensitivity.[15] In our study, Western blot and RT-PCR analyses indicated that expression of NL1 was decreased in the spinal cord of BCP rats in comparison with sham controls. It has been demonstrated that NL1 is mainly concentrated on excitatory postsynaptic membranes where it regulates the excitatory synaptic transmission.[21,22] Co-localization of NL1 and GluR1 on excitatory synapses of inhibitory (glutamic acid decarboxylase-immunoreactive) neurons was observed in rats, suggesting that NL1 is not fully restricted to participate in the regulation of excitatory or inhibitory transmission. The expression of NL1 was decreased in the spinal cords of carcinoma-bearing rats compared with controls, and our electrophysiological analysis indicated that the frequency and amplitude of sEPSCs were significantly decreased in spinal slices. This is in line with previous studies, in which the suppression of NL1 decreased EPSCs of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs) and NMDARs.[8,23] Whilst simultaneous knockdown of NL1, NL2, and NL3 mediated the most robust reduction of inhibitory terminals, exclusive inhibition of NL1 by specific shRNA knockdown reduced spine and vesicular GABA transporter (vGAT) sensitivity.[24] Therefore, in this study, the reduction in NL1 expression levels presumably decreased the excitatory potential of interneurons, especially GABAergic neurons, which resulted in disinhibition of superficial projection neurons and enhancement in the sensitivity of interneurons to noxious stimuli, and thus induced pain in carcinoma-bearing rats. Conversely, NL1 overexpression reversed the aforementioned phenomena and mitigated mechanical hyperalgesia in BCP rats. NL1 overexpression in hippocampus has been reported to lead to increase in the expression of vGAT and increased excitation rather than altered inhibition.[25] Our whole-cell patch-clamp recordings demonstrated that the sEPSC amplitude was increased in cultured cortical neurons on NL1 overexpression. Based on our IHC results, NL1 overexpression may have possibly increased the excitatory potential of inhibitory interneurons, consequently enhancing the transmission of noxious stimuli information. Although the mechanisms underlying our observations remain unresolved, NL1 likely contributes to the development and maintenance of BCP.

According to previous studies, NL2 is localized at the inhibitory postsynaptic membrane regulating inhibitory synaptic transmission.[26] Knockout of NL2, but not of NL1, reduces inhibitory synaptic neurotransmission in the hippocampus and somatosensory cortex.[27] The frequency and amplitude of sIPSCs as well as the expression of NL2 were decreased in carcinoma-bearing rats in our study, and using immunofluorescence we could show that NL2 was co-expressed with GABARγ2 and vGlut2. Altogether, these findings suggest that the inhibition of excitatory interneurons was weakened, which resulted in facilitated transmission of noxious stimuli to the central nervous system. Consequently, the carcinoma-bearing rats were hypersensitive to mechanical stimulation due to reduced NL2 levels in the spinal cord. However, hyperalgesia was reversed through overexpression of NL2 using lentiviruses. Our electrophysiological results showed that the frequency and amplitude of sIPSCs were increased in acute spinal slices in response to the overexpression of NL2 in the spinal cord of BCP model rats as well as in cultured cortical neurons. The disparities between cortical neurons and spinal slices of adult rats regarding depolarization time and threshold of APs evoked by a current of 200 pA may have resulted from the different densities of neurons in each setting.[28] Overexpression of NL2 selectively causes moderate increase in inhibitory synapses and enhances inhibitory synaptic function in cultured hippocampal neurons.[29] Based on our immunofluorescence staining combined with electrophysiological experiments, we speculate that NL2 alleviated bone cancer-induced pain by decreasing the activity of glutamatergic neurons, which directly reduced interneuronal excitability. In

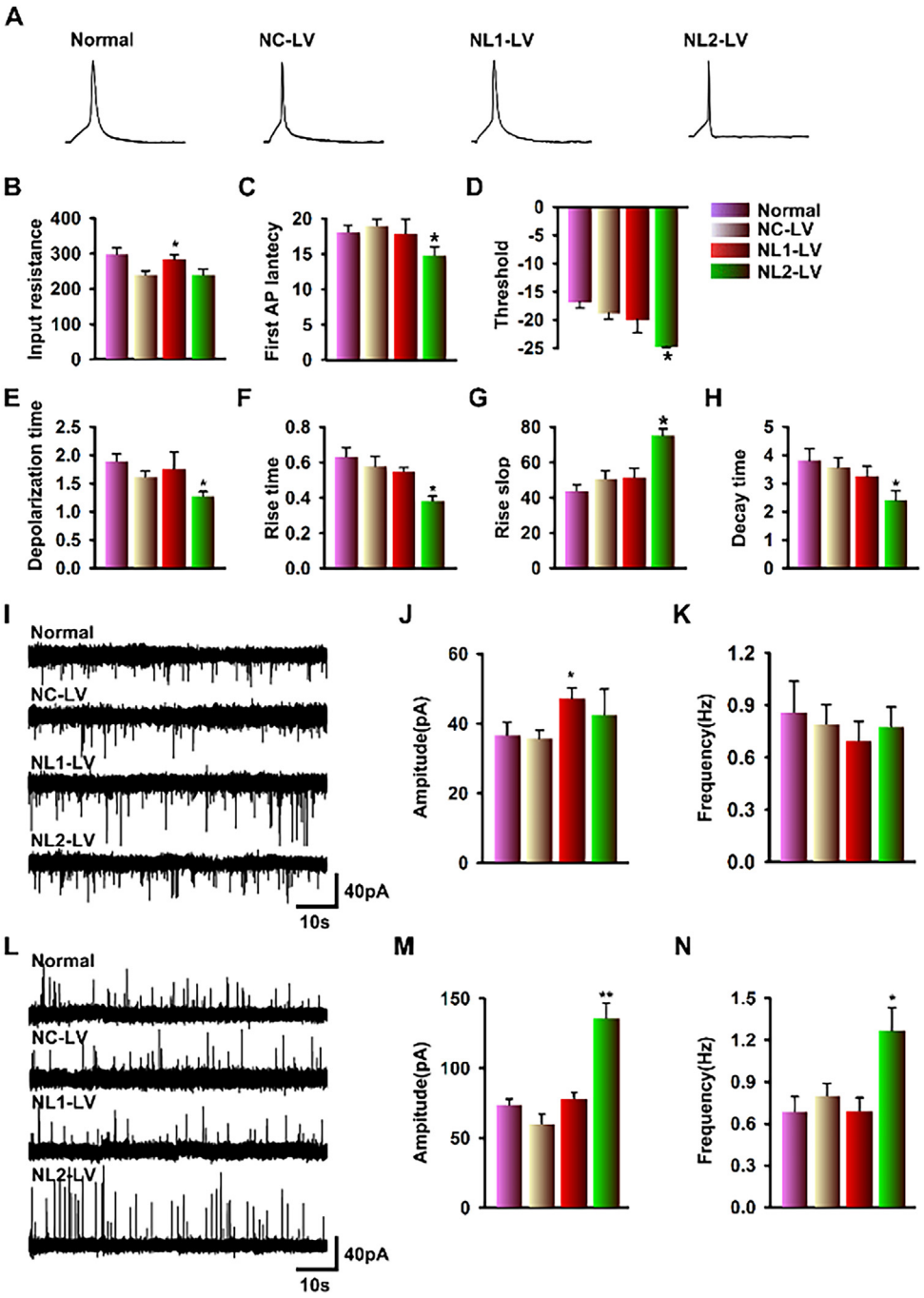

Figure 5 Electrophysiological properties of primary cultured rat cortical neurons with NL1 or NL2 overexpression. (A) Representative traces of evoked APs of untransfected, NC-LV, NL1-LV, or NL2-LV transfected cortical neurons of neonatal rats. (B) NL1 overexpression increased the input resistance of neurons compared with those transfected with NC-LV (n = 32 for untransfected, n = 39 for NC-LV, and n = 26 for NL1-LV; $*p < 0.05$ compared with NC-LV). (C—H) Overexpression of NL2 decreased the latency, rise time, and decay time, and increased the rise slope of the first AP. NL2 overexpression decreased the depolarization time and increased the threshold of APs evoked by a current of 200 pA compared to neurons transfected with NC-LV (n = 32 for untransfected, n = 39 for NC-LV, and n = 17 for NL2-LV; $*p < 0.05$ compared with NC-LV). (I) Traces of spontaneous EPSCs of untransfected, NC-LV, NL1-LV, or NL2-LV transfected cortical neurons. (J–K) Frequency (J) and amplitude (K) of spontaneous EPSCs (n = 13 for untransfected, n = 31 for NC-LV, n = 30 for NL1-LV, and n = 25 for NL2-LV; $*p < 0.05$ compared with NC-LV). (L) Traces of spontaneous IPSCs of untransfected, NC-LV, NL1-LV, or NL2-LV transfected cortical neurons. (M–N) Frequency (J) and amplitude (K) of spontaneous IPSCs (n = 13 for untransfected, n = 27 for NC-LV, n = 33 for NL1-LV, and n = 25 for NL2-LV; $*p < 0.05$ compared with NC-LV).

summary, our data strongly implicate NL2 in the regulation of inhibitory synaptic transmission of glutamatergic interneurons in BCP.

Accumulating evidence associates NL3 mutations with autism.[30] Pain has been reported to strongly correlate with the development of depression,[31,32] and mental and psychological disorders are in turn associated with autism. In our experiments, NL3 was decreased in the spinal cords of carcinoma-bearing rats. However, overexpression of NL3 in the spinal dorsal horn did not alleviate the hyperalgesia of BCP rats, suggesting that NL3 is not involved in BCP. The underlying mechanism causing NL3 to be decreased in BCP rats needs further investigation.

Our study also has some limitations. In in vitro electrophysiological experiments, due to hard to dissociate and culture of spinal cord neuron from a neonatal or fetal rats, after several times failure of culture the spinal cord neurons, in the present study, we performed the cellar experiment using the cortical neurons. We hope these experiments can support the conclusion. Besides, the mechanism of bone cancer pain is complex, involving the impact of the tumor on the whole system.

This artical is accordance with the "Quality of methods reporting in animal models of colitis" of EQUATOR Reporting Guideline (Fig. 6).

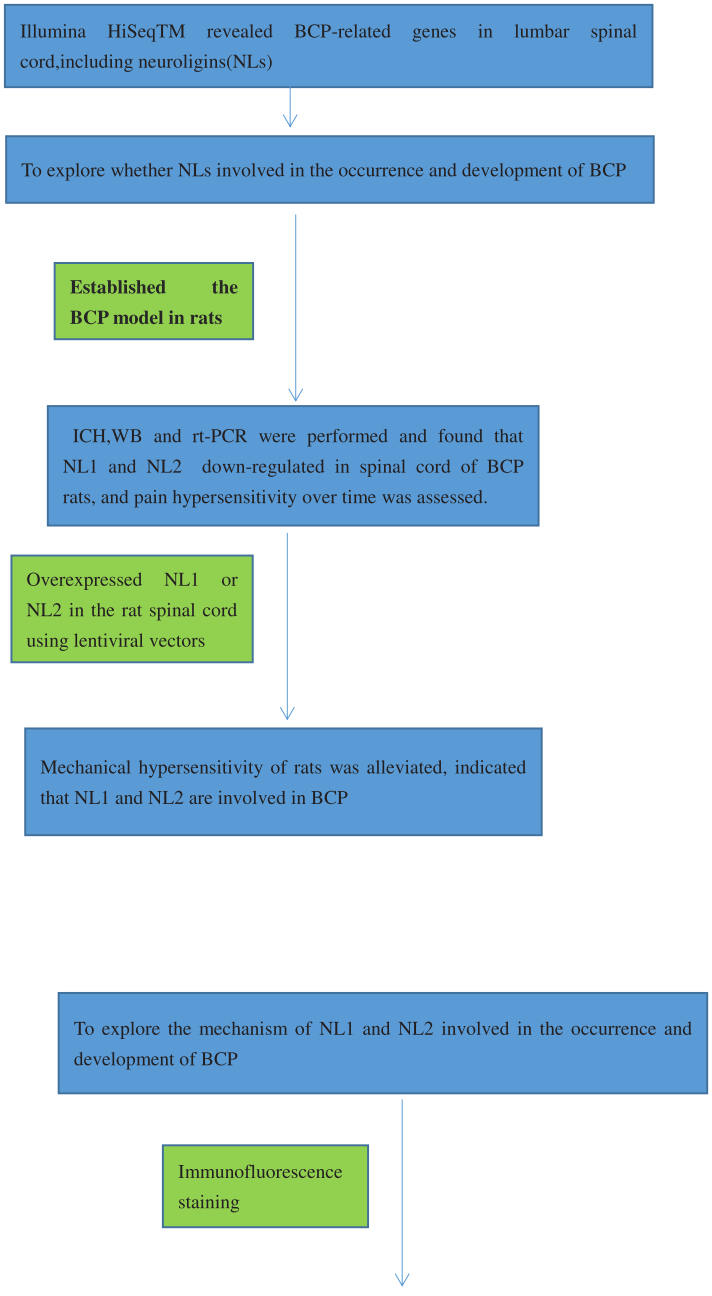

Figure 6 Flowchart.

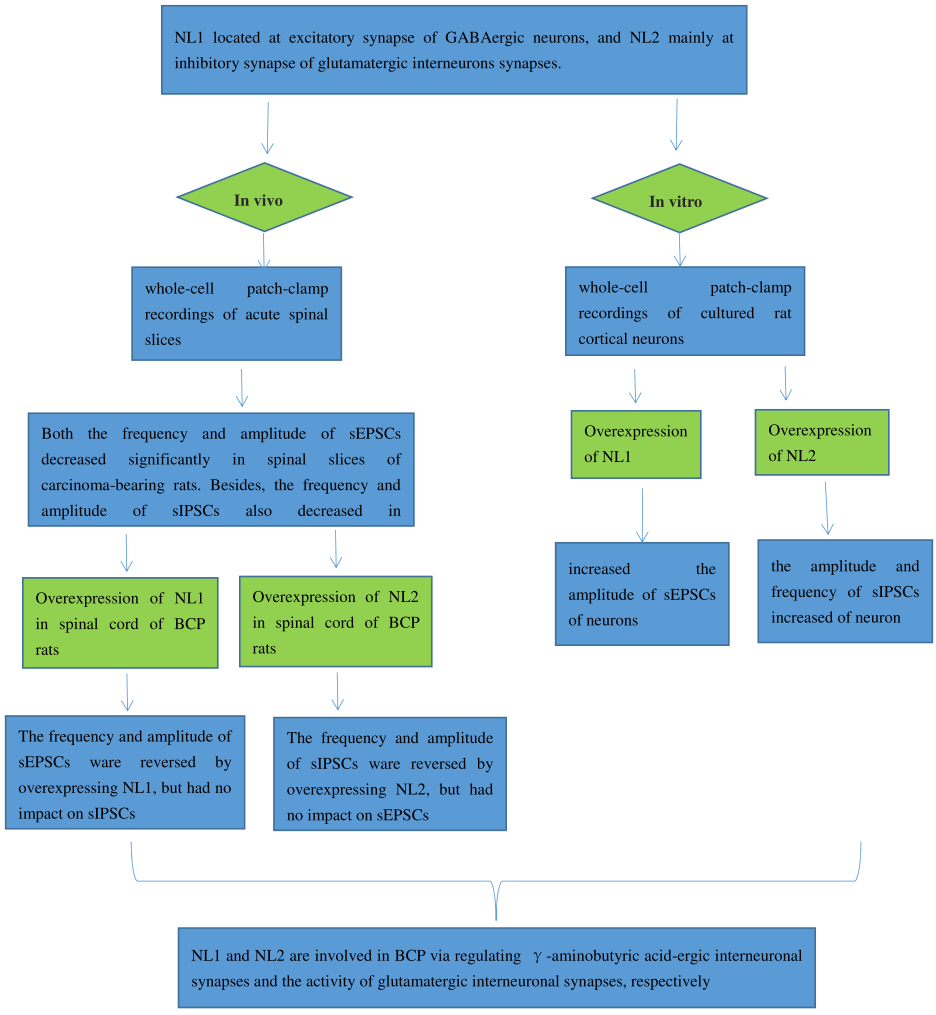

Figure 6 Continued.

Conclusions

Our study identified a novel mechanism of bone cancer-induced pain regulated by NL1 and NL2 in spinal cord. In rats with carcinoma inoculation, NL1 and NL2 may reduce the excitability of GABAergic interneurons and the release of inhibitory synaptic neurotransmitters by glutamatergic interneurons, respectively, which in turn affect the balance of the excitatory and inhibitory potential of interneurons and may cause the hyperalgesia of carcinoma-bearing rats. These results provide novel insights into the onset and progression of BCP.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2023.02.001.

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ORIGINAL INVESTIGATION

Chronic pain after hospital discharge on patients hospitalized for COVID-19: an observational study

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Chronic pain;
COVID-19;
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SARS-CoV-2;
Survivors

Abstract
Background: There are few studies related to Coronavirus Disease 2019 (COVID-19) on the prevalence and nature of pain symptoms after hospital discharge, especially in individuals who develop moderate to severe disease forms. Therefore, this study aimed to evaluate the presence of chronic pain in patients discharged after hospitalization for COVID-19, and the relationship between the presence of chronic pain and intensive care stay, demographics, and risk factors for the worst Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) outcome.
Methods: A cross-sectional observational study was carried out on patients with COVID-19 who recovered after hospitalization. Patients were recruited at the least 3 months after discharge and their hospital's health files were prospected. The variables evaluated were demographics, the severity of SARS-CoV-2 infection (considering the need for intensive care), and the presence of chronic pain. The results were shown in a descriptive manner, and multivariate analysis expressed as Odds Ratios (ORs) and respective Confidence Intervals (CIs) for the outcomes studied. Statistical significance was set at $p < 0.05$.
Results: Of 242 individuals included, 77 (31.8%) reported chronic pain related to COVID-19, with no correlation with the severity of infection. Female sex and obesity were associated with a higher risk for chronic pain with ORs of 2.69 (Confidence Interval [95% CI 1.4 to 5.0]) and 3.02 (95% CI 1.5 to 5.9). The limbs were the most affected areas of the body.
Conclusion: Chronic pain is common among COVID-19 survivors treated in hospital environments. Female sex and obesity are risk factors for its occurrence.
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Introduction

Coronavirus Disease 2019 (COVID-19), a disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was officially declared by the World Health Organization as a pandemic on March 11, 2020.[1] This infection is known to cause acute onset of respiratory symptoms 4—5 days after exposure to the virus, which lasts for 7—10 days. However, up to 87.5% of hospitalized patients have persistent symptoms that continue for several weeks or even months and include a variety of pain complaints. [2—4] Although initially believed to be a disease that exclusively affects the respiratory system, it is now known that it is a systemic illness that can lead to multiple organ failures during the acute phase, affecting the renal, nervous, circulatory, and hematological systems.[5] For this, many patients demand intensive care treatment and may develop post-intensive therapy syndrome, characterized by physical, cognitive, and psychiatric dysfunctions.[6]

In data collected between February and April 2020 in the United Kingdom, it was observed that the demand for intensive care of patients hospitalized for COVID-19 was approximately 17%, of which 50% required mechanical ventilation. Of these individuals, 27% required continuous care after the infection, to the detriment of only 20% who were discharged without further repercussions.[5] Thus, dysfunctions related to post-intensive care syndrome may be observed, including chronic pain as one of them, and may have a commonality with the so-called post-acute COVID-19 syndrome.

Post-acute COVID-19 syndrome is a multisystem condition that more frequently affects patients with mild to severe COVID-19 and is characterized by fatigue, dyspnea, cough, pain, anosmia, and manifestations related to persistent organ dysfunction.[7,8] The pathophysiology of late sequelae of COVID-19 is not clear and may be related to, but not limited to, direct organ damage, persistent hyperinflammatory state, hypercoagulable state, or poor host immune response.[9]

Chronic pain is defined by the International Association for the Study of Pain as persistent or recurrent pain that persists for more than 3-months or beyond the normal period of tissue recovery.[10,11] However, the effect of chronic pain on patients surviving SARS-CoV-2 infection remains poorly understood.[5] Even though nowadays there is a lower risk of severe COVID-19 infection due to mass vaccination,[12] we still have a large number of survivors living with chronic pain as a consequence of this disease. To date, few studies have characterized how hospitalized patients are affected by chronic pain after recovery from SARS-CoV-2 infection.

We hypothesized that patients with COVID-19 who present with more severe forms of infection (treated with intensive care) might be more susceptible to the presence of chronic pain after recovery. Therefore, this study aimed to evaluate the presence of chronic pain in survivors hospitalized for treatment of SARS-CoV-2 infection. As secondary outcomes, we studied the relationship between the presence of chronic pain and the use of intensive care, demographics, and risk factors for the worst disease outcome.

Methods

Study design

A cross-sectional observational study was carried out on patients with COVID-19 who recovered after hospitalization between 2020 and 2021. The study followed the research guidelines described by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Reporting of studies Conducted using Observational Routinely collected health Data statement (RECORD).[13,14]

Setting and variables

The study was performed in a tertiary teaching hospital at Sao Paulo State University's Medical School, Brazil. Data were obtained through telephone interviews with respect to the social distancing imposed during the pandemic. The interviewers read and explained the informed consent term before beginning the survey questionnaire application.

Participants

We invited adult patients of both sexes to participate in the study, with a past diagnosis of COVID-19 disease confirmed by real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) test and who required hospitalization for the treatment of mild to severe SARS-CoV-2 infection. Patients were recruited 3-months after discharge from the hospital in accordance with the list of individuals admitted to a tertiary teaching hospital for COVID-19 treatment from April 2020 to March 2021. The exclusion criteria were as follows: participants with cognitive impairment easily observed during the phone interview by asking patient's name and age, weekday, and the time that interview has been conducted; those who presented significant hearing loss or speech problems; or individuals with chronic pain not related to SARS-CoV-2 infection in accordance with the participant's perception. Participants with incomplete data were excluded.

Interviewers

The interviewers were third- and fifth-year undergraduate medical students who acted voluntarily; therefore, they did not receive any financial compensation. Participants were evenly divided among participating students. The interviews were conducted from January to May 2021.

Variables

A questionnaire formulated by the researchers was hosted on Google Forms to facilitate data collection. The variables evaluated were: demographic data, the severity of SARS-CoV-2 infection based on the need for intensive care, potential risk factors associated with severe illness, and the presence or absence of chronic pain (defined as any pain recurring or persisting after hospital discharge up to the date of the interview, lasting longer than 3 months according to the current International Association for the Study of Pain definition).[10,11] The Brief Pain Inventory (BPI) was used for the evaluation of chronic pain (location, pain intensity

measured by a numeric scale 0 to 10, frequency, treatment in use, and the impact of pain on daily life activities).[15] For the completion of the pain diagram of the BPI, we requested the patients to describe the locations where the pain was present. We also have requested the patient to score their frequency of pain one week before the interview and the pain treatment in use.

If the patient presented with chronic pain, we asked their opinion if it was a consequence of COVID-19 or a result of another context.

Data sources/measurement

The research questionnaire consisted of three parts. The first one included the identification of patients, basic demographics, and information related to hospitalization data that was collected from the patient hospital's health file, including the period of admission and the need for intensive care and mechanical ventilation. Risk factors considered to be most frequently associated with SARS-CoV-2 infection at the time of hospital admission were documented. These risk factors included in the study were hypertension, obesity, and chronic lung and cardiovascular diseases.[16]

The second part was composed of questions related to the presence of chronic pain and its relationship to SARS-CoV-2 infection. The last part of the questionnaire was composed of the BPI.[15] As the interviews were performed through phone calls, the body diagram on the BPI was replaced by oral questions on pain sites.[17] The interviews were pre-scheduled to include participants on the best day and time of their preference. The interviews did not last for more than 15 minutes.

Ethical considerations

This study was approved by the Institutional Research Ethics Committee (CAAE 39112720.0.0000.5411, opinion number 4.340.406) prior to its execution. All participants were informed that their participation would only consist of answering questionnaires about sociodemographic aspects, health status, and pain. The requirement for informed consent on paper was waived by the Institutional Research Ethics Committee, as it was only necessary to read it aloud with the verbal acceptance of the invited individual.

Statistical analysis

Sample size was determined as convenience. Qualitative variables were presented as absolute and relative frequencies, and quantitative variables as medians and quartiles, as they did not present a normal distribution in the histogram analysis and the Shapiro-Wilk test. The Chi-Square and Fisher's exact tests were used to compare qualitative variables with the final outcome (occurrence of chronic pain related to COVID-19), and the Mann-Whitney test was used for qualitative variables.

The variables that presented p-values up to 0.20 in the associations with the main outcome of pain related to COVID-19 (female sex, number of risk factors for worst outcome of COVID-19, obesity, and diabetes) were analyzed in a binary logistic regression model to assess the independence of association. In univariate analyses, a cut-off points of 0.20 was chosen to maintain the model's parsimony and to reduce the risk of type 2 error. The Hosmer-Lemeshow test was used to assess the degree of agreement between the model and the results of the analysis. Multivariate data were expressed as Odds Ratios (ORs) and respective Confidence Intervals (CIs) for the outcome studied. Statistical significance was set at $p < 0.05$.

Results

A total of 341 patients were discharged from the hospital after admission for COVID-19 treatment from April 2020 to March 2021. However, we did not include 91 patients due to misinformation in the telephone numbers (79 individuals), refusal to participate (8 individuals), or death after hospital discharge (4 individuals). In addition, four participants were excluded due to hearing impairment, three due to speech disorders, and one with missing hospitalization data (Fig. 1).

Of those 242 patients analyzed, 77 (31.8%) presented chronic pain considered by the participant as caused by COVID-19. More than 75% of the patients were hospitalized for less than 15 days. Hospitalization occurred exclusively in the ward in 71.4% and 72.2% of those with or without chronic pain, respectively. There was no difference in the incidence of chronic pain after COVID-19 according to the place of hospitalization (ward or Intensive Care Unit [ICU]) or the presence of mechanical ventilation; however, female patients and those with obesity showed higher occurrences of chronic pain in the univariate analysis (Table 1). The odds for the occurrence of COVID-19-related chronic pain remained higher among female patients (p = 0.002; OR = 2.69; 95% CI 1.43—5.05) and those with obesity (p = 0.001; OR = 3.02; 95% CI 1.53—5.94) after multivariate analysis (Table 2).

When present, the pain was scored by the participants as a median of 6 and the limbs were the most frequent site of its occurrence. In the week prior to the interview, 75.3% of the participants described their pain as often or uninterrupted. Non-opioid analgesics, such as acetaminophen and metamizole, and opioids were used by 44.2% and 6.5% of patients with pain, respectively, while 24.6% did not use any kind of analgesics (Table 3).

Pain represents variable impacts on different daily life activities. General activities, walking, and enjoyment of life were the most impacted (median scores 7, 6, and 6, respectively), while personal relations were the least impacted activity (median score 2) (Table 4).

Discussion

This observational study evaluated the occurrence of chronic pain after hospitalization for the treatment of moderate-to-severe forms of COVID-19. Our study was unable to establish a correlation between the severity of COVID-19 (considering the site of hospitalization) and the presence of chronic pain. However, COVID-19-related chronic pain after hospitalization was detected in a considerable number of participants, representing 31.8% of the analyzed sample.

A review of the literature points to the incidence of chronic pain ranging from 36.5% to 62.5% of those infected.[18] One study that included a smaller number of

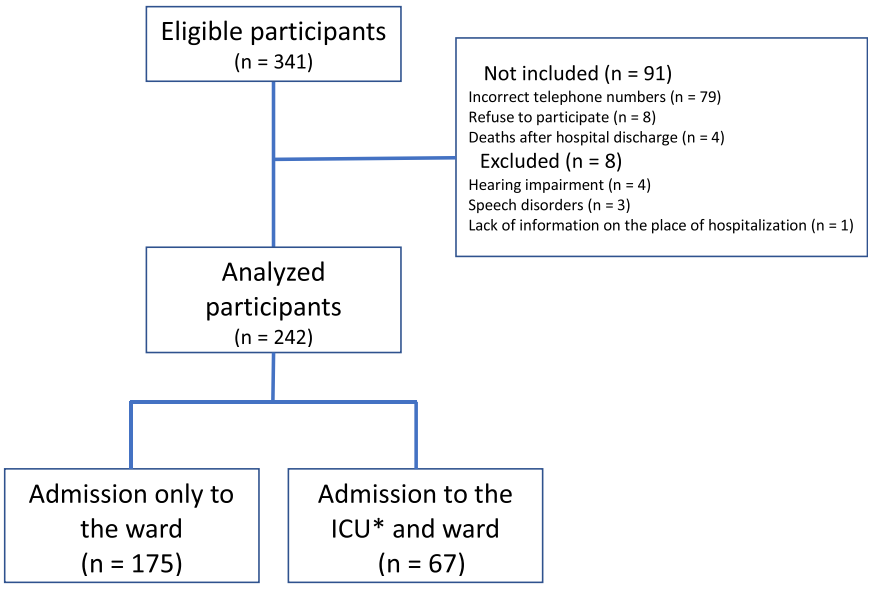

Figure 1 Participants flowchart. *ICU, Intensive Care Unit.

patients after discharge for COVID-19 treatment found an incidence of chronic pain of 19.6%, while other research found *de novo* pain in 33.7% of COVID-19 survivors.[19,20] Although fatigue and dyspnea are the most frequently reported symptoms by patients who have recovered from the disease, pain, more specifically joint and chest pain, is reported by 15% to 20% of individuals.[21] In patients mildly affected by COVID-19, the most painful sites were the head/face, chest, lower extremities, and migratory locations. Generalized pain was self-reported by 75% of participants, and a diagnosis of fibromyalgia, according to the 2016 criteria, was suspected in 40% of participants.[22] In our study, the most affected areas were the limbs and torso; likewise, in the study of Fernández-de-las-Peñas et al., 2022, where torso was the most affected area, followed by generalized body pain.[20]

A similar study through telephone interviews with hospitalized patients, without defining whether there was a need for intensive care, was conducted in Turkey. The estimated post-COVID-19 pain among patients was 7.9%. Also in this study, the highest occurrence of pain was observed in patients aged > 50 years (16.1%). These authors did not observe significant associations between sex, body mass index, presence of chronic diseases, and the occurrence of post-COVID-19 pain.[23] In our study, only obesity and female sex were risk factors for the presence of chronic pain.

The number of individuals with COVID-19 who require intensive care has already been alarming. It is known that

Table 1 Demographics and Coronavirus Disease 2019 (COVID-19) risk factors for hospitalization and disease severity data of patients admitted to the hospital for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection treatment.

	COVID-19 related chronic pain		*p*
	Yes (n = 77)	No (n = 165)	
Female[a]	47 (61%)	61 (37.2%)	**0.001**
Age (years)[b]	56 (45.0 / 62.5)	57 (44.0 / 67.0)	0.616
Presence of risk factors for COVID-19 worse outcome[a]	67 (87%)	142 (86.1%)	0.841
Number of COVID-19 risk factors for worse outcome	2 (1 / 4)	2 (1 / 3)	0.151
Obesity	34 (44.2%)	39 (23.6%)	**0.001**
Older than 60 years	26 (33.8%)	62 (37.6%)	0.566
Diabetes	30 (46.9%)	54 (35.3%)	0.110
Length of hospitalization[b]	10 (7.0 / 15.0)	10 (7.0 / 15.0)	0.485
Hospitalization place[a]			0.798
Ward	55 (71.4%)	120 (72.7%)	
ICU[c]	22 (28.6%)	45 (27.3%)	
Mechanical ventilation[a]	9 (11.7%)	16 (9.7%)	0.646

Chi-Square and Fisher's tests: qualitative variables with the final outcome (occurrence of pain after COVID-19); Mann-Whitney test: for other qualitative variables.

[a] Data are expressed in absolute and relative frequencies.

[b] Data are expressed as medians and quartiles.

[c] ICU, Intensive Care Unit.

Table 2 Multivariate analyses for binary logistic regression for chronic pain after COVID-19 hospitalization (n = 77).

Variable	Chronic pain related to COVID-19		
	Odds Ratio	Confidence Interval 95%	*p*-value
Female sex	2.69	1.43–5.05	**0.002**
Number of COVID-19 risk factors for worse outcome	0.98	0.78–1.23	0.871
Obesity	3.02	1.53–5.94	**0.001**
Diabetes	1.54	0.75–3.17	0.234

Hosmer Lemeshow: 0.126.

many of these patients survive after hospitalization, but not without multiple consequences for their health. Thus, there is an urgent need to prepare ourselves to continue treating these individuals, which implies adequate treatment of pain.[24] In COVID-19 patients, pain may be the sixth most prevalent symptom 48 days after hospital discharge. Thirty percent of patients admitted to the ICU reported pain during this period compared to 15% of those treated in the ward.[25] In our study, individuals undergoing mechanical ventilation or who were subjected to intensive care treatment, which are associated with more severe infections, presented similar rates of post-COVID-19 chronic pain than those who were affected in a milder way.

However, an interesting study that evaluated the occurrence of a post-COVID-19 syndrome, without specific emphasis on pain but including pain as a symptom related to it, observed that the risk of its incidence was higher among hospitalized individuals. Similar to our results, the authors did not observe an increased risk of its occurrence among those who received intensive care compared to that of ward care.[26] Usually patients who received mechanical ventilation were usually treated in a prone position during moderate to severe acute respiratory distress syndrome due to SARS-CoV-2. In patients treated in prone position, complications such as peripheral nerve injury have been reported, which may lead to chronic neuropathic pain.[27] In our study no nerve injuries were reported by patients.

Central pain and headache are another potential manifestation of post-COVID-19. Generalized inflammation, cell storming, vascular damage, and damage to macrophages may explain the developmental mechanism of pain. Still more research is needed to detect the exact mechanisms that lead to the development of COVID-19 pain.[28] Our study did not specifically assess the presence of chronic pain with neuropathic features.

It is known that up to 25% of patients admitted to the ICU for COVID-19 still have persistent inflammation after 3 months of discharge.[29] We believe that future evaluation for persistent changes in certain serum biomarkers, such as bradykinin and interleukin-6 for general pain, and perhaps Calcitonin Gene-Related Peptide (CGRP) for headache, among patients with COVID-19 may provide insight into pain mechanisms.[19] Theories hypothesize that SARS-CoV-2 cytokines and interleukin-induced storms may lead to sensitization of pain pathways in nociplastic pain as a result of the imbalance between neuromodulation systems of nociception. Anxiety levels and the intensity of pain symptoms in COVID-19 survivors are independently associated with central pain sensitization, suggesting a significant overlap with the psychological construct of the presence of pain in these patients.[20] Patients with obesity may be at higher risk for chronic pain after COVID-19 as these individuals present a low-grade chronic inflammation.[30]

In addition to pain, neuropathy and myopathy are very common in critically ill patients due to coronavirus

Table 3 Characteristics of pain after COVID-19 and actual use of analgesics in accordance with the brief pain inventory (n = 77).

Pain characteristics	n (%)
Pain site	
Limbs	30 (39%)
Torso	18 (23.4%)
Other	52 (62.4%)
Pain score – verbal numeric scale (0–10)[a]	6 (5.0 / 8.0)
Pain frequency at the last week	
Rarely	4 (5.2%)
Eventually	3 (3.9%)
Often	24 (31.2%)
Uninterrupted	34 (44.1%)
Missing info	12 (15.6%)
Pain treatment[b]	
None	15 (19.5%)
Non-opioids analgesics	31 (40.3%)
Opioids	5 (6.5%)
Physical therapy	5 (6.5%)
Others	7 (9.1%)
Cannot remember	3 (3.9%)
Missing info	12 (15.6%)

Data are expressed as absolute and relative frequencies.
[a] Data are expressed as medians and quartiles.
[b] More than one treatment could be in use at the same time.

Table 4 Impact of pain after COVID-19 on daily life activities in accordance with the brief pain inventory (n = 77).

Daily life activities[a]	Scores (0–10)
General activities	7 (4.0 / 9.5)
Mood	4 (0.0 / 9.0)
Walking	6 (2.5 / 8.5)
Working	6 (4.0 / 9.0)
Personal relations	2 (0.0 / 6.0)
Sleep	5 (0.0 / 8.0)
Enjoyment of Life	6 (2.0 / 8.5)

[a] Impairment in daily life is measured on a scale from 0 to 10, where 0 represents “no impact” and 10 represents “completely impacted”. Data are expressed as medians and quartiles.

infection. According to current clinical experience, patients receiving ICU treatment for COVID-19 often develop early-stage motor deficits, which may be due to neuropathy superimposed on myopathy.[31] The neuropathy and myopathy may explain the high score for general activity and walking pain interferences observed among the included participants in our study.

The pandemic imposed a restructuring on health systems worldwide, and in this context, most chronic pain services were considered non-essential at peak times of the occurrence of cases. Thus, as in most specialties, outpatient visits were reduced or interrupted to reduce the risk of viral spread. Due to the interruption of services, the treatment of chronic pain has been significantly impacted on a global scale. This circumstance may have complicated the comprehension of the correlation between symptoms and the extent of cases in patients who have recovered.[32] Curiously, patients with chronic pain prior to infection presented a higher risk of hospitalization for COVID-19.[33]

Our study has several limitations. Most importantly, we conducted interviews via telephone owing to sanitary restrictions and did not use a standardized tool to evaluate cognitive impairment of participants. This imposed important restrictions such as the use of a physical exam. In addition, as this was a single-center study carried out with patients treated at a tertiary teaching hospital, the results may not reflect the reality of patients admitted to other less complex health institutions. We must also consider that data on the presence of previous chronic pain may have been liable to recall bias, which is why we may have included participants with pre-existing chronic pain. Data prospect in health files also can be incomplete. In addition, we did not assess the participants' quality of life, although pain interference in daily activities was evaluated. We did not study the presence of neuropathic pain, mood, or catastrophism among the included participants. These results must be interpretated taking in consideration all informed bias.

Conclusion

Thus, we concluded that chronic pain is frequent among patients with COVID-19 after hospital discharge, but the severity of the infection cannot be associated with a higher prevalence of chronic pain. Furthermore, female patients and those with obesity had higher odds of chronic pain after hospital discharge. Future studies may reveal better characteristics of COVID-19-related pain and, hopefully, provide insights into its physiopathology, prevention, and treatment.

Data availability statement

The authors state that the data can be made available upon request.

Ethics approval statement

The study was approved by the Institutional Research Ethics Committee (CAAE 39112720.0.0000.5411, opinion number 4.340.406) before its execution.

Patient consent statement

Patient consent was verbally obtained from all the participants.

Clinical trial registration

As this was not a clinical trial, but an observational study no registration was performed.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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ORIGINAL INVESTIGATION

Fluid therapy and pulmonary complications in abdominal surgeries: randomized controlled trial

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KEYWORDS
Anesthesia;
Digestive system surgical procedures;
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Hemodynamic monitoring;
Organism hydration status;
Postoperative complications

Abstract

Background: There is no consensus on the most effective strategy for Postoperative Pulmonary Complication (PPC) reduction. This study hypothesized that a Goal-Directed Fluid Therapy (GDFT) protocol of infusion of predetermined boluses reduces the occurrence of PPC in patients undergoing elective open abdominal surgeries when compared with Standard of Care (SOC) strategy.

Methods: Randomized, prospective, controlled study, conducted from May 2012 to December 2014, with ASA I, II or III patients undergoing open abdominal surgeries, lasting at least 120 min, under general anesthesia, randomized into the SOC and the GDFT group. In the SOC, fluid administration was according to the anesthesiologist's discretion. In the GDFT, the intervention protocol, based on bolus infusion according to blood pressure and delta pulse pressure, was applied. Patients were postoperatively evaluated by an anesthesiologist blinded to the group allocation regarding PPC incidence, mortality, and Length of Hospital Stay (LOHS).

Results: Forty-two patients in the SOC group and 43 in the GDFT group. Nineteen patients (45%) in the SOC and 6 in the GDFT (14%) had at least one PPC ($p = 0.003$). There was no difference in mortality or LOHS between the groups. Among the patients with PPC, four died (25%), compared to two deaths in patients without PPC (3%) ($p = 0.001$). The LOHS had a median of 14.5 days in the group with PPC and 9 days in the group without PPC ($p = 0.001$).

Study conducted at the Institutional Research Board of Faculdade de Medicina de Botucatu – Univesidade Estadual Paulista on 7th May 2012. This study was registered at The Brazilian Registry of Clinical Trials (ReBEC) on 5th April 2021, UTN code: U1111-1207-3998, RBR-6ybk8kr, https://ensaiosclinicos.gov.br/rg/RBR-6ybk8kr.

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Conclusion: The GDFT protocol resulted in a lower rate of PPC; however, the LOHS and mortality did not reduce.
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Introduction

Postoperative Pulmonary Complications (PPC) are one of the main factors affecting morbidity and mortality in the postoperative period, leading to a longer length of hospital stay (LOHS), increased mortality, and rising costs.[1] The PPC incidence range is 6—80%, depending on the presence of risk factors and the definition adopted, including conditions ranging from atelectasis to Acute Respiratory Distress Syndrome (ARDS).[2]

PPC have a high incidence and a negative impact on clinical outcomes, particularly in patients undergoing abdominal surgery; hence, strategies reducing their occurrence should be developed.[3] Thus, Goal-Directed Fluid Therapy (GDFT) has been proposed as a possible intervention, since both "liberal" and "restrictive" strategies are associated with PPC.[4-6] However, there is no consensus on the most effective strategy or protocol for prevention of PPC.[7]

This study hypothesized that a GDFT protocol of infusion of predetermined boluses reduces the occurrence of PPC in patients undergoing elective open abdominal surgeries compared to the standard of care (SOC) volume replacement strategy. The primary outcome was PPC incidence in patients undergoing different intraoperative fluid replacement strategies, while the secondary outcomes included LOHS, renal function, and 30-day mortality.

Methods

This clinical, randomized, prospective, controlled study was conducted at the Hospital das Clínicas da Faculdade de Medicina de Botucatu (HC-FMB/UNESP) from May 2012 to December 2014. The FMB-UNESP Research Ethics Committee approved it, and the participants provided written informed consent. This study was registered at The Brazilian Registry of Clinical Trials (ReBEC – U1111-1207-3998, RBR-6ybk8kr).

Eight-five adult patients with ASA (American Society of Anesthesiologists) physical status I, II, or III, undergoing elective medium or major open abdominal surgeries (sigmoidectomy, colectomy, hemicolectomy, splenectomy, rectosigmoidectomy, pancreatectomy, intestinal transit reconstruction, abdominoperineal amputation, biliary bypass, gastrectomy, exploratory laparotomy, partial hepatectomy, and gastro-pancreatoduodenectomy) under general anesthesia were included in the present study.

All patients undergoing one of the above-mentioned open surgeries that were booked to last at least 120 min were included. Patients presenting with body mass index > 35 kg.m^{-2}, pregnancy, chronic obstructive pulmonary disease or bronchial infection, coagulopathies, preoperative renal function changes (creatinine > 1.3 mg.dL^{-1}), sepsis or signs of systemic inflammatory response syndrome, symptoms of liver failure, urgent or emergency surgery were not included in the study. Moreover, refusal of study participation, loss of postoperative follow-up, or deviation from the allocated protocol resulted in exclusion from the study. The visual representation of participant flow throughout the study, encompassing enrollment, randomization, and follow-up processes, is depicted in Figure 1.

Anesthesia was induced using sufentanil (0.5—0.7 μg.kg^{-1}), etomidate (0.3 mg.kg^{-1}), or propofol (2 mg.kg^{-1}), according to individual clinical needs. Neuromuscular blockade (NMB) was monitored and maintained continuously using SX TOF-Watch® monitor. Rocuronium (0.6 mg.kg^{-1}) or cisatracurium (0.2 mg.kg^{-1}) was administered for muscle relaxation. Anesthesia was maintained with continuous isoflurane inhalation at variable concentrations, according to each procedure and patient, associated with continuous remifentanil infusion (0.1—0.3 μg.kg^{-1}.min^{-1}). NMB was maintained by administering subsequent doses of 20% of the initial amount of the same neuromuscular blocker used for anesthesia induction when the Train-of-Four ratio (TOF) was ≥ 2. All patients underwent orotracheal intubation (OTI) and volume-controlled ventilation (tidal volume, 6—8 mL.kg^{-1}; positive end-expiratory pressure, 5 cmH_2O), without recruitment maneuvers and with the necessary respiratory rate to maintain the expired end-tidal CO_2 fraction at 35—40 mmHg. At the end of the surgery, NMB was reversed by administering sugammadex or neostigmine along with atropine, according to the neuromuscular blocker used. Postoperative analgesia was managed with intravenous medications (2 g dipyrone and 100 mg tramadol) 1 hour before the end of the surgery. Rescue morphine was administered in the postanesthesia care unit (PACU) for pain, and the dose was titrated based on the verbal rating scale (0—10). Additionally, antiemetic medications were administered at the end of the procedure (10 mg metoclopramide and 8 mg ondansetron). All patients were monitored with invasive blood pressure, and a central venous line was inserted in accordance with the hospital's standard protocols at the time, which determined the technique and site for central venous catheter insertion, without any influence from our study.

Volume replacement was divided into the following three periods:

1) Preoperative: All patients received 5% glucose solution (1 mL.kg^{-1}.h^{-1}) from fasting until admission to the operating room. Patients undergoing colon preparation additionally received Ringer's Lactate (RL) solution (1 mL.kg^{-1}.h^{-1}) until entrance to the operating room.
2) Intraoperative: Patients were randomized using computer code generation into two groups: SOC or GDFT. The group allotment was sealed in opaque envelopes that were opened immediately after the patient was monitored and before anesthesia induction.

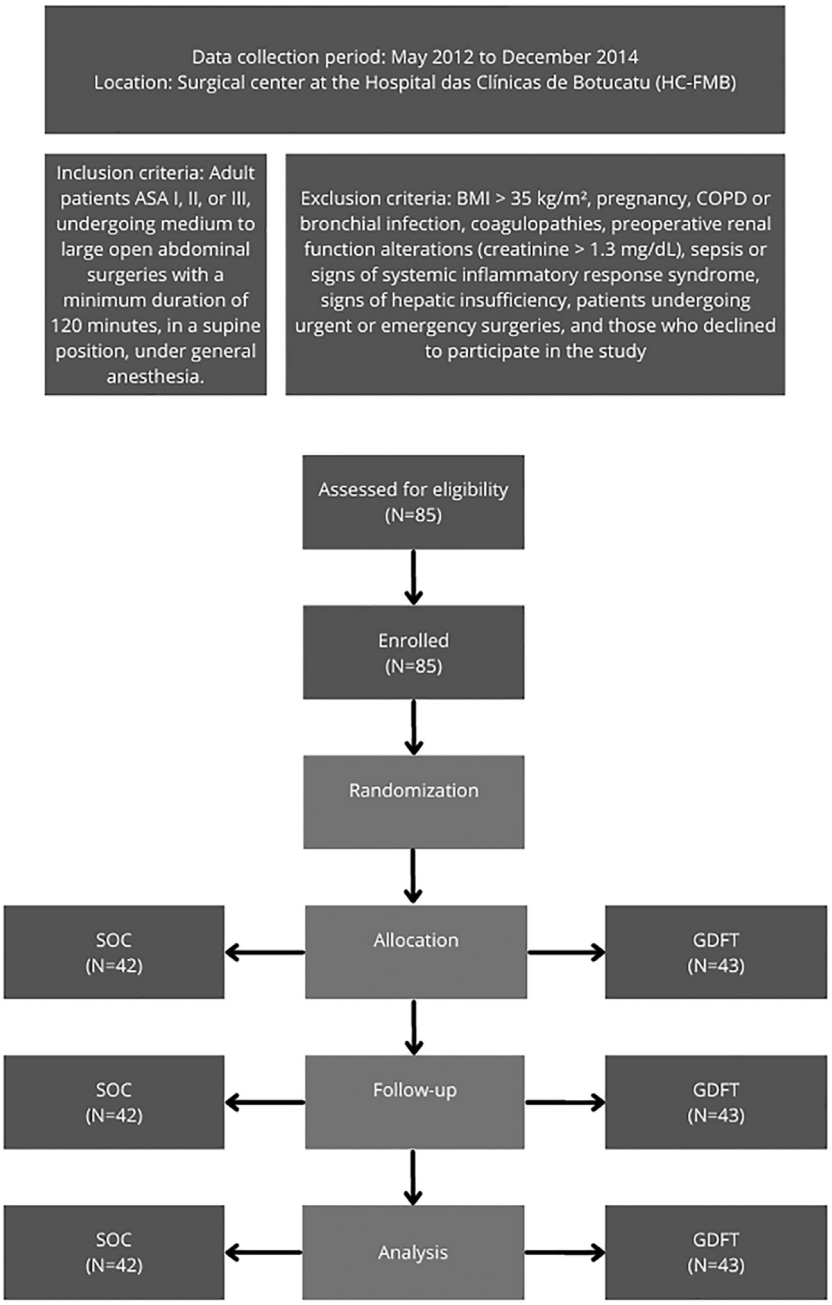

Figure 1 Participant flow diagram.

During the intraoperative period, both groups had identical hemodynamic targets: mean arterial pressure (MAP) of 65—80 mmHg and delta pulse pressure (dPP) ≤ 12%. Despite these common targets, the methodology for achieving them differed markedly between groups. In the SOC group, anesthesiologists had complete discretion over fluid administration, including the choice of fluid type, volume, and infusion rate. This approach led to a diverse range of infusion strategies and typically resulted in higher overall fluid volumes, reflecting the variability inherent in individual clinical judgment. Conversely, the GDFT group adhered to a strict, predefined protocol. This protocol dictated specific fluid types, volumes, and rates of administration, based strictly on changes in MAP and dPP. This structured approach aimed to standardize fluid therapy, reduce variability, and potentially mitigate the risks associated with fluid overload in the perioperative period. The detailed GDFT protocol is depicted in Figure 2.

Blood products were available for administration in both groups. Red blood cell (RBC) concentrates were administered when the plasma hemoglobin (Hb) concentration was $< 8\ g.dL^{-1}$, except in cardiac patients ($< 10\ g.dL^{-1}$). Fresh frozen plasma (FFP), cryoprecipitates, and platelet concentrates were administered according to the plasma fibrinogen concentration and platelet count in the intraoperative and immediate postoperative periods.

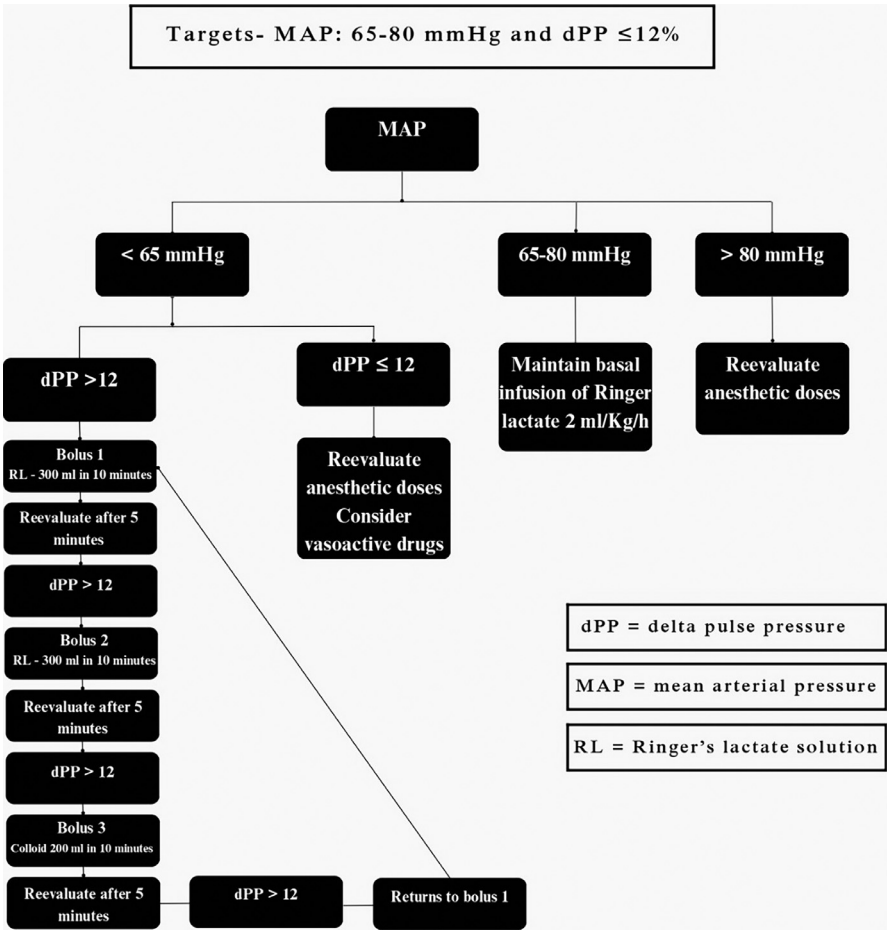

Figure 2 Algorithm for fluid replacement for the GDFT group. MAP, Mean Arterial Pressure; dPP, Delta Pulse Pressure; RL, Ringer's Lactate solution

3) Immediate postoperative: The same fluid infusion regimen used in the intraoperative period was followed for volume replacement at the PACU according to the group. In both groups, the hemodynamic target in this period was limited to changes in MAP since patients were breathing spontaneously.

During the intraoperative and immediate postoperative periods, patients in both groups received a continuous infusion of two $mL.kg^{-1}.h^{-1}$ of LR to replace insensible fluid losses and diuresis. The diuresis volume was measured using an indwelling urinary catheter after anesthesia induction. The initial volume immediately after catheterization was discarded, and the volumes collected during the surgical procedure were noted.

The total fluid volume administered to each group, type of infusion (crystalloids, colloids, and blood products) and need for vasoactive medications were evaluated. Moreover, the patients were analyzed for the total time MAP and dPP were within the target ranges.

Central venous blood samples (1.5 mL) were collected from all patients immediately before anesthesia induction and every hour until PACU discharge to assess central venous oxygen saturation ($ScvO_2$). Arterial blood samples were collected to evaluate Hb and lactate levels. Renal function was analyzed based on the perioperative urine output and plasma markers (creatinine, Neutrophil Gelatinase-Associated Lipocalin [NGAL], and cystatin C) assessed before anesthesia induction, 48 hours, and 5 days after surgery.

The patients were postoperatively evaluated by an anesthesiologist blinded to the group allocation. The following PPC were assessed: pneumonia, unscheduled postoperative OTI, and pulmonary thromboembolism. Moreover, LOHS and 30-day mortality were also studied. We also evaluated LOHS and mortality among patients who developed PPC regardless of the groups they were initially allocated.

Statistical analysis

Study data were collected by multiple evaluators and transcribed into an individual evaluation form explicitly developed for this purpose.

The sample size was calculated based on data from previous studies on PPC. An absolute 30% reduction in overall PPC was considered clinically significant, requiring approximately 66 patients for a Type I error of 0.05 and 80% test power. We decided to include 85 patients in the randomization to ensure the minimum sample size even with a loss of 25%. Initially, descriptive analyses included calculating means and standard deviations for quantitative variables and frequencies and percentages for qualitative variables,

Table 1 Comparison between groups for demographic and clinical variables and surgical duration.

	Groups		
	SOC (n = 42)	GDFT (n = 43)	
Variable	**Mean ± SD**	**Mean ± SD**	***p*-value**
Age (years)[a]	49.1 ± 11.0	49.1 ± 13.9	1.00
Weight (kg)[a]	68.8 ± 14.7	69.8 ± 16.3	0.77
Height (cm)[a]	164.4 ± 9.5	165.4 ± 9.5	0.63
Total surgical duration (min)[a]	270.2 ± 114.5	250.7 ± 92.2	0.39
Variable	**n (%)**	**n (%)**	***p*-value**
Sex[b]			
Male	22 (52)	21 (49)	0.91
ASA			
I[b]	11 (26)	7 (16)	0.39
II[b]	26 (62)	31 (72)	0.44
III[c]	5 (12)	5 (12)	1.00
Morbidities	**n (%)**	**n (%)**	***p*-value**
Diabetes Mellitus[b]	5 (12%)	6 (14%)	0.97
Systemic Arterial Hypertension[b]	8 (19%)	15 (35%)	0.16
Alcoholism[c]	4 (9.5%)	4 (9.3%)	1.00
Smoking[b]	12 (28.6%)	12 (27.9%)	0.86

SOC, Standard of Care; GDFT, Goal-Directed Fluid Therapy; SD, Standard Deviation; ASA, American Society of Anesthesiologists classification – patient's physical status.
[a] Student *t*-test for independent samples.
[b] Chi-Square test at 5% for association between categorized variables.
[c] Fisher's exact test.

stratified by group. For the quantitative variables with normal distribution, the Student's *t*-test was used to compare independent samples. A generalized linear model with gamma distribution was used for variables without normal distribution. Count data variables were compared according to a generalized linear model with Poisson distribution or negative binomial distribution, depending on the extra variation found. Qualitative variables were compared between groups using the difference of proportions test. Associations between qualitative variables and groups were compared using the chi-square and/or Fisher's exact test.

Quantitative variables repeated over time with normal distribution were analyzed by an adjusted repeated measures model followed by the adjusted Tukey multiple comparison test. Variables without normal distribution were analyzed using the same model, adjusted considering a gamma distribution, followed by the Wald multiple comparison test.

All analyses were performed using SAS software 9.3 for Windows, with a significance level set at 0.05 for all tests.

Results

The study analyzed 85 patients, 42 in the SOC group and 43 in the GDFT group. No patients were excluded from the study due to loss of follow-up, protocol deviation, or any other reason.

Patient characteristics

The groups were homogeneous for anthropometric parameters, sex, total surgical duration, patient's physical status, and presence of previous morbidities. The main comorbidities in both groups were smoking, systemic arterial hypertension, diabetes mellitus, and alcoholism, with no statistically significant differences (Table 1). The profile of surgeries and the profile of patients who were reintubated according to the groups are described in Tables 1 and 2 in the Supplementary Material.

Volume loss and intraoperative volume replacement

The groups were homogeneous for total intraoperative bleeding volume. Despite the fluid balance at the end of the surgery being less positive in the GDFT group than in the SOC group, the difference was not statistically significant. There was a statistically significant decrease in the total volume infused in the GDFT patients due to the smaller amount of crystalloids administered. The volume of synthetic colloids, RBC, and FFP administered during surgery was similar between the groups (Table 2).

Blood gas data

Lactate values increased over time and were statistically similar in both groups, except at 120 min, when lactate was higher in the SOC group. This was probably due to the exogenous administration of lactate, which was present in the LR and infused in greater volume in this group of patients. The $ScvO_2$ values increased during surgery compared to the preoperative values in both groups and returned to the baseline values before PACU discharge. Compared to the preoperative values, Hb levels decreased in both groups during different periods but without statistically significant differences between them during the same period. Blood data are

Table 2 Data regarding the total volume infused, total volume of crystalloids (Ringer's lactate solution) and colloids (Voluven®) infused, red blood cells count, fresh frozen plasma administered, total volume losses, fluid balance, and intraoperative bleeding in the studied groups.

	Groups		
	SOC (n = 42)	GDFT (n = 43)	
Variable	Mean ± SD	Mean ± SD	*p*-value
Total volume infused (mL)[a]	4879.9 ± 2147.3	3810.4 ± 2126.9*	0.02
Ringer's lactate solution (mL)[a]	3901.2 ± 1475.1	2982.9 ± 1524.0*	0.006
Voluven® 6% (mL)[1a]	737.8 ± 383.2	779.7 ± 565.1	0.71
Voluven® 6% (mL.kg^{-1})[a]	10.7 ± 5.9	10.8 ± 6.6	0.94
Red blood cells (mL)[b]	484.4 ± 298.3	348.6 ± 146.0	0.08
Fresh frozen plasma (mL)[b]	296.1 ± 139.8	245.2 ± 80.1	0.37
Losses (mL)[b]	5062.9 ± 3287.5	4364.5 ± 2920.6	0.29
Fluid balance (mL)[a]	1566.8 ± 1546.9	1025.6 ± 1443.1	0.10
Intraoperative bleeding (mL)[b]	1283.2 ± 959.7	1100.1 ± 851.1	0.34

SOC, Standard of Care; GDFT, Goal-Directed Fluid Therapy; SD, Standard Deviation.
[a] Student *t*-test for independent samples.
[b] Generalized linear model with gamma distribution to compare two groups.

described in Graphs 1, 2 and 3 provided in the Supplementary Material.

Renal function

The groups were homogeneous for the urinary output, both in absolute values and in mL.kg^{-1}.h^{-1}, and for the other parameters used to assess renal function (Table 3). There was a statistical difference in the NGAL values in the SOC group during different periods (preoperative < postoperative day 2 = postoperative day 5) (Graph 4 in the Supplementary Material).

Protocol efficiency

The intervention protocol was as efficient as the SOC in restoring the circulating volume lost intraoperatively when evaluating the pre-established protocol targets, albeit with less infused fluids (Table 2). Data referring to MAP and dPP are described in Table 3.

Postoperative complications

The volume replacement protocol based on bolus infusion resulted in a low rate of postoperative and pulmonary complications. Nineteen patients (45%) in the SOC group, compared to 6 (14%) in the GDFT group, had at least one postoperative complication ($p = 0.003$). There was a statistically significant difference between the SOC and GDFT groups regarding PPC (36% vs. 2%; $p = 0.001$). The groups were homogeneous in the individual analyses of other complications (renal, cardiovascular, infectious, and surgical) (Table 4).

The groups did not differ in the need for vasoactive drugs, including ephedrine, metaraminol, or noradrenaline. Ephedrine was the most commonly used medication in both groups.

Comparison between patients with and without PPC

The incidence of PPC in this study was 19%. In total, sixteen patients presented with at least one PPC. Among these

Table 3 Data referring to episodes of hypotension (MAP < 65 mm.Hg), hypovolemia (dPP > 12%), and urinary output in the studied groups.

	Groups		
	SOC	GDFT	
	Mean ± SD	Mean ± SD	*p*-value
% Time with MAP < 65 mmHg during surgery[a]	16.8 ± 18.7	16.7 ± 15.2	1.0
dPP episodes > 12%[b]	45.4 ± 19.6	49.0 ± 22.4	0.43
% Time with dPP > 12%	21.5 ± 21.6	18.2 ± 15.2	0.47
Urinary output (mL)c[3c] in the intraoperative period	583.8 ± 426.3	465.3 ± 296.4	0.10
Urinary output (mL.kg^{-1}.h^{-1})[c] in the intraoperative period	1.9 ± 1.0	1.6 ± 0.9	0.15

SOC, Standard of Care; GDFT, Goal-Directed Fluid Therapy; MAP, Mean Arterial Pressure; dPP, Delta Pulse Pressure; SD, Standard Deviation.
[a] Generalized linear model with negative binomial distribution for comparison of two groups.
[b] Student *t*-test for independent samples.
[c] Generalized linear model with gamma distribution for comparison of two groups.

Table 4 Comparison between groups for postoperative complications. Results are presented according to the number of patients who had the complication.

Postoperative complications	SOC (n = 42) (%)	GDFT (n = 43) (%)	*p*-value
Pneumonia	4 (10%)	0	0.12
Non-predicted postoperative OTI	14 (33%)	1 (2%)	0.0005
Surgical wound infection	2 (5%)	0	0.46
Abdominal wall dehiscence	2 (5%)	0	0.46
Anastomosis dehiscence	2 (5%)	2 (5%)	1.0
Surgical retreatment	5 (12%)	4 (9%)	0.97
ICU admission	16 (38%)	9 (21%)	0.13
Deep vein thrombosis	0	1 (2%)	1.0
Pulmonary thromboembolism	1 (2%)	1 (2%)	1.0
Cardiac arrhythmias	1 (2%)	1 (2%)	1.0
Acute kidney injury	1 (2%)	2 (5%)	1.0
Need for dialysis	0	1 (2%)	1.0
Sepsis/septic shock	2 (5%)	3 (7%)	1.0
Bleeding	1 (2%)	0	1.0
Death up to 30-days	4 (10%)	2 (5%)	0.43

OTI, Orotracheal Intubation; ICU, Intensive Care Unit; SOC, Standard of Care; GDFT, Goal-Directed Fluid Therapy.

patients, four died (25%) compared to two deaths among those patients who presented no PPC (3%) (p = 0.001). The LOHS had a median of 14.5 days in patients with PPC and 9 days in those without PPC (p = 0.001).

Discussion

This study showed that the GDFT was more effective in reducing the incidence of PPC than the SOC. This could be attributed to a smaller fluid volume administered in the perioperative period in the GDFT group, specifically of crystalloids (approximately 1000 mL less in our intervention group). Although the difference in volume is not highly expressive at first, our results align with some previously published data. For example, we want to draw attention to a relevant finding in the study by Corcoran and colleagues that compared three fluid delivery groups: restrictive, liberal, and GDFT.[4]

Corcoran's study[4] highlights that patients in the liberal fluid group received significantly larger intraoperative and total perioperative fluid volumes than those in the restrictive group, with a notable difference of approximately 1,570 mL. The disparity resulted in higher complications, including pneumonia and pulmonary edema, in the liberal groups. Conversely, patients in the GDFT group, which received a similar fluid volume compared with the volume administered to the patients in the liberal group, also experienced fewer cases of pneumonia.

This observation supports the notion that the mere volume of fluid administered may not be the sole determinant of postoperative complications. Instead, the timing, quality, and route of fluid administration, exemplified by goal-directed strategies, can be pivotal in mitigating complications. In line with the literature, a judicious and goal-directed approach to fluid management may significantly impact postoperative outcomes more than the absolute volume of fluid infused.[4]

PPC are prevalent postoperative complications associated with increased LOHS and short- and long-term mortality.[8] In the US, over one million PPC are estimated to occur yearly, with approximately 46,200 related deaths and 4.8 million extra hospitalization days.[9] In patients undergoing abdominal surgery, PPC represent an additional cost of USD 30,000 per patient and 6–9 extra hospitalization days.[10] The incidence of PPC in the present study was 19%, corroborating literature reports. In the LAS VEGAS observational study conducted in 146 hospitals in 29 countries, the ARISCAT score correlated with an increased risk of PPC in surgical patients. Patients with an ARISCAT score $\geq$ 26 showed a PPC incidence of 19.2% and in-hospital mortality of 1.7%, while those with a score < 26 showed a PPC incidence of 7% and in-hospital mortality of 0.2%.[11] Patel et al reported a PPC incidence of 12% in patients undergoing major abdominal surgery. Moreover, the hospital stay was more extended (10 vs. 3 days), and 30-day mortality was higher (12.5% vs. 0%) in those with PPC than in those without, indicating that PPC are common and significantly affect patient outcomes. Therefore, strategies to reduce the incidence are necessary.[3]

The development of PPC seems to be related to local lung physiologic changes associated with anesthesia and the inflammatory effects of major surgeries, as well as mechanical ventilation.[12] Therefore, multidisciplinary interventions could reduce PPC incidence, such as fluid administration management, preoperative oxygenation, blood loss control, duration of anesthesia, and protective ventilatory strategies.[2]

The present study analyzed a fluid therapy intervention based on strong scientific evidence that administering excess fluids in the perioperative period contributes to the onset of PPC, leading to ARDS.[13,14] Both liberal and more restrictive fluid resuscitation strategies were associated with complications. A systematic review[7] suggests that perioperative GDFT can improve postoperative recovery after major abdominal surgery. However, the most effective GDFT

strategy has yet to be determined. The strategy described in the present study could be a viable option because it efficiently maintained the hemodynamic parameters within the predetermined range, similar to the SOC strategy, but requiring a smaller volume of crystalloid administration.

Although PPC incidence reduced with the intervention, the length of hospital stay did not decrease significantly. The median LOHS were 11.1 (SD = 6.2) and 11.5 (SD = 6.5) in the SOC and GDFT groups, respectively (p = 0.58). These results corroborate the POEMAS study,[15] wherein the average hospitalization duration was 10.5 days and 11.5 days in the group receiving conventional volume replacement and that receiving GDFT, respectively (p = 0.87).

In the present study, the mortality rate did not differ significantly between the SOC and GDFT groups (9.5% vs. 4.6%; p = 0.433). This result corroborates the POEMAS study[15] results as well, wherein the mortality rate was 5.7% and 4.2% in the usual volume replacement group and the GDFT group, respectively, without a statistically significant difference.

However, the analysis of patients with and without PPC showed a statistically significant difference for LOHS and mortality. Patients with and without PPC were hospitalized for 14.5 days and 9 days, respectively (p = 0.001), while the mortality rates were 25% and 3%, respectively (p = 0.01). Both results corroborate the findings of Dimick et al. who reported that PPC occurrence increases the LOHS by 6–9 days,[10] and those of Khuri et al., who reported a 30-day mortality rate of 22% and 2% in patients with and without PPC, respectively.[16,17]

The Enhanced Recovery After Surgery Plus (ERAS+) protocol was created based on increasingly robust evidence of the importance of perioperative lung care. It added a few steps to the ERAS protocol, mainly focused on lung-related issues such as oral hygiene, increased physical activity, breathing exercises, and educational videos for patients and families. These measures reduced the PPC incidence in patients undergoing major surgeries (oncologic resections) from 18.7% to 10.5% (p = 0.017) immediately after implementation. Despite the favorable results, the ERAS+ required training for an entire multidisciplinary team and those explicitly hired to conduct the protocol. Conversely, the intervention proposed in the present study is easier to implement, consisting of a single intervention performed by the anesthesiologist, therefore minimizing the need for extensive staff training, equipment, or unusual medications.

The limitations of this study include being a single-center study, implying the use of the same team of surgeons and anesthesiologists and the analysis of a specific group of patients undergoing abdominal surgery. These characteristics may limit the generalizability of the results to other populations and clinical contexts. Moreover, the data was collected almost a decade ago, when the ERAS protocols were not the SOC in most of the health care centers in Brazil. However, this may still be the reality of many hospitals worldwide where the costs of implementing this multidisciplinary bundle of interventions may be challenging. Finally, the intervention used in our study was limited to the intraoperative and early postoperative periods. PPC were multifactorial complications, and fluid replacement, among other interventions implemented in the later postoperative period, may have contributed to the results encountered in the present study. Therefore, future multicenter studies with larger samples and extended periods of observation are needed to confirm and extend the findings of this study.

Conclusion

The GDFT intervention proposed in this study is based on the infusion of predetermined volume boluses, and it significantly reduced the incidence of PPC; however, the LOHS and mortality did not reduce. Although further studies are warranted to evaluate this strategy in different scenarios or larger populations, it seems a viable option for perioperative fluid management, allowing for easy implementation and good results compared to SOC fluid replacement. Moreover, the implementation of this strategy can be done without extra staff training or additional equipment and medications.

Authors' contributions

Gabriel Isaac Pereira de Castro: Conception and design of the study, acquisition of data, analysis and interpretation of data; drafting the article, and revising it critically for important intellectual content.

Renata Sayuri Ansai Pereira de Castro: Drafting the article, and revising it critically for important intellectual content.

Rodrigo Moreira e Lima: Conception and design of the study, acquisition of data, analysis and interpretation of data; drafting the article and revising it critically for important intellectual content.

Bruna Nogueira dos Santos: Drafting the article, and revising it critically for important intellectual content.

Lais Helena Navarro e Lima: Conception and design of the study, acquisition of data, analysis and interpretation of data; drafting the article, and revising it critically for important intellectual content.

Declaration of competing interest

The authors declare no have conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844500.

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ORIGINAL INVESTIGATION

Comparison of arterial hypotension incidence during general anesthesia induction — target-controlled infusion vs. bolus injection of propofol: a randomized clinical trial☆

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Abstract

Background: The incidence of arterial hypotension during induction of general anesthesia is influenced by the method of propofol administration, but there is a dearth of randomized clinical trials comparing bolus injection and target-controlled infusion in relation to arterial hypotension. This study seeks to compare the incidence of arterial hypotension between these two methods of propofol administration.

Methods: This prospective, randomized, single-center, non-blinded study included 60 patients (aged 35 to 55 years), classified as ASA physical status I or II, who were undergoing non-cardiac surgeries. They were randomly allocated using a computer to two groups based on the method of propofol administration during the induction of general anesthesia: the Target Group, receiving target-controlled infusion at 4 μg.mL^{-1}, and the Bolus Group, receiving a bolus infusion of 2 mg.kg^{-1}. Both groups also received midazolam 2 mg, fentanyl 3 μg.kg^{-1}, and rocuronium 0.6 mg.kg^{-1}. Over the first 10 minutes of anesthesia induction, Mean Arterial Pressure (MAP), Heart Rate (HR), level of Consciousness (qCON), and Suppression Rate (SR) were recorded every 2 minutes.

Results: Twenty-seven patients remained in the TCI group, while 28 were in the Bolus group. Repeated measure analysis using mixed-effects models could not reject the null hypothesis for the effect of group-time interactions in MAP (p = 0.85), HR (p = 0.49), SR (p = 0.44), or qCON (p = 0.72). The difference in means for qCON (60.2 for TCI, 50.5 for bolus, $p < 0.001$), MAP (90.3 for TCI, 86.2 for bolus, $p < 0.006$), HR (76.2 for TCI, 76.9 for bolus, p = 0.93), and SR (0.01 for

☆ Registered on the Brazilian Registry of Clinical Trials (REBEC RBR-69px3cj) on 06/23/2022 – https://ensaiosclinicos.gov.br/rg/RBR-69px3cj Research Ethics Committee approval number CEP 3.468.330 (http://fm.unb.br/cep-fm) – approved on 07/24/2019.

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TCI, 5.5 for bolus, $p < 0.001$), irrespective of time (whole period means), revealed some significant differences.
Conclusion: Patients who received propofol bolus injection exhibited a lower mean arterial pressure, a greater variation in the level of consciousness, and a higher suppression rate compared to those who received it as a target-controlled infusion. However, the interaction effect between groups and time remains inconclusive.
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Introduction

Arterial hypotension occurring during general anesthesia significantly increases mortality and contributes to organ dysfunction during the perioperative period.[1-4] The duration and severity of hypotension are closely linked to the type and extent of organ dysfunction.[1-5] Maheshwari et al[6] revealed that nearly one-third of intraoperative hypotension episodes occur during the time between anesthesia induction and the start of surgery.

Intraoperative hypotension can have various causes, with some anesthetic agents, such as propofol, playing a significant role in inducing hemodynamic changes. Propofol, a commonly used hypnotic agent, is known to be associated with arterial hypotension and a reduction in Systemic Vascular Resistance (SVR).[7,8]

Propofol can be administered during the induction of general anesthesia using different methods, including bolus injection, Manually Controlled Infusion (MCI), or Target-Controlled Infusion (TCI), all based on pharmacokinetic models. Bolus injection is thought to produce more pronounced hemodynamic effects due to the rapid increase in plasma concentration.[9] Conversely, TCI ensures a gradual and consistent attainment of the therapeutic target. Despite a multitude of studies[3,9-11] comparing different propofol administration techniques, the existing evidence is characterized either by its low quality or by conflicting results.

The primary goal of this study is to assess the influence of the propofol infusion protocol (TCI or Bolus) on Mean Arterial Pressure. Secondary outcomes encompass the effects on Heart Rate (HR), level of Consciousness (qCON), and Suppression Rate (SR) when comparing these two administration methods.

Methods

This prospective, randomized, single-center, non-blinded study was carried out at the Hospital Universitário de Brasília from March 2022 to September 2022. Ethical approval for the study was obtained from the Research Ethics Committee of Faculdade de Medicina da Universidade de Brasília in July 2019 (approval number: CEP 3.468.330). It was also registered with the Brazilian Registry of Clinical Trials (REBEC RBR-69px3cj). The complete anonymized dataset (https://doi.org/10.7910/DVN/QOGOYX) and data analysis (https://rpubs.com/gabrielmng/AnaGGVNov23c) are publicly available.

This study enrolled patients aged 35 to 55 years with ASA (American Society of Anesthesiologists) physical status I or II, who were scheduled for elective non-cardiac surgeries under general anesthesia. All participants provided informed written consent and willingly participated in the research. Patients with heart conditions other than chronic arterial hypertension, those requiring combined anesthesia, rapid sequence induction, awake intubation, or intubation under conscious sedation were excluded from the study. Exclusion criteria encompassed protocol deviations, such as variations in dosages or medication injections due to complications during anesthesia induction, as well as data loss.

Patients were divided into two groups using a carefully planned randomization process. Initially, one author prepared 30 identical sealed opaque envelopes for each protocol. These envelopes were then shuffled randomly. A computer was employed to generate a list of 60 numbers, which was organized by a pseudo-random function seeded with the current time in milliseconds by a second author. Subsequently, a third author received these envelopes and sequentially wrote a number on the top of each envelope based on the list generated by the computer. Once the inclusion criteria were satisfied for a patient, the envelope with the lowest available number was selected. The envelope was then handed over to the anesthesiologist responsible for conducting the study protocol. One group of patients received propofol via target-controlled infusion (Target Group) during the induction of anesthesia, while the other group received bolus administration (Bolus Group). The anesthesiologist meticulously recorded study data using electronic records.

Upon entering the operating room, patients were subjected to monitoring, including ECG, pulse oximetry (SpO_2), noninvasive blood pressure (NIBP), and a level of consciousness monitor (CONOX®). After the initial blood pressure measurement, patients received 2 mg of intravenous (IV) midazolam for anxiolysis. Pre-oxygenation was initiated with 100% oxygen at a rate of 5 liters per minute using a face mask. Blood pressure was re-evaluated after 5 minutes, and the resulting Mean Arterial Pressure (MAP) was regarded as the baseline measurement (designated as minute zero or t0).

The Target Group received target-controlled infusion (TCI) of propofol at 4 $\mu g.mL^{-1}$, commencing 2 minutes after an IV bolus of fentanyl (3 $\mu g.kg^{-1}$) at t0, followed by bolus administration of rocuronium (0.6 $mg.kg^{-1}$) after the loss of the eyelash reflex. The plasma concentration was adjusted to a level 30% above the effect-site concentration at which loss of consciousness occurred.

Patients in the Bolus Group had general anesthesia induced with an IV bolus of fentanyl (3 $\mu g.kg^{-1}$) at t0, propofol (2 $mg.kg^{-1}$) at t2, and rocuronium (0.6 $mg.kg^{-1}$) after

the loss of the eyelash reflex. Propofol was infused in about 15 seconds.

Following apnea, face mask ventilation was initiated in volume-controlled ventilation (VCV) mode with a tidal volume (VT) of 6—7 mL.kg^{-1}, no Positive End-Expiratory Pressure (PEEP), and 100% oxygen. Tracheal intubation was performed by direct laryngoscopy 2 minutes after rocuronium administration, and mechanical ventilation began in VCV mode with a VT of 6—7 mL.kg^{-1} (based on ideal weight) and PEEP set at 5 cm H_2O. In the Bolus Group, propofol infusion was initiated after intubation with a target of 1 μg. mL^{-1}, adjusted to maintain the qCON between 40 and 60.

Starting from the initiation of anesthetic induction (t0), measurements for MAP, heart rate (HR), level of consciousness (qCON), and suppression rate (SR) were recorded every 2 minutes until the 10th minute (t10). After intubation, patients were maintained without painful stimuli until t10 to prevent measurement bias. Figure 1 shows the study protocol design.

The sample size calculation was conducted using GPower® software. It considered a mean blood pressure variation of -16.11% in the Target group and -23.08% in the Bolus Group, based on data from a pilot study. The significance level (alpha) was set at 5%, and the study aimed for 80% power. An effect size of 0.82, estimated through the Glass delta method, was used in the calculation. The allocation ratio between the two groups was equal, at 1:1. Based on these parameters, the estimated sample size was 60 patients, allowing for the possibility of up to four patients being lost from each group.

Results

Sixty patients were initially randomized, with 30 assigned to the Target Group and 30 to the Bolus Group. However, five patients had to be excluded from the statistical analysis due to protocol deviations. These deviations included two cases of intubation complications and one case of altered blood pressure in the Target Group, as well as one case of data loss and one case involving unforeseen medication in the Bolus Group (Fig. 2). Detailed patient characteristics can be found in Table 1.

We employed Mixed Effects Models to assess the outcomes of MAP, HR, qCON, and SR within patients, treating patient ID as a random effect. We considered time, group allocation, and the interaction between time and group allocation as fixed effects in our analysis. The primary focus was on group-time interaction, which reflects the longitudinal impact of the interventions.

Additionally, we conducted an analysis of the outcome means, irrespective of time, between the two groups. This analysis revealed significant differences in means for qCON (60.2 for TCI, 50.5 for Bolus, $p < 0.001$), MAP (90.3 for TCI, 86.2 for Bolus, $p < 0.006$), HR (76.2 for TCI, 76.9 for Bolus, $p = 0.93$), and SR (0.01 for TCI, 5.5 for Bolus, $p < 0.001$). Figure 3 illustrates the longitudinal variation of these outcomes between the two groups.

Discussion

The results revealed that the group receiving bolus administration had a lower Mean Arterial Pressure, decreased qCON values, and a reduced SR when looking at the entire ten-minute measurement period compared to the TCI group. However, our mixed-effect analysis could not dismiss the null hypothesis for the group-time interaction, possibly due to the small sample size, which represents the primary limitation of this study.

Propofol is a commonly used hypnotic agent thanks to its swift onset of action, short context-sensitive half-time, and antiemetic properties. However, it is also associated with lowering blood pressure and systemic vascular resistance. These hemodynamic effects of propofol stem from its direct

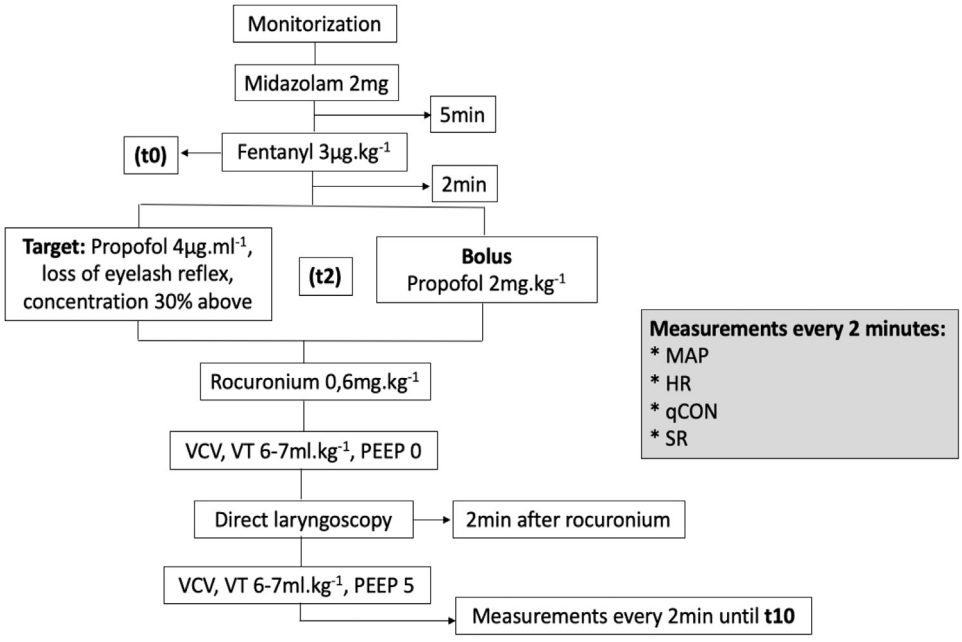

Figure 1 Study protocol design.

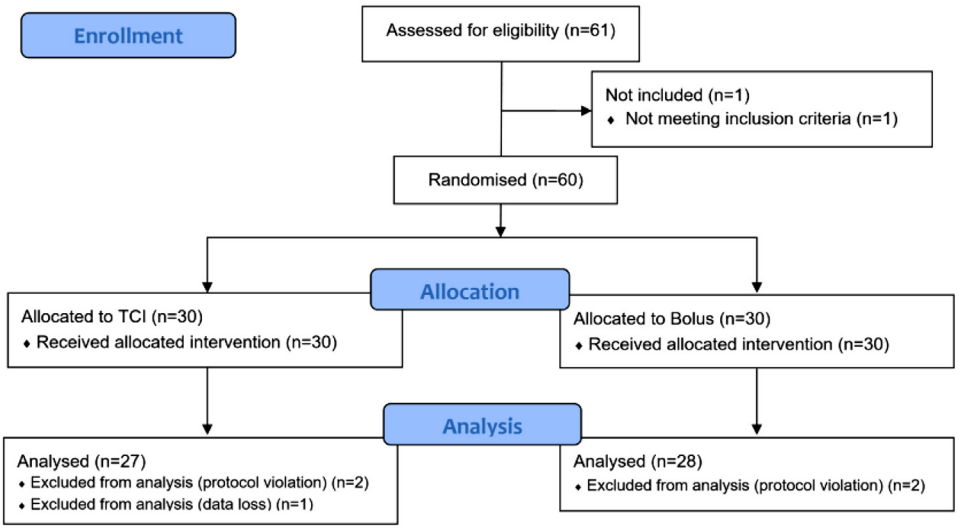

Figure 2 Study Flow Diagram.

Table 1 Characteristics and preoperative data of patients receiving TCI or bolus. Values are mean ± SD.

	Target Group (n = 27)	Bolus Group (n = 28)
Age (years)	44.8 ± 6.57	45.2 ± 6.23
Weight (kg)	68.6 ± 15.55	75.3 ± 7.01
Height (m)	1.64 ± 0.08	1.63 ± 0.12
Body Mass Index (kg.m^{-2})	25.3 ± 4.21	28.1 ± 7.38
Sex		
Female	17 (63%)	21 (75%)
Male	10 (37%)	7 (25%)
Physical status		
ASA I	11 (41%)	13 (46%)
ASA II	16 (59%)	15 (54%)
Procedures		
VLP cholecystectomy	7	9
ERCP	2	5
VLP hernioplasty	3	1
Septoplasty	1	2
Tympanomastoidectomy	2	1
Sinusectomy	3	0
Laryngeal microsurgery	2	1
Lumpectomy/Sectorectomy	2	1
Hysterectomy	1	1
Others	4	7
Comorbidities		
Apnea Syndrome	5	5
Type 2 Diabetes (NID)	1	4
Hypothyroidism	1	1
Asthma	2	0
Others	7	6

VLP, Videolaparoscopic; ERCP, Endoscopic Retrograde Cholangeopancreatography; NID, Non-Insulin Dependent.

impact on the peripheral vascular system, the myocardium, and its depression of the central nervous system, all contributing to a reduction in sympathetic tone.

This study specifically included patients classified as ASA I and II, aged between 35 and 55 years, without an in-depth evaluation of their cardiovascular capacity. The assumption here was that these patients would exhibit a similar hemodynamic response to propofol induction. It is important to note that the hemodynamic effects of propofol are dose dependent. Bolus administration can result in a higher plasma concentration within a shorter timeframe, potentially explaining the lower MAP observed in the bolus group.

The infusion pump used in this study operated based on the Marsh pharmacokinetic model, which solely takes

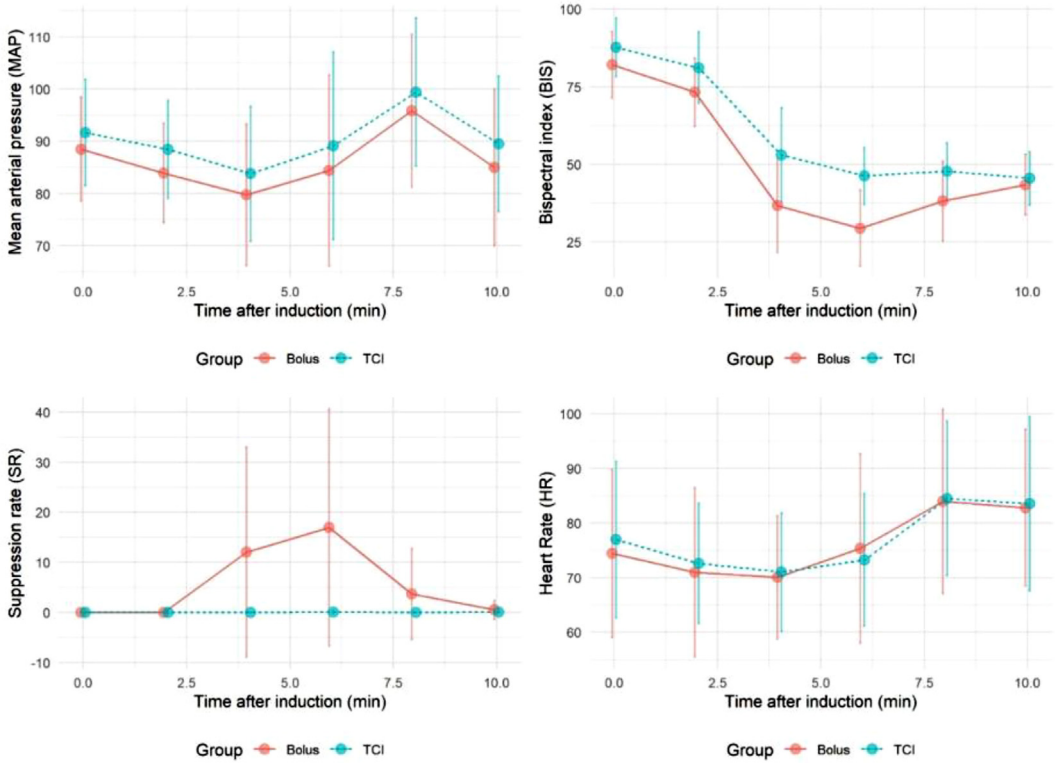

Figure 3 Outcomes longitudinal variation.

patient weight into account when determining compartment volume. However, the propofol dose was tailored for each patient to reach a sufficient concentration at the effector site for hypnosis induction. This approach in TCI, guided by a plasma target, offers a more stable drug administration profile, likely contributing to the fewer observed hemodynamic consequences in the TCI group.

The increased variation in the level of consciousness and suppression rate in the bolus group could be attributed to the relative overdose delivered during bolus induction. Administering a propofol bolus can lead to a plasma concentration significantly higher than necessary to induce hypnosis in an adult patient. Monitoring the level of consciousness during anesthesia induction remains crucial for patient safety and for mitigating postoperative morbidity.

Additionally, the propofol target in the TCI group was adjusted to 30% more than the expected for the loss of consciousness instead of being guided by qCON or Bispectral Index. This deviation may have contributed to a more substantial drop in MAP and qCON than usual. Future studies should consider setting the propofol target after induction based on qCON or the Bispectral Index.

Regarding group-time interaction, we were unable to reject the null hypothesis in relation to the outcomes, as shown in Table 2. Therefore, interpreting coefficients from this model would be misleading.

As limitations, this study could not compare the total dose used in both modes of administration as loss of consciousness propofol concentrations were not recorded. The fasting time was not standardized for all participants, which could raise concerns about their volume status. Also, the lack of information about diastolic function could significantly impact the results in a potential multivariate analysis.

Table 2 Hypothesis tests *p*-values for repeated measurements using mixed effect models.

Variable	*p*-value for Initial Group Difference	Group-Time Interaction *p*-value
Mean Arterial Pressure	0.236	0.859
Suppression Rate	0.042	0.446
qCON	0.001	0.726
Heart Rate	0.604	0.492

Conclusion

This study found that in adults aged 35 to 55 years-old, there was a lower mean arterial pressure, a greater variation in the level of consciousness, and a higher suppression rate in patients who received propofol bolus injection compared to those who received it as a target-controlled infusion, but the group-time effect interaction is still not clear.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgments

No competing interests were declared.

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ORIGINAL INVESTIGATION

Postoperative intensive care allocation and mortality in high-risk surgical patients: evidence from a low- and middle-income country cohort

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Postoperative Complications/prevention & control

Abstract

Background: The escalation of surgeries for high-risk patients in Low- and Middle-Income Countries (LMICs) lacks evidence on the positive impact of Intensive Care Unit (ICU) admission and lacks universal criteria for allocation. This study explores the link between postoperative ICU allocation and mortality in high-risk patients within a LMIC. Additionally, it assesses the Ex-Care risk model's utility in guiding postoperative allocation decisions.

Methods: A secondary analysis was conducted in a cohort of high-risk surgical patients from a 800-bed university-affiliated teaching hospital in Southern Brazil (July 2017 to January 2020). Inclusion criteria encompassed 1431 inpatients with Ex-Care Model-assessed all-cause postoperative 30-day mortality risk exceeding 5%. The study compared 30-day mortality outcomes between those allocated to the ICU and the Postanesthetic Care Unit (PACU). Outcomes were also assessed based on Ex-Care risk model classes.

Results: Among 1431 high-risk patients, 250 (17.47%) were directed to the ICU, resulting in 28% in-hospital 30-day mortality, compared to 8.9% in the PACU. However, ICU allocation showed no independent effect on mortality (RR = 0.91; 95% CI 0.68–1.20). Patients in the highest Ex-Care

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[1] These authors contributed equally to this work (study design, data collection and analysis, preparation of the manuscript and submission).

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risk class (Class IV) exhibited a substantial association with mortality (RR = 2.11; 95% CI 1.54 −2.90) and were more frequently admitted to the ICU (23.3% vs. 13.1%).
Conclusion: Patients in the highest Ex-Care risk class and those with complications faced elevated mortality risk, irrespective of allocation. Addressing the unmet need for adaptable postoperative care for high-risk patients outside the ICU is crucial in LMICs. Further research is essential to refine criteria and elucidate the utility of risk assessment tools like the Ex-Care model in assisting allocation decisions.
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Introduction

The global demand for surgical procedures is on the rise, surpassing 310 million annually,[1,2] particularly in countries with limited healthcare spending (< US$ 40/per capita).[1] A staggering 4.8 billion people lack access to safe surgical treatments, resulting in a shortfall of at least 143 million surgical procedures yearly, mainly in Low- and Middle-Income Countries (LMIC).[3] This surge in demand, coupled with the increasing severity of patients, strains healthcare systems, especially in high-complexity settings like Intensive care Units (ICU).

High-risk surgical patients, facing a 5−25% mortality and frequent complications,[4] often need routine ICU admissions. However, ICU beds are costly, have limited resources, and lack clear criteria for admission leading to potential disparities in access.[2,5,6] In LMICs where resources are scant, this issue becomes critical. In Brazil alone, with 4 million annual surgical procedures and mortality rates ranging from 1.7% to 2.8%,[7] the high-risk population constitutes 10−12% of patients.[8,9] ICU data in Brazil reveal mortality rates of 9.6−16.7% within 30 days and complication rates of 30−38%.[10]

Globally, less than 15% of high-risk surgical patients are admitted to the ICU due to the absence of clear admission criteria.[4] In Brazil, multicentric studies highlight low rates of ICU admissions after noncardiac surgeries (3.5%) and insufficient standardization regarding indications. In response to these challenges, we developed the Ex-Care risk model to identify high-risk surgical patients,[8] categorizing them as high-risk (5 −10% likelihood of death) or very high-risk (>10% probability of death). A care bundle for these patients was successfully implemented in surgical wards,[11] with a particular interest in the outcomes of high-risk patients electively admitted to ICU.

The primary objective of this study is to explore the association between postoperative ICU allocation and in-hospital postoperative mortality in a cohort of high-risk surgical patients in an LMIC setting. The secondary aim is to assess the association between Ex-Care risk classes, ICU admissions, and mortality. The hypothesis posits that postoperative ICU allocation influences in-hospital postoperative mortality among high-risk surgical patients in LMICs. Furthermore, it suggests an association between Ex-Care risk classes, ICU admissions, and mortality.

Methods

Study design and setting

This is a secondary analysis of a follow-up study of high-risk surgical patients from a single-center, 800-bed quaternary hospital in southern Brazil (Hospital de Clínicas de Porto Alegre − HCPA). The protocol was approved by the National Research Ethics Committee (CAAE 0444.8018.8.0000.5327) and registered in Clinical Trials (identifier: NCT04187664). The study was approved by the local Institutional Review Board, which granted informed consent clearance. Our report was based on the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement (Supplementary material S1 Table).[12]

Study population and data source

The cohort comprised consecutive high-risk adults that underwent surgery between July 2017 and January 2020 and were referred either to the ICU or PACU immediately after surgery. High surgical risk, defined as probability of death ≥5%, was determined using the Ex-Care model[8] (Supplementary material S2 Table). We excluded patients aged less than 16 years, and those who underwent outpatient, diagnostic and cardiac procedures, transplants, and procedures under local anesthesia.

Data on the surgical procedure, comorbidities, complications, and outcomes were obtained from electronic medical records and corrected for missing values using complete case analysis. The researchers were physicians trained to find information of preoperative comorbidities, surgery/anesthesia, postoperative complications, and deaths (the detailed variables collected are outlined in the section below). We defined pre-existing medical conditions as those fulfilling at least one of the following: appeared in medical records; registered in preanesthetic documents; confirmed by laboratory results.

Outcomes definition

The primary outcome was in-hospital postoperative mortality, censored at 30 days after surgery if the patient was still alive and in hospital. Secondary outcome was mortality in patients allocated at an ICU within 30 days after surgery, based on their respective Ex-Care risk model classes.

Exposure

The exposure of interest was immediate postoperative allocation at either ICU or PACU. The ICU group comprised patients who were directly transferred to an ICU as determined by the surgical/anesthetic team and were not in the PACU at any time. Criteria for direct postoperative ICU admission vary among surgical specialties, surgical severity, and ICU availability. Organ dysfunction or instabilities are

the main prioritization criteria for ICU allocation in our institution.

The PACU group comprised high-risk patient's ineligible for ICU or due to ICU bed unavailability. The PACU emphasizes short-stay recovery and is staffed by consultant anesthesiologists and nurses to provide 24-hour care. It focuses on continuous monitoring, pain management, hemodynamic optimization, and immediate postoperative complications. After meeting discharge criteria (Supplementary material S3 Table), patients transition to surgical wards. Admission, staffing, and physical structure criteria for ICU/PACU/standard wards remained consistent throughout the study.

To adjust for different sites of postoperative allocation, high-risk patients were classified using the Ex-Care model, based on death probability within 30 days (Class III: 5.0—9.9%, Class IV ≥ 10%).[8] Developed and validated in the same hospital, the model, encompassing age, ASA-PS (American Society of Anesthesiologists physical status), surgical severity, and nature, demonstrated high discriminative power for postoperative in-hospital death. A non-proprietary smartphone application for the Ex-Care model is available on mobile platforms.

Variables

In the analysis, variables included age, gender, ASA-PS,[13] surgical severity[14] and nature (elective or urgent). Surgical specialties were categorized into general (upper abdomen, lower gastrointestinal and hepatobiliary), vascular, orthopedics, urology, thoracic, neurosurgery and others (breast, head and neck, gynecology, and plastics).

Major complications within 7 days were: previous diagnosis of ventilatory support, postoperative vasopressor usage, acute kidney injury, transfusion, myocardial infarction, stroke, arrhythmia, thromboembolic event, delirium, wound dehiscence, sepsis, abdominal complication, or surgical reintervention within 7 days. Data collection followed definitions from the European Perioperative Clinical Outcome (EPCO),[15] World Health Organization (WHO), Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), and POMS questionnaire domains[16,17] (Supplementary material S4 Table).

Process outcomes were additionally assessed, including unplanned readmissions for patients previously assigned to the ICU or unplanned ICU admissions for those primarily designated to PACU, calls to the Rapid Response Team (RRT) within 7 days, and length of hospital stay. Hospital readmissions and unplanned surgical reinterventions within 30 days were also recorded.

Statistical analysis

The baseline characteristics of the two cohorts (ICU and PACU) were described in terms of continuous and categorical variables. The crude rates of death, complications and process measures were presented according to the postoperative allocation and Ex-Care risk classes.

For the primary analysis, we conducted a complete case analysis, excluding patients with missing data. We examined the independent association between in-hospital 30-day mortality and postoperative ICU allocation using Poisson regression with robust error variance, capable of directly estimating relative risks and avoiding the risk of overestimations from odds ratios.

To control for potential confounding factors, we built successive multilevel models adjusting for a group of variables based on a conceptual framework that describes the relationship between risk-factors.[18] For all models, forced simultaneous entry (all candidate variables remained in the model) was used rather than automated stepwise selection. The blocks of covariates were: first, preoperative risk class defined by Ex-Care model; second, surgical specialties (general surgery as the reference); third, postoperative complications (transfusion, cardiovascular, abdominal, sepsis, delirium, and acute kidney injury); fourth, postoperative instability (need of ventilatory or hemodynamic support). A power analysis was not conducted for this exploratory study, which relied on a convenience sample.

The significance level for all analyzes was 5%. Data were analyzed using the Statistical Analysis System (SAS Studio® 9.4. Cary. NC. USA) and R (version 3.5.1).

Results

Patient selection and postoperative allocation

During the study period, a total of 30,419 surgeries were performed. After excluding 15,983 cases (reoperations, transplants, diagnostic, cardiac and ambulatory procedures), 14,436 procedures were conducted at the main surgical unit, with 1,208 (8.36%) directly admitted to ICU. Among the 1,558 (10.79%) high-risk patients, 1,431 were eligible after excluding 127 patients who were preoperatively in the ICU. Postoperatively, 250 (17.47%) high-risk patients were referred to the ICU.

Regarding risk class, 23.3% (143/613) of the very high-risk group (Ex-Care Class IV) and 13.0% (107/818) of the high-risk group (Ex-Care Class III) were allocated to the ICU. Patient inclusion is depicted in Figure 1.

High-risk patient characteristics

The mean (SD) age of patients allocated at ICU was 65.72 (12.61) and 68.42 (11.3) years for the PACU group. Among patients directly admitted to the ICU in the postoperative period, there was a higher proportion of ASA-PS ≥ IV (28.0% vs. 10.2% at PACU, $p < 0.01$), and of those with predicted mortality ≥10% (57.2% vs. 39.8% at PACU, $p < 0.01$). Baseline characteristics of the study population are shown in Table 1.

Regarding surgical aspects, the nature of the procedures (elective or urgent) was not different between groups while major surgeries were more frequent in the ICU group (82.4% vs. 66.0% at PACU, $p < 0.01$). The most prevalent surgeries were abdominal, vascular, urological, and orthopedic. Neurosurgical patients were more frequently admitted to the ICU (24.0% vs. 3.4% at PACU, $p < 0.01$). As for comorbidities, there was a higher incidence of cancer and preoperative sepsis in those admitted to the ICU (Table 1).

Incidence of complications

Major complications occurred in 79.6% of patients allocated to the ICU versus 49.1% of those referred to PACU ($p < 0.01$). Patients allocated to the ICU had a higher incidence of bleeding and transfusion, ventilatory support (51.6% vs. 7.3% at

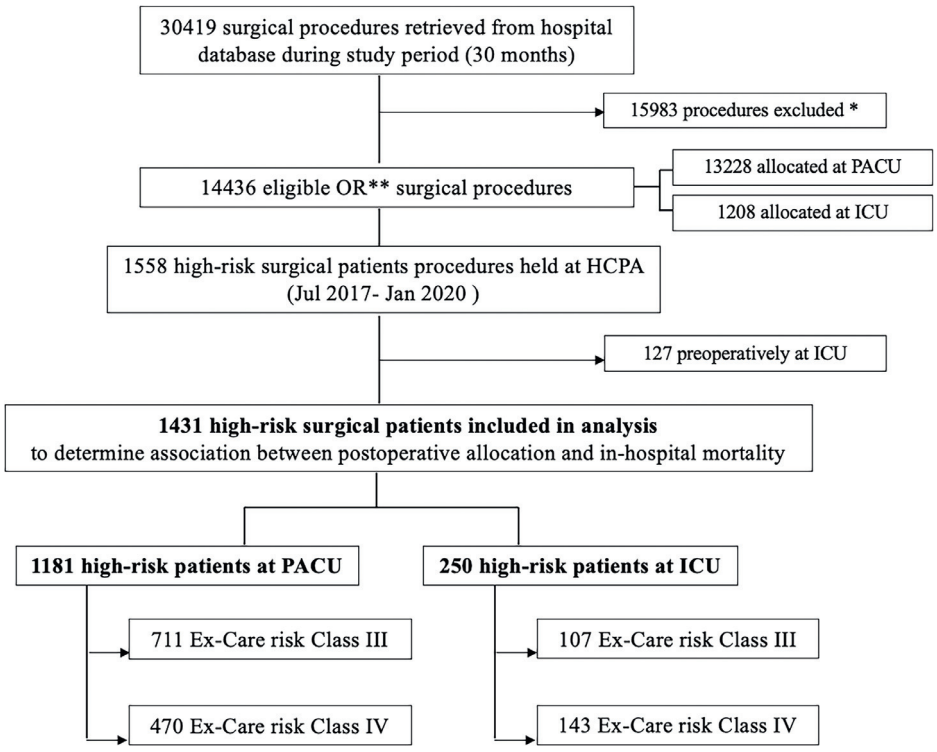

Figure 1 Flow chart of study cohort selection. OR, Operating Room; ICU, Intensive Care Unit; PACU, Postanesthetic Care Unit; HCPA, Hospital de Clínicas de Porto Alegre. * Reoperations, transplants, diagnostic, cardiac and ambulatory procedures. ** Procedures held at the main surgical unit.

PACU, $p < 0.01$), hemodynamic support (55.6% vs. 0.4% at PACU, $p < 0.01$), acute kidney injury, arrhythmia, delirium, abdominal complications, and sepsis. We observed no differences in hospital readmission between groups (13.4% vs. 12.4% in PACU group, $p = 0.67$). More surgical reinterventions occurred in the PACU group (11.8% vs. 7.2% in ICU, $p < 0.03$). Table 2 describes the outcomes.

Data regarding process outcomes showed no difference in unplanned admission or readmission to ICU (7.6% vs. 7.5% in PACU group, $p = 0.96$). Furthermore, for those who experienced unplanned ICU admission, mortality exceeded 40% in both groups (46.0% in PACU group vs. 42.1% in ICU group, $p = 0.87$). Postoperative length of stay was significantly longer in the ICU group, with a median of 10 (6–17) vs. 7 (4–11) days for those allocated at PACU (Table 2).

Association between mortality and postoperative allocation

Amongst 1431 high-risk surgical patients included in the analysis we identified 12.2% overall mortality. In the group allocated at the ICU, 70/250 patients (28.0%) died within 30 days vs. 105/1181 (8.9%) allocated at the PACU (Table 2). Before adjustment, the RR for death was 3.19 (95% CI 2.43–4.20) for ICU in relation to the PACU group. We adjusted risk for confounding factors included in successive models that considered preoperative risk class, surgical specialty, postoperative complications, and instabilities (need for hemodynamic and/or ventilatory support). After risk adjustment, there was no independent effect of ICU allocation in the immediate postoperative period on mortality (RR = 0.91; 95% CI 0.68–1.20) (Table 3).

In this analysis, the independent factors associated with 30-day postoperative mortality were Ex-Care Class IV (RR = 2.11; 95% CI 1.54–2.90), postoperative abdominal complications (RR 1.47; 95% CI 1.06–2.05), sepsis (RR 2.63; 95% CI 1.1.84–3.77) and acute kidney injury (RR = 1.87; 95% CI 1.41–2.49). An association of mortality with postoperative hemodynamic and/or ventilatory instabilities was also demonstrated (RR = 3.91; 95% CI 2.63–5.80). The adjusted RRs associated with mortality for variables included in the multivariable models are in Table 3.

Association between Ex-Care risk classes and mortality

To identify whether very high-risk patients (predicted mortality ≥ 10%) could benefit from allocation to intensive care, we analyzed two subgroups of patients regarding their Ex-Care risk classes (Class III and IV). We explored inpatient 30-day mortality and its relationship with surgical aspects, postoperative complications, and allocation.

The subgroup of Class IV patients confirmed predictions with substantially higher mortality rates (20.71% vs. 5.37% at Class III). Class IV patients were more frequent at general surgery procedures (44.0%) and reinterventions (12.6%). Major postoperative complications occurred in above 90% of high-risk patients who died in contrast with rates of 43.0% at risk Class III and 63.3% at risk Class IV. The most frequent complications and their rates by subgroup are presented at Figure 2. The group of Class IV patients was more frequently admitted to ICU (23.3% vs. 13.1% of Class III). The rates of ICU admission were higher also for Class IV patients who died within 30 days (44.9% vs. 27.3% of Class III) (Fig. 2 and

Table 1 Clinical characteristics stratified by postoperative allocation group.

	Missing data, n (%)				*p*-value
	PACU (n = 1181)	ICU (n = 250)	PACU (n = 1181)	ICU (n = 250)	
Demographic					
Age (yr)	68.42 (11.03)	65.72 (12.61)	–	–	<0.01
Male	671 (56.8)	122 (48.8)	–	–	0.31
Composite risk scales					
ASA-PS					<0.01
II	25 (2.1)	2 (0.8)	–	–	
III	1035 (87.6)	178 (71.2)			
IV	117 (9.9)	58 (23.2)			
V	4 (0.3)	12 (4.8)			
Risk of death (Ex-Care model)[a]					<0.01
Predicted mortality 5.0—9.9%	711 (60.2)	107 (42.8)	–	–	
Predicted mortality ≥ 10%	470 (39.8)	143 (57.2)			
Operative					
Procedure type					<0.01
Abdominal	411 (34.8)	103 (41.2)	–	–	
Vascular	287 (24.3)	40 (16.0)			
Orthopedic	103 (8.7)	9 (3.6)			
Urologic	141 (11.9)	23 (9.2)			
Thoracic	113 (9.6)	8 (3.2)			
Neurosurgical	40 (3.4)	60 (24.0)			
Other	86 (7.3)	7 (2.8)			
Surgical severity					<0.01
Minor	147 (12.4)	14 (5.6)	–	–	
Intermediate	254 (21.5)	30 (12)			
Major	780 (66.0)	206 (82.4)			
Urgent surgery	556 (47.1)	124 (49.6)	–	–	0.46
Comorbidities					
Coronary artery disease	204 (17.3)	39 (15.6)	–	–	0.52
Heart failure	114 (9.7)	25 (10.0)	–	–	0.86
COPD	170 (14.4)	46 (18.4)	–	–	0.10
Cancer	500 (42.3%)	125 (50.0)	–	–	0.02
Insulin-dependent DM	176 (14.9%)	32 (12.8)	1	–	0.38
Cerebrovascular disease	181 (15.3%)	39 (15.6)	–	–	0.91
Sepsis	87 (7.4%)	52 (20.8)	–	1	<0.01
Anemia[b]	764 (64.8%)	148 (59.7)	2	–	0.12
Dialysis	65 (5.7%)	65 (5.7)	50	8	0.45
Acute kidney injury	150 (13.0%)	42 (16.5%)	31	1	0.15
Chronic renal failure	344 (30.0%)	68 (27.3%)	33	2	0.40

All characteristics have no missing data unless otherwise stated. Data are presented as mean (±SD), median (IQR) or absolute values (%). Patient ages and hemoglobin were compared with Student's *t*-test; serum creatinine, eGFR, surgical duration and length of stay were compared with Mann-Whitney test; all other comparisons were performed with two-tailed Chi-Square test.

[a] Ex-Care risk model was determined using calculator available online.

[b] Anemia was defined as Hemoglobin (Hb) < 13 $g.dL^{-1}$ for men and < 12 $g.dL^{-1}$ for women.

PACU, Postanesthetic Care Unit; ICU, Intensive Care Unit; ASA-PS, American Society of Anesthesiologists Physical Status; COPD, Chronic Obstructive Pulmonary Disease; DM, Diabetes Mellitus; PO, Postoperative.

Table 4). Elsewhere, at the final Poisson regression model, the very-high risk group demonstrated to be strongly associated with mortality (RR = 2.11; 95% CI 1.54—2.90).

Discussion

The primary objective of our study was to evaluate the outcomes and allocation scenarios for high-risk surgical patients in a Brazilian public hospital setting. Our analysis revealed that 8.3% of all surgical inpatients and only 17.4% of high-risk inpatients had planned ICU admissions. A key finding emerged as we failed to identify evidence supporting the beneficial impact of postoperative critical care on the survival of high-risk surgical patients. Notably, patients in the highest Ex-Care preoperative risk class (≥10%) and those experiencing complications like sepsis, acute kidney injury, or hemodynamic/ventilatory instabilities faced a significantly elevated risk of death, regardless of allocation.

Table 2 Process measures, postoperative complications, and mortality by allocation.

	PACU (n = 1181)	ICU (n = 250)	*p*-value
Process Measures			
Unplanned ICU admission (30 days)	89 (7.5%)	19 (7.6%)	0.96
Mortality (30 days)	41 (46.0%)	8 (42.1%)	0.87
RRT Calls (7 days)	199 (16.9%)	27 (10.8 %)	0.01
PO Length of stay (days); median (IQR)	7 (4−11)	10 (6−17)	<0.01
Complications (7 days)			
Surgical bleeding > 500 mL	144 (12.2%)	71 (28.8%)	<0.01
Ventilatory support	86 (7.3%)	129 (51.6%)	<0.01
Hemodynamic support	123 (10.4%)	139 (55.6%)	<0.01
Acute kidney injury	176 (14.9%)	58 (23.2%)	0.01
Transfusion	161 (13.6%)	66 (26.4%)	<0.01
Myocardial infarction	11 (0.9%)	5 (2.0%)	0.30
Stroke	10 (0.8%)	4 (1.6%)	0.27
Arrhythmia	49(4.1%)	27 (10.8%)	<0.01
Thromboembolic event	102 (8.6%)	29(11.6%)	0.14
Delirium	83 (7%)	32 (12.8%)	0.02
Wound dehiscence	18 (1.5%)	10 (0.8%)	0.37
Abdominal	171 (14.5%)	63 (25.2%)	<0.01
Sepsis	91 (7.7%)	63 (25.2%)	<0.01
Hospital readmission (30 days)	158(13.4%)	31 (12.4%)	0.67
Surgical reintervention (30 days)	139 (11.8%)	18 (7.2%)	<0.03
Major complication[a]	580 (49.1%)	199 (79.6%)	<0.01
30-day mortality	105 (8.9%)	70 (28.0%)	<0.01

Data are presented as median (IQR) or absolute values (%). PACU, Postanesthetic Care Unit; ICU, Intensive Care Unit; RRT, Rapid Response Team; PO, Postoperative.

[a] Major complication: previous diagnosis of ventilatory support, postoperative vasopressor usage, acute kidney injury, transfusion, myocardial infarction, stroke, arrhythmia, thromboembolic event, delirium, wound dehiscence, sepsis, abdominal complication, or surgical reintervention within 7 days.

Our finding, indicating that ICU allocation does not correlate with a survival advantage, aligns with findings from previous cohorts.[19,20] Additionally, our cohort's ICU admission rates slightly exceeded those from the EuSOS[21] and from the South-African study SASOS,[22] possibly due to our institution's nature as a quaternary and regional reference for complex cases. A noteworthy fact is that only 23.1% of all ICU admissions were high-risk patients. More than 70% of high-risk and 55% of very-high-risk patients who died were not immediately allocated to ICU postoperatively. In a similar way, the majority of EuSOS patients who died (73%) were not admitted to ICU at any time, and among those who died after ICU admission, 43% occurred after an uneventful first passage through the unit.[21] Similarly, the mortality after unplanned ICU admissions in our study exceeded 40%. These findings emphasize a systematic failure in the allocation process of critical care resources, particularly in high-complexity hospitals in LMIC.[22]

The inconsistency in results regarding the potential mortality-reducing effects of ICU allocation and the observed increase in unfavorable outcomes raise questions about routine ICU allocation and the criteria guiding it.[23] A multicenter study by the International Surgical Outcomes Study group found an association between ICU allocation and increased mortality in high-risk patients (OR = 2.32; 95% CI 1.44−3.74).[2] Conversely, a UK-based population study reported lowest mortality rates in trusts with a higher number of critical care beds relative to provider size.[24] This indicates a complex relationship influenced by unadjusted confounding variables, since they are population-based studies using standard databases.

Our study highlights how such confounders considerably impact the final model, and perhaps contributes to identifying the variables that actually lead to high mortality rates besides the place of allocation itself. In fact, the high rate of major complications reported (close to 80% in the ICU group and 50% in the PACU), underscores the significant impact of unstable patients on mortality. On the other hand, as described by Gillies et al, the traditional role of an ICU is to provide organ support, such as invasive ventilation, inotropes/vasopressors, and renal replacement therapy in unstable patients.[25] The Society of Critical Care Medicine guidelines include as ICU/level 3 and highest priority level (Priority 1) critically ill patients who require organ support and intensive monitoring.[26]

However, few surgical patients require organ support after surgery, even in the high-risk group. What these patients need is prompt treatment of pain, hypothermia, mild cardiorespiratory compromise and fluid imbalance, early mobilization, enteral nutrition, and surveillance for deterioration signs. Surgical teams often refer their patients to ICUs because their staff is used to meeting those needs, but other units can also provide such proactive care. For instance, we identified at our setting a high prevalence of neurosurgical patients admitted to ICU (24.0% vs. 3.4% at PACU), especially due to sensory monitoring demand. We have already shown that adequate surgical

Table 3 Unadjusted and adjusted association between ICU allocation and in-hospital death within 30 days in 1431 patients — Poisson regression model.

Baseline Model	RR (95% CI)	*p*-value
ICU allocation vs. PACU	3.19 (2.43—4.2)	<0.01
Model 1: preoperative risk		
ICU allocation vs. PACU	2.41 (1.78—3.26)	<0.01
Ex-Care model[a]		
Predicted mortality 5.0—9.9%	1 (REF)	
Predicted mortality ≥ 10%	4.26 (3.12—5.81)	<0.01
Model 2: preoperative risk + specialty		
ICU allocation vs. PACU	2.50 (1.82—3.43)	<0.01
Ex-Care model risk class		
III (predicted mortality 5.0—9.9%)	1 (REF)	
IV (predicted mortality ≥ 10%)	3.74 (2.68—5.21)	<0.01
Surgical Specialty		
General	1 (REF)	
Vascular	0.69 (0.46—1.04)	0.08
Orthopedics	0.77 (0.40—1.46)	0.42
Urology	0.79 (0.48—1.30)	0.36
Thoracic	0.78 (0.43—1.42)	0.42
Neurosurgery	0.49 (0.29—0.82)	<0.01
Other	0.37 (1.14—0.99)	<0.05
Model 3: preoperative risk + specialty + PO complications		
ICU allocation vs. PACU	1.42 (1.04—1.95)	0.02
Ex-Care model risk class		
III (predicted mortality 5.0—9.9%)	1 (REF)	
IV (predicted mortality ≥ 10%)	2.27 (1.60—3.23)	<0.01
Surgical Specialty		
General	1 (REF)	
Vascular	1.11 (0.73—1.67)	0.61
Orthopedics	1.11 (0.64—1.93)	0.68
Urology	0.94 (0.50—1.52)	0.80
Thoracic	1.26 (0.70—2.28)	0.43
Neurosurgery	1.49 (0.86—2.15)	0.15
Other	0.61 (0.23—1.60)	0.31
PO complications		
PO transfusion	1.20 (0.87—1.66)	0.25
Cardiovascular	0.98 (0.63—1.54)	0.95
Abdominal	1.50 (1.04—2.14)	0.02
Sepsis	4.14 (2.85—6.02)	<0.01
Delirium	1.20 (0.83—1.74)	0.31
Acute kidney injury	2.28 (1.69—3.07)	<0.01
Final Model[b]: preoperative risk + specialty + PO complications + PO instability		
ICU allocation vs. PACU	**0.91 (0.68—1.20)**	**0.52**
Ex-Care model risk class		
III (predicted mortality 5.0—9.9%)	1 (REF)	
IV (predicted mortality ≥ 10%)	2.11 (1.54—2.90)	<0.01
Surgical Specialty		
General	1 (REF)	
Vascular	1.08 (0.68—1.49)	0.96
Orthopedics	1.26 (0.72—2.19)	0.41
Urology	0.92 (0.58—1.44)	0.71
Thoracic	1.10 (0.61—1.98)	0.74
Neurosurgery	1.59 (0.95—2.68)	0.07
Other	0.65 (0.25—1.68)	0.37
PO complications		
PO transfusion	1.06 (0.79—1.42)	0.68
Cardiovascular[b]	0.98 (0.63—1.50)	0.92
Abdominal	1.47 (1.06—2.05)	0.02
Sepsis	2.63 (1.84—3.77)	<0.01

Table 3 (*Continued*)

Baseline Model	RR (95% CI)	*p*-value
Delirium	1.20 (0.85–1.68)	0.28
Acute kidney injury	1.87 (1.41–2.49)	<0.01
PO instability[c]	3.91 (2.63–5.80)	<0.01

RR, Relative Risk; CI, Confidence Interval; ICU, Intensive Care Unit; PACU, Postanesthetic Care Unit; REF, Reference Category; PO, Postoperative.

[a] Ex-Care risk model considers age, ASA-PS, nature (urgent or elective) or severity of surgery (major vs. non-major).

[b] Including myocardial infarction, arrhythmias, and stroke.

[c] PO instability was defined as the need of ventilatory or hemodynamic support.

ward teams improve patient safety and can reduce the incidence of postoperative complications and mortality.[11] Therefore, in hospitals that provide excellent ward-based care, the incremental benefit of ICU admissions for stable patients will be reduced.[27]

To address the subjectivity in postoperative allocation decisions and optimize the use of this precious resource, we advocate for better criteria and instruments. Technical basis becomes even more necessary considering the great inequity of ICU beds in the Brazilian Unified Health System (SUS – Sistema Único de Saúde).[28] Although guidelines suggest not using scoring systems alone to determine the level of care because they are not highly accurate in predicting individual mortality, they can offer guidance when considering physiologic variables.

Our study focused on postoperative allocation in a limited-resource setting, using preoperative risk classes defined by the Ex-Care risk model. Notably, very high-risk patients (Class IV) showed significantly higher rates of intensive care admissions, particularly among those who died. Implementing such risk models into routine clinical practice could enhance decision-making for perioperative teams, map critical bed utilization, and streamline surgical schedules. This finding is corroborated by the Royal College of Surgeons of England's recommendation that all high-risk general surgical patients should be considered for critical care and, as a minimum, patients with an estimated risk of death of $\geq$ 10%.[29] Other major studies worldwide, such as the Surgical Risk Preoperative Assessment System (SURPAS)[5] and the Combined Assessment of Risk Encountered in Surgery (CARES),[30] have also shown promising results using a surgical risk calculator for accurate prediction of mortality and need for ICU admission.

Among the strengths of our study are the significant number of high-risk patients and using a context-sensitive risk stratification model which allowed comparison for similar patients allocated to different standards of care. Moreover, the adjustment of baseline risk variables and the description of postoperative complications, individually reviewed in medical records, enabled building robust statistical models. Furthermore, our data can be relevant to plan critical care in resource-limited environments.

The study has several limitations. Firstly, being a single-center study restricts external validity. While conducted at a highly representative public hospital, it does not encompass minor district hospitals or private healthcare facilities. Secondly, its observational nature introduces bias and precludes drawing conclusions regarding causality. However, conducting randomized clinical trials to evaluate care processes is challenging. Thirdly, we assessed outcomes solely in the immediate postoperative period, lacking insights into long-term mortality, functional independence, or quality of life. Moreover, the lack of detailed information on illness severity (SAPS, POSSUM, SOFA) restricts the conclusions. Lastly, a power analysis was not conducted for this exploratory study, which relied on a convenience sample.

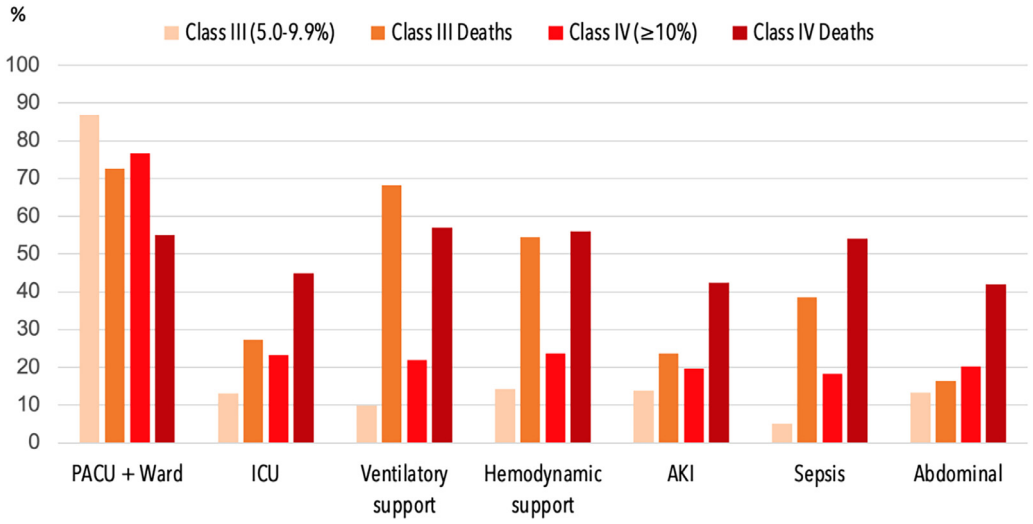

Figure 2 Outcomes according to each risk class of Ex-Care model in high-risk surgical patients. PACU, Postanesthetic Care Unit; ICU, Intensive Care Unit; AKI, Acute Kidney Injury.

Table 4 Outcomes according to each risk class of Ex-Care model in high-risk surgical patients.

	Class III (mortality 5.0%–9.9%)		Class IV (mortality ≥ 10%)	
	Total (n = 818)	Deaths (n = 44)	Total (n = 613)	Deaths (n = 127)
Operative				
Surgical Specialty				
General	245 (30.0)	14 (5.7)	269 (44.0)	74 (27.5)
Vascular	195 (23.8)	10 (5.1)	132 (21.5)	19 (14.4)
Orthopedics	63 (7.7)	5 (7.9)	49 (8.0)	5 (10.2)
Urology	98 (12.0)	5 (5.1)	66 (10.8)	12 (18.2)
Thoracic	90 (11.0)	6 (6.7)	31 (5.1)	5 (16.1)
Neurosurgery	60 (7.3)	2 (3.3)	40 (6.5)	10 (25.0)
Other	67 (8.2)	2 (3.0)	26 (4.2)	2 (7.7)
Surgical bleeding > 500 mL	145 (17.7)	11 (25.0)	71 (11.6)	14 (11.0)
Reintervention	80 (9.8)	7 (15.9)	77 (12.6)	14 (18.2)
PO complications				
Ventilatory support	80 (9.8)	3 (6.8)	135 (22.0)	71 (57.0)
Hemodynamic support	117 (14.3)	24 (54.5)	145 (23.7)	71 (56.0)
Acute kidney injury	114 (13.9)	27 (23.7)	120 (19.6)	51 (42.5)
Thromboembolic event	61 (7.5)	3 (6.8)	70 (11.4)	12 (17.1)
Abdominal	110 (13.4)	18 (16.4)	124 (20.2)	52 (42.0)
Sepsis	42 (5.1)	17 (38.6)	112 (18.3)	69 (54.0)
Major complication[a]	352 (43.0)	41 (93.2)	390 (63.3)	115 (90.5)
Allocation				
PACU	711 (86.9)	32 (72.7)	470 (76.6)	70 (55.1)
ICU	107 (13.1)	12 (27.3)	143 (23.3)	57 (44.9)

Data are presented as absolute values (%). PACU, Postanesthetic Care Unit; ICU, Intensive Care Unit; PO, Postoperative.

[a] Major complication: previous diagnosis of ventilatory support, postoperative vasopressor usage, acute kidney injury, transfusion, myocardial infarction, stroke, arrhythmia, thromboembolic event, delirium, wound dehiscence, sepsis, abdominal complication, or surgical reintervention within 7 days.

In conclusion, our study provides valuable insights into the complex decision-making process of postoperative ICU allocation. While we were unable to establish a direct impact of ICU allocation on outcomes, we found indications that ICU stay itself does not significantly affect mortality. Therefore, addressing the unmet need for adaptable postoperative care for high-risk surgical patients outside the ICU is crucial, particularly in LMICs. Further research is essential to refine criteria and elucidate the utility of risk assessment tools such as the Ex-Care model in assisting allocation decisions, especially in resource-limited countries.

Conflicts of interest

The authors declare no conflicts of interest.

Assistance with this study

None.

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Presentation

Preliminary data for this study were presented as a poster presentation at the Euroanaesthesia meeting, 3–5 June 2023, Glasgow.

Trial Registration

Clinicaltrials.gov identifier: NCT04187664.

Institutional Research Board Approval

National Research Ethics Committee (CAAE 0444.8018.8.0000.5327).

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844517.

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REVIEW ARTICLE

Cannabinoid products for pain management: recommendations from the São Paulo State Society of Anesthesiology

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Review

Abstract There is growing interest in using cannabinoids across various clinical scenarios, including pain medicine, leading to the disregard of regulatory protocols in some countries. Legislation has been implemented in Brazil, specifically in the state of São Paulo, permitting the distribution of cannabinoid products by health authorities for clinical purposes, free of charge for patients, upon professional prescription. Thus, it is imperative to assess the existing evidence

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regarding the efficacy and safety of these products in pain management. In light of this, the São Paulo State Society of Anesthesiology (SAESP) established a task force to conduct a narrative review on the topic using the Delphi method, requiring a minimum agreement of 60% among panelists. The study concluded that cannabinoid products could potentially serve as adjuncts in pain management but stressed the importance of judicious prescription. Nevertheless, this review advises against their use for acute pain and cancer-related pain. In other clinical scenarios, established treatments should take precedence, particularly when clinical protocols are available, such as in neuropathic pain. Only patients exhibiting poor therapeutic responses to established protocols or demonstrating intolerance to recommended management may be considered as potential candidates for cannabinoids, which should be prescribed by physicians experienced in handling these substances. Special attention should be given to individual patient characteristics and the likelihood of drug interactions.
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Introduction

There is worldwide interest in using cannabinoid products for management of several conditions. The United Nations (2020) acknowledged the medicinal potential of cannabinoids and excluded them from Annex IV of the 1961 Single Convention on Narcotic Drugs, enabling a less restrictive clinical use of cannabinoids.[1] Some European countries have legalized the prescription of plant derivatives of *Cannabis sativa* for several conditions, including pain management, neglecting the usual regulatory processes foreseen for the commercialization of medicines.[2]

On January 31, 2023, the State of São Paulo, Brazil, approved law number 17,618 establishing the state public policy for the free distribution of cannabinoid products when prescribed by healthcare professionals. In Brazil, this marked the first regulation enabling medicines and herbal remedies containing cannabinoids to be systematically provided to patients through the Public Health System. The law contemplates the availability of Cannabidiol (CBD) based medicines of plant origin, in association with other cannabinoid substances, including Tetrahydrocannabinol (THC).[3] As a result of the enactment of the law, a task force was established by the São Paulo State Health Department with the participation of representatives from different areas of society with an interest in the matter. The main objective of the working group is to establish protocols for supplying these products in different clinical scenarios, including pain.

Specifically concerning pain management, despite recent studies suggesting the benefits of medicinal cannabis, robust clinical evidence, such as that found in meta-analyses, is lacking. This is attributed to the high dropout rate of participants in clinical studies due to side effects, as well as the significant heterogeneity and inconsistency in the products and concentrations administered, which adversely affects the reliability of meta-analyses.[4]

It is believed that *Cannabis sativa* has been cultivated for over 12,000 years, though its medicinal use only emerged in China around 2,700 BC. In Western civilization, the earliest documented use occurred in 1839, when a pioneering study was conducted on its potential as an analgesic. More recently, particularly after the 1960s, extensive research has been undertaken on cannabinoids' potential as analgesics and anti-inflammatories, as well as their ability to modulate the nociceptive pathway. However, conclusive evidence authorizing their routine prescription has yet to be established.[5]

Other factors pose challenges to acquiring clinical evidence on cannabinoids as analgesics, including practical obstacles to conduct research:[4,6] 1) Existence of excessively restrictive regulatory measures; 2) Cannabis-based products available on the market are not covered by federal research funds, which makes difficult access for research purposes; 3) Published research has a predominance of private funding, which generates biases in results, making it urgent to create public policies to encourage research with these products; 4) There is a wide variety of drugs and products available for sale, hindering direct comparisons among them.

More than 538 chemical substances derived from *Cannabis sativa* are known. Of these, 100 cannabinoid products have been isolated, posing a massive challenge in obtaining scientific evidence for their clinical use.[7] During the preparation of the present narrative review, 16 products containing isolated cannabidiol and 11 products containing extracts from the *Cannabis sativa* plant in various proportions were approved by the National Health Surveillance Agency (Anvisa) for sale in pharmacies in Brazil (Table 1).[8] It is important to emphasize that the several routes of administration also pose a greater challenge to obtaining evidence. Some studies utilize the inhalation route for administering the products, which is potentially iatrogenic and not recommended by either the Federal Drug Administration (FDA) of the United States of America or the Brazilian Anvisa.

The terminology used in cannabinoid medicine also presents challenges. A comprehensive understanding of these terms is essential for clarity regarding the substances, the various types, and products available, and to prevent misuse. Table 2 outlines some important terms and definitions.[1,9,10]

Thus, it is vital to review the evidence on the efficacy and safety of cannabinoids in pain management due to the sizable number of products available for prescription and the vast existing literature. Therefore, a task force was established by the São Paulo State Society of Anesthesiology (SAESP) to examine the existing evidence related to cannabinoid-based product use for pain management.

Consensus working method

The present narrative review, which involved anesthesiologists' experts in pain management, used the Delphi method to achieve consensus. All pain specialists who are members of the SAESP Pain and Palliative Medicine Committee were

Table 1 Cannabis products registered with the National Health Surveillance Agency (Anvisa) in Brazil and available for sale in pharmacies, categorized by their active ingredients*.

Active Ingredient	Manufacturer	CBD Concentration	THC Concentration	Drops per mL
Cannabidiol	Active Pharmaceutica	20 mg.mL^{-1}	<0.2%	NA
	Aura Pharma	50 mg.mL^{-1}	NI	NA
	Belcher	150 mg.mL^{-1}	NI	NA
	Collect	20 mg.mL^{-1}	<0.2%	NA
	Ease Labs	100 mg.mL^{-1}	<0.2%	30
	Farmanguinhos	200 mg.mL^{-1}	NI	NA
	Greencare	23.75 mg.mL^{-1}	<0.2%	30
	Mantecorp Farmasa	23.75 mg.mL^{-1}	<0.2%	30
	Nunature	17.18 and 34.36 mg.mL^{-1}	<0.2%	50
	Prati-Donaduzzi	200; 20 and 50 mg.mL^{-1}	NI	NA
	Promediol	200 mg.mL^{-1}	NI	36
	Verdemed	23.75 and 50 mg.mL^{-1}	<0.2%	NA
Cannabis sativa extract	Cann 10 Pharma	200 mg.mL^{-1}	<0.2%	37
	Cannabr	10 mg.mL^{-1}	NI	NI
	Greencare	79.14 and 160.32 mg.mL^{-1}	2.4 mg.mL^{-1} and 0.06 mg.mL^{-1}	30
	Mantecorp Farmasa	79.14 and 160.32 mg.mL^{-1}	0.08 mg.mL^{-1}	30
	Promediol	200 mg.mL^{-1}	<0.2%	37
	Zion Medpharma	200 mg.mL^{-1}	<0.2%	37
	Herbarium	43 mg.mL^{-1}	2.01 mg.mL^{-1}	30
	L. Aura Farma	200 mg.mL^{-1}	<0.2%	37
	Ease Labs	79.14 mg.mL^{-1}	<0.2%	NI
	Extrato de *cannabis sativa* Cannten 200 mg.mL^{-1}	200 mg.mL^{-1}	<0.2%	37

NA, Not applicable; NI, Not informed.
Anvisa website accessed on April 27, 2023.

Table 2 Definitions and terms used in cannabinoid medicine.[9,10]

Cannabis sativa: A plant from the Cannabaceae family (*Magnoliopsida urticales*) yields active components with varying concentrations and proportions, showcasing pharmacological effects. It is crucial to underline that cannabis is a heterogeneous plant, comprising various chemical constituents and types of phytocannabinoids.
Marijuana: Commonly referred to as "maconha" in Portuguese, denotes the cannabis plant without its isolated components.
Cannabis: This is the technical term for marijuana, referring to the plant itself without any specific medicinal application.
Medicinal cannabis: This term pertains to the therapeutic utilization of both the plant and its components for medical treatments.
Endocannabinoids: Endogenous ligands found in humans and other animals, possessing affinity and activity on cannabinoid receptors.
Cannabinoids: Plant components that activate receptors distributed throughout the body. Cannabinoids can exist in natural forms, referred to as phytocannabinoids, or they can be semi-synthetic or synthetic.
Phytocannabinoid: Cannabinoids naturally occurring in the plant.
Cannabidiol (CBD): Major cannabinoid found in the cannabis plant, exhibiting pharmacological effects without producing psychoactive effects.
Cannabinoid acids, cannabinol, cannabigerol, and cannabivarins: Phytocannabinoids that demonstrate pharmacological properties but do not induce psychoactive effects.
Tetrahydrocannabinol (delta-9-tetrahydrocannabinol — THC): Cannabinoid with psychoactive properties and primarily responsible for the majority of the effects associated with cannabis.
Terpenes and flavonoids: These are aromatic oils naturally occurring in the plant, responsible for imparting the characteristic smell and flavor unique to each plant, as well as contributing to its overall quality.
Clone: A selected plant chosen for replication, wherein a portion of the plant is cultivated to produce a new plant with identical genetic characteristics. This process is utilized for the selection and production of products intended for medicinal use.
Full spectrum: This refers to a product that contains all elements of the cannabis plant, providing what is known as the entourage effect, where multiple elements synergistically interact. The product may predominantly contain CBD or THC or be balanced, depending on the proportion of cannabinoids in its formulation.
Broad spectrum: A product that includes all elements of the cannabis plant except THC. It is recommended when THC is contraindicated.
Isolated product: A product containing only one component of the plant, with other cannabinoids removed.

Table 3 Strategy used for article search.

('guideline' [All Fields] AND 'systematic review' [All Fields]) AND 'chronic pain') [All Fields] AND 'cannabis' [All Fields] OR 'marijuana' [All Fields] OR 'hashish' [All Fields] OR 'cannabinoids' [All Fields] OR 'dronabinol' [All Fields] OR 'marinol' [All Fields] OR 'nabilone' [All Fields] OR 'cesamet' [All Fields] OR 'tetrahydrocannabinol' [All Fields] OR 'cannabidiol' [All Fields] OR ('nabiximols' [Supplementary Concept] OR 'nabiximols' [All Fields] OR 'sativex' [All Fields]) AND 'OR' [All Fields] AND ('nabiximols' [Supplementary Concept] OR 'nabiximols' [All Fields])

invited to participate in the study panel. Additionally, renowned experts from several Brazilian states, totaling seventeen members, joined the panel. Initially, the group convened virtually to discuss the working method and determine the search mechanism to access the highest quality of evidence in the literature.

To establish consensus in the Delphi rounds, experts evaluated the themes by scoring them on a Likert scale from 1 to 5 (1 — Completely disagree; 2 — Disagree; 3 — Neither agree nor disagree; 4 — Agree; 5 — Totally agree). Scores of 1 and 2 were interpreted as disagreement, while scores of 4 and 5 were considered agreement. Panelists were allowed to freely enter their considerations, comments, and observations into the text. Identical weight was assigned to all individual opinions. To perform this review, an agreement coefficient higher than or equal to 60% was sought among the panelists to determine consensus.[11]

The members of the working group initially decided to include only review articles with meta-analysis available in the National Library of Medicine (PubMed) database. For this purpose, we utilized the search strategy outlined in Table 3.[2] Studies addressing pain management were included, without restriction on the pathophysiology of pain, publication date, or language. However, only five meta-analyses were identified (Table 4). Subsequently, the working group opted to incorporate additional articles, provided that the subject matter addressed in the present review had not been covered in the content of the initially included publications.

Table 4 Studies incorporated into the review following the consideration of the search strategy.

Aviram, Joshua, and G. Samuelly-Leichtag. "Efficacy of cannabis-based medicines for pain management: a systematic review and meta-analysis of randomized controlled trials". Pain physician 20.6 (2017): E755.[5]
Meng, Howard, et al. "Selective cannabinoids for chronic neuropathic pain: a systematic review and meta-analysis". Anesthesia & Analgesia 125.5 (2017): 1638-1652.[12]
Haeuser, Winfried, et al. "Efficacy, tolerability and safety of cannabis-based medicines for cancer pain: A systematic review with meta-analysis of randomized controlled trials". Schmerz (Berlin, Germany) 33.5 (2019): 424-436.[13]
Dykukha, Igor, et al. "Nabiximols in chronic neuropathic pain: a meta-analysis of randomized placebo-controlled trials". Pain Medicine 22.4 (2021): 861-874.[14]
Bilbao, Ainhoa, and Rainer Spanagel. "Medical cannabinoids: A pharmacology-based systematic review and meta-analysis for all relevant medical indications". BMC medicine 20.1 (2022): 259.[15]

After assigning tasks among the authors of this review and distributing the aforementioned texts to be evaluated by the panelists, the first Delphi round was conducted electronically,[16] involving all members of the working group. The initial consensus was reached with approximately 80% agreement, although some divergences persisted. Subsequently, a face-to-face meeting was convened with the participation of 15 authors to discuss the highlighted disagreements in the text.

One month after the initial meeting, the second Delphi round was conducted, also electronically, with the participation of all authors. During this round, approximately 90% agreement among authors was achieved. Additionally, a second face-to-face meeting was convened to finalize the manuscript. The recommendations provided in the present text are directed towards physicians who intend to prescribe medicinal cannabis to treat pain, as well as for physicians treating patients interested in receiving such prescriptions. This review focuses on pain scenarios for which data from the literature are available regarding the use of cannabinoids in pain management, as outlined below.

Results

Cannabinoids in cancer pain management

Experimental data from acute and chronic pain models have demonstrated synergistic analgesic effects between cannabinoids and opioids. Colocalization of cannabinoid and opioid receptors has been observed in the brain and spinal cord areas involved in pain modulation. Additionally, the release of endogenous opioid precursors has been noted following cannabinoid use. Therefore, it would be reasonable to expect a beneficial effect from the combined use of cannabinoids and opioids. However, clinical research in humans remains inconclusive regarding the benefit of combining cannabinoids and opioids for the management of cancer-related pain.[17]

A previous study observed only a modest analgesic effect in patients experiencing cancer-related pain who were administered daily doses of 10 or 20 mg of THC. The 10 mg dose was well tolerated, and despite the sedative effects, it exhibited analgesic potential. However, the 20 mg dose resulted in drowsiness, dizziness, ataxia, and blurred vision.[18] Despite these promising results, subsequent randomized clinical trials failed to replicate the findings of the study.

A placebo-controlled study conducted by Johnson et al. (2010) reported the superiority of THC:CBD solution in reducing pain intensity; however, no reduction in opioid consumption was observed. Moreover, a higher incidence of nausea and vomiting was also observed with THC:CBD compared to the placebo group.[19] These findings were not replicated in three other similar studies. Furthermore, Lynch et al. (2014) did not demonstrate the usefulness of nabiximols (synthetic cannabinoid) in managing pain related to chemotherapy-induced neuropathy.[20]

In a more recent review, the administration of nabiximols and THC via oral mucosa did not show significant differences from placebo in terms of reducing pain intensity, improving

sleep, reducing opioid consumption, or incidence of adverse events. However, more patients reported improvement in general status with nabiximols and THC compared to placebo, although the Number Needed to Treat (NNT) was 16. Conversely, the rates of withdrawal from the study due to adverse events, represented by a Number Needed to Harm (NNH) of 20, indicated a higher occurrence with nabiximols and THC than with placebo. In summary, in this study, the NNT was very close to the NNH, rendering the clinical use of cannabinoids inadvisable in this scenario.[13]

In another review, the authors observed a reduction in pain intensity, improvement in sleep quality, and a reduction in opioid use among patients with cancer-related pain. The studies evaluated the effectiveness of THC and CBD-based treatments, with doses ranging from 2.7 to 43.2 mg/day of THC and 0 to 40 mg/day of CBD. Higher doses were associated with a higher incidence of side effects, including mental confusion (60%—70%), drowsiness (70%—100%) and euphoria (40% —50%). The most common side effects included fatigue, dry mouth, dizziness, and nausea, followed by drowsiness, hypotension, mental confusion, nausea, and vomiting.[2,21]

However, following a quantitative analysis of the literature, cannabinoids were not found to be superior to placebo in alleviating pain in cancer patients. Supporting these findings, the Multinational Association of Supportive Care in Cancer (MASCC) recently published a guideline based on a literature review. In their review, the authors stressed that no clinical study has revealed a reduction in opioid consumption by using cannabinoids for cancer-related pain management. Thus, MASCC does not recommend prescribing cannabinoids for cancer-related pain, further suggesting that the possible risk of harm and adverse events should be carefully considered for cancer patients.[2,22]

Recommendations: The authors of the present review do not recommend cannabinoids for the management of cancer-related pain.

Cannabinoids in neuropathic pain management

A meta-analysis review that included patients presenting neuropathic pain, compared oral spray administration of CBD:THC to placebo. The authors of the meta-analysis observed pain intensity relief beyond that achieved with conventional analgesic strategies, suggesting potential usefulness for neuropathic pain management. Theoretically, CBD exhibits immunomodulatory and neuroprotective activities, which could contribute to neuropathic pain management. According to the authors' analysis, the use of CBD and THC should be regarded as a third-line option.[14]

Wallace et al., in 2020, reported that both low or high doses of THC did not reduce pain intensity, whereas doses falling within a hypothetical and subjective therapeutic window led to pain intensity reduction in cases of pain related to diabetic peripheral neuropathy. In their study, aerosol doses of THC at proportions of 1%, 4%, or 7% were compared to placebo in terms of pain intensity and cognition after 4 hours. Additionally, blood samples were collected to quantify plasma THC concentration at various time points (0, 15, 30, 45, 60, 150, and 240 minutes after administration). Low and high plasma levels of THC did not result in pain reduction, while plasma concentrations between 16 and 31 ng. mL^{-1} induced analgesia. This effect could potentially be attributed to the expression of the Cannabinoid receptor type 1 (CB1) in the presence of nerve injury. Thus, the CB1 receptor may be considered a novel therapeutic target for analgesia in cases of diabetic peripheral neuropathy. Cannabinoid receptor type 2 (CB2), known to be abundantly found peripherally, represents another potential target for the management of pain related to neuronal injuries.[23]

A meta-analysis involving patients with neuropathic pain compared selective cannabinoids, such as dronabinol and nabilone, with conventional treatments (pharmacotherapy and/or physiotherapy) and placebo. This meta-analysis revealed a reduction in pain when cannabinoids were used; however, the decrease in pain intensity did not show a statistical difference. Despite this finding, the authors concluded that cannabinoids represent an important option for patients who are refractory to conventional neuropathic pain management or for those who are unable to adhere to conventional treatment due to side effects. Moreover, patients demonstrated improvements in sleep quality and overall quality of life without experiencing major adverse effects.[12]

The Canadian Pain Society categorizes selective cannabinoids as a third-line option for neuropathic pain management, whereas the International Association for the Study of Pain (IASP) underscores that there is insufficient evidence to fully support their use. However, IASP recommends against withdrawing their use for patients who show improvement, suggesting instead that supervision by a specialist is warranted.[24,25]

Recommendations: The authors of the present review recommend that cannabinoids should only be prescribed by specialists and considered as a third-line option for managing neuropathic pain.

Cannabinoids in nociceptive pain management

Musculoskeletal pain

Musculoskeletal pain was previously a common reason for prescribing medicinal cannabis for adults.[26] In a systematic review comprising 11 studies, seven noted a significant analgesic effect of cannabinoids, along with improvements in secondary pain-related symptoms, such as sleep patterns, muscle stiffness, and spasticity. The most common adverse effects were mild to moderate fatigue and dizziness, which were generally well tolerated.[27]

A recent scoping review underscored the scarcity of clinical trials studying the analgesic effect of cannabinoids on musculoskeletal pain. Conversely, it revealed that available publications reported improvements in pain scores and secondary symptoms, such as psychological well-being and a reduction in the consumption of analgesics, particularly opioids and adjuvants for pain management. The authors cautioned about the short follow-up in the included studies, as well as the observed methodological limitations.[26]

Recommendations: The authors of the present review recommend weighing the potential benefits and adverse effects before prescribing cannabinoids for the management of musculoskeletal pain, given their narrow therapeutic effective plasma concentration range.

Osteoarthritis

Osteoarthritis, the most prevalent musculoskeletal disorder, manifests primarily through pain. The expression of CB1 and

CB2 receptors in the synovium suggests the involvement of the endocannabinoid system in this condition. Nonetheless, inhibition of the fatty acid amide hydrolase enzyme did not produce analgesic effects in patients with knee osteoarthritis.[27] Thus, the prescription of cannabinoids for the disorder remains questionable.

In a 12-week randomized clinical trial involving 320 participants with a mean age of 69 years, topical CBD was applied to the skin adjacent to the knees of osteoarthritis patients. Participants were assigned to three groups: a placebo group and two groups using 4.2% CBD gel at doses of 250 mg/day and 500 mg/day. The primary analysis did not reveal any changes in pain scores. However, the secondary analysis showed a reduction of more than 30% in physical function assessed by the Western Ontario and McMaster Universities Arthritis Index. Male patients exhibited better responses than females, and dry mouth and headache were the most common adverse effects.[28] Conversely, applying synthetic CBD (nabiximols) for 12 weeks in 136 individuals with hand osteoarthritis did not improve pain scores, sleep quality, or mood disorders.[28] Clinical trials investigating oral or topical CBD, either alone or in combination with THC, for osteoarthritis management are currently underway, with most of them in phase 2.

Recommendations: The authors of the present review do not consider the existing evidence sufficient to support the routine prescription of cannabinoids for pain management in patients with osteoarthritis.

Cannabinoids in nociplastic pain management

Fibromyalgia

Malfunctioning of the endocannabinoid system is believed to contribute to the pain experienced by patients with fibromyalgia. The endocannabinoid system plays a role in modulating inflammation, the endocrine system, cognition, memory, nausea, vomiting, and pain itself. Consequently, cannabinoids are theoretically considered a potential management option.[29]

However, several studies utilizing nabilone and dronabinol for fibromyalgia management reported a significant incidence of adverse effects, resulting in low tolerability to cannabinoids, poor treatment adherence, and unfavorable outcomes. Recent research with nabilone and varying proportions of THC and CBD also revealed unsatisfactory results.[30]

In a systematic review that included only two clinical trials involving 72 patients and with a short follow-up period, the tolerability of the cannabinoid used was low, with reports of dizziness, drowsiness, and vertigo. Furthermore, there was no improvement in fibromyalgia symptoms compared to placebo.[30] When inhaled cannabis was administered to patients with fibromyalgia, no significant effects were observed in spontaneous pain or sensitivity to electric shock.[31] According to the authors, the THC:CBD ratio might have influenced the outcomes, suggesting that THC may have a more suitable profile for pain management in patients with fibromyalgia.[30,31]

A clinical trial using THC and CBD sublingually at the mean dose of 4.4 and 0.08 mg, respectively, showed a significant reduction in fibromyalgia impact scores, and improved well-being, pain, and fatigue. Observational studies administering cannabinoids via different routes reported improvements in pain, quality of sleep, or quality of life. However, most patients included in these studies had previously used cannabinoids recreationally, and the mental effects linked to the substance may have influenced the results. The most commonly reported adverse effects were drowsiness, dry mouth, cough, and gastrointestinal symptoms, along with improvements in mood and libido as accompanying effects.[32–35]

Recommendations: In fibromyalgia, the authors of the present review do not consider the existing evidence sufficient to recommend the routine prescription of cannabinoids. They also caution about the incidence of adverse effects associated with cannabinoid treatment in patients with fibromyalgia.

Visceral pain and chronic pelvic pain management

Experimental models of pancreatitis, esophagitis, hepatitis, and cystitis have shown that the stimulation of cannabinoid receptors exhibits tissue protective effects alongside analgesic and anti-hyperalgesic properties.[36]

The number of randomized and controlled clinical trials addressing irritable bowel syndrome surpasses those focused on inflammatory bowel disease. These studies suggest that while cannabinoids do not promote disease remission, they do alleviate pain intensity, anxiety, and depression, decrease opioid usage, thus mitigating their side effects, and ultimately enhance overall quality of life.[37–39] However, routine clinical use of cannabinoids for these disorders should not be recommended.

Regarding male and female chronic pelvic pain, few observational studies support the cannabinoid prescription, rendering the results questionable.[40–42] Most of the current literature comprises retrospective or cohort studies using different products, administration routes, and doses.[43]

Recommendations: The authors of this review do not recommend the routine administration of cannabinoids for visceral pain and chronic pelvic pain management.

Headaches and orofacial pain management

In a meta-analysis comprising 12 studies, which included case reports and series involving 1,980 participants, various doses of cannabinoids were administered using different administration routes aiming to evaluate their effects on abortive and preventive treatment of migraine. Individuals taking cannabinoids experienced a significant reduction in the number of episodes per month and in the occurrence of nausea and vomiting during episodes. However, this improvement did not persist beyond the sixth month of use. CBD:THC products showed a similar effect to amitriptyline in reducing the number of episodes per month. Combining both drugs (amitriptyline + cannabinoids) had an additive effect in reducing episodes, although moderate side effects were seen in 43.75% of patients, including tolerance and the subsequent need to increase doses.[44] There are limited studies on migraine and other headaches to support the routine prescription of cannabinoids.

Similarly, there is a scarcity of clinical trials assessing cannabinoids for orofacial pain. In a systematic review, oral administration of cannabinoids as a preventive approach for orofacial procedures did not demonstrate superiority over ibuprofen or naproxen. However, lower analgesic consumption was observed in the cannabinoid group during the first eight hours, albeit without statistical significance. When pain was compared during the mobilization and the rest of the jaw, cannabinoid and placebo groups also showed no significant difference. Topical

application of cannabinoids in the masseter area significantly reduced pain compared to placebo, accompanied by a reduction in electromyographic activity and pain at rest.[45]

Likewise, few clinical trials have investigated cannabinoids for nociplastic conditions and primary chronic pain. A systematic review encompassing acute and chronic facial pain included five studies with a total of 288 participants. These studies showed heterogeneity in terms of cannabinoid formulations, administration routes, target populations, and diagnosis, ranging from nociplastic pain and cancer-related pain to neuropathic pain.[46]

Recommendations: Although cannabinoids show promise in managing headaches and orofacial pain conditions, the current evidence is insufficient to justify their routine use.

Cannabinoids in acute pain management

There are more studies investigating cannabinoids for chronic pain than for acute pain management, leading to limited published evidence supporting their use. Gazendam et al. conducted a systematic review and meta-analysis in 2020 which included six randomized, placebo-controlled clinical trials with 678 participants.[6] They found a statistically significant reduction in subjective pain scores in the cannabinoid groups compared to placebo groups for participants with acute postoperative pain, although the clinical significance was negligible. Intriguingly, pain reduction was observed only with the intramuscular route of administration, which is not widely available in many countries. However, the review had limitations, including variations in the overall quality and number of trials, as well as inconsistencies in reporting results. There was significant heterogeneity among the studies, including variations in cannabinoid type, dosage, duration, and administration route.[6]

In another meta-analysis published in 2020, evaluating cannabinoids for acute postoperative pain management across different types of surgeries, no significant difference was found in pain intensity or oral morphine consumption compared to control groups. Surprisingly, patients who received cannabinoids reported higher pain scores at 12 hours postoperatively, and they were also more likely to experience postoperative hypotension.[47] Similarly, a 2017 systematic review and meta-analysis revealed that placebo groups achieved better outcomes compared to cannabinoid groups in terms of efficacy and adverse event incidence for postoperative pain.[5]

Recommendations: The authors of the present review do not recommend cannabinoids for acute pain management.

Adverse effects, contraindications, and pharmacological interactions

The incorporation of cannabis-based products into clinical practice requires careful consideration by prescribing physicians, respecting individual clinical responses, adverse effects, and potential pharmacological interactions.[48] THC is responsible for most of the therapeutical and adverse effects of cannabis, including its psychostimulant properties, whereas CBD lacks psychostimulant effect.[48,49] Extreme caution is warranted when administering cannabis-based products to patients with specific genetic predispositions or psychiatric disorders such as psychosis, bipolar disorder, panic syndrome, anxiety, phobias, paranoia, abnormal liver or kidney function, amotivational syndrome of adolescence, and schizophrenia.[50]

Common adverse effects associated with THC include anxiety, panic syndrome, drowsiness, dry mouth, euphoria, hilarity, relaxation, and abnormal perception of distances. High doses may induce fear, agitation, psychotic manifestations, and impairments in attention and memory. Notably, even low doses can lead to adverse effects in individuals with increased sensitivity. Conversely, adverse effects associated with CBD are typically limited to changes in stool consistency, drowsiness, and hypotension.

Adverse effects are generally dose-dependent and can be mitigated by titrating doses accordingly.[51] Most contraindications to cannabinoids are dose-dependent and primarily related to THC (Table 5). Although data on pharmacological

Table 5 Group of individuals and clinical scenarios requiring caution when prescribing medicinal cannabis.

Individuals below 25 years of age (relative contraindication): evidence indicates that high daily doses of THC can affect cognitive development, which continues until this age. It is associated with diminished motivation and poor academic performance.[50]
Personal history of substance abuse: presence of adult substance use disorder.[50,52]
Patients with psychiatric disorders: THC is contraindicated due to the risk of triggering crises in cases of moderate to severe disorder or poorly controlled disorder.[49,51]
Uncontrolled heart disorder: THC has been observed to increase heart rate.[53] Additionally, patients who have used inhaled cannabis show a higher risk of perioperative acute myocardial infarction within the first 1 to 2 hours. When considering other routes of cannabinoid administration (non-inhalation), it is crucial to evaluate the risks and benefits before proceeding with elective surgery due to the temporal association of cannabis use and adverse cardiovascular effects.[54] A study examined the risk of visiting cardiovascular emergency services and hospital admission among 18,653 adult patients authorized to use medicinal cannabis in Ontario, Canada, from 2014 to 2017. Medicinal cannabis was associated with an increased risk of emergency room visits or hospital admission related to cardiovascular events, including stroke and acute coronary syndrome.[55]
Patients with uncontrolled respiratory disorders: inhaled use is contraindicated for these patients. It is important to note that inhalation, or even vaporization, is prohibited in Brazil and should never be recommended by a physician. However, there are vaporizers approved for medicinal use in other countries.[53]
Pregnancy and lactation: there are a lack of safety data supporting the use of medicinal cannabis in these scenarios. Reports have detailed instances of newborns born to mothers who chronically used smoked cannabis, resulting in lower-than-average birth weights. In animal studies, THC has been observed to pass through the placenta, resulting in fetal plasma levels of approximately 10% of maternal levels after acute exposure, with significantly higher concentrations noted after repetitive exposure.[56] Wide variations in cannabinoid concentrations in breast milk have been documented, persisting for an extended period and detectable up to six days after maternal consumption.[57]
Personal history of liver dysfunction: there may be an increase in liver enzymes with the use of CBD in patients who have a personal history of liver disorders. Therefore, it is crucial to identify patients with a history of liver disease and to conduct liver function tests before initiating CBD treatment, with subsequent testing every 3 months.[58]

interactions with medicinal cannabis are limited, it is metabolized by cytochrome CYP450 in the liver, which is also the metabolic pathway for several other drugs. CYP450-inducers like rifampicin reduce the maximum plasma concentration and area under the curve of THC and CBD, while inhibitors such as ketoconazole elevate the area under the curve relationship.[52] Therefore, caution is advised to avoid potential interactions.

In theory, THC may reduce serum concentrations of clozapine, haloperidol, duloxetine, olanzapine, cyclosporine, cyclobenzaprine, and theophylline, as they compete for the same metabolic pathway.[48,51,52] Conversely, CBD could increase serum concentrations of haloperidol, antipsychotics, tricyclic antidepressants, calcium channel blockers, atorvastatin and simvastatin, beta-blockers, antihistamines, antiretrovirals, opioids, clobazam, macrolides, sildenafil, cyclosporine, tamoxifen, and warfarin.[49,59,52] Most reported pharmacological interactions are associated with the concomitant use of CNS depressants, such as alcohol and benzodiazepines. Pimozide stands as an absolute contraindication for concurrent use with medicinal cannabis due to an increased risk of QT interval widening (Supplementary Material).[48,51,52,59,60]

Other potentially harmful pharmacological interactions occur with checkpoint inhibitor immunotherapy for cancer treatment. Tumoral cells express cannabinoid receptors that can act as suppressors of tumor growth and metastases, or conversely promote neoplastic growth and present metastatic potential. Currently, immunotherapy employing inhibitors of various targets is an essential treatment for some histological tumor types. Since cannabinoids possess immunosuppressive properties, they can hinder the response of immunotherapeutic drugs. Studies have shown a decrease in time to tumor progression, reduced survival, or both, in cancer patients treated with cannabinoids and checkpoint inhibitors.[61,55]

It is important to note that liver function tests are recommended for all patients with a history of previous or active liver disorder. These tests should include measurements of aspartate Aminotransferase (AST), alanine Aminotransferase (ALT), bilirubin, gamma-glutamyl transferase, alkaline phosphatase, lactic dehydrogenase, total proteins, and prothrombin time. Clinical monitoring should be conducted grounded on baseline test results, with tests repeated every three months. If any test results show changes, the cannabinoid treatment should be halted, and the underlying causes should be investigated.[48,51,52,62]

Additionally, it is worth emphasizing that the CYP2D6 enzyme metabolizes many antidepressants. Therefore, CBD can increase serum concentrations of selective neurotransmitter reuptake inhibitor antidepressants, tricyclic antidepressants, antipsychotics, beta-blockers, and opioids, including codeine and oxycodone.[63,64] Regular assessment of the patient and gradual dose adjustment are crucial. This approach allows for the monitoring of adverse effects and ensures the adherence to the pharmacovigilance plan. Treatment should be discontinued if there is no effectiveness, persistent adverse effects, or non-compliance with agreements previously established between the physician and the patient.[10,33,53]

In summary, monitoring liver function is clinically essential, especially in cases of pre-existing liver disorders. Moreover, the immunosuppressant effects of cannabinoids should be considered, particularly concerning cancer patients undergoing checkpoint inhibitor therapy, as they may negatively impact treatment outcomes.

Conclusions

The risk-benefit assessment of cannabinoid use will evolve over time, alongside the determination of appropriate doses and its impact on pain relief, functional recovery, and quality of life.[65] Cannabinoids can serve as allies in pain management when used judiciously. However, this task force does not recommend cannabinoids for the treatment of acute pain and cancer-related pain. In other clinical scenarios, currently recommended treatments should always be the first choice, especially in cases where published protocols exist, such as neuropathic pain. Only patients with inadequate clinical response or intolerance to recommended treatments should be considered as potential candidates for cannabinoids, which should be prescribed solely by specialists experienced in handling these substances.

Special attention should also be given to patient characteristics, particularly regarding the presence of pre-existing mental illnesses and the concurrent use of other drugs that may lead to potential drug interactions. Like other treatment modalities, cannabinoid therapy should be discontinued if it proves ineffective, if persistent adverse effects arise, or if the patient fails to comply with previously established agreements between physician and patient.

Conflicts of Interest

The authors declare no have conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844513.

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REVIEW ARTICLE

Unravelling the analgesic effects of perioperative magnesium in general abdominal surgery: a systematic review and meta-analysis of randomized controlled trials

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KEYWORDS
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Analgesia

Abstract

Background: Prior research has established the effectiveness of magnesium in relieving postoperative pain. This article aims to evaluate magnesium sulfate for perioperative analgesia in adults undergoing general abdominal surgery under general anesthesia.

Objective: The primary aim was to assess pain scores at 6 and 24 hours postoperatively in patients receiving magnesium sulfate vs. the control group. Secondary outcomes were postoperative opioid consumption, perioperative complications, and time to rescue analgesia.

Methods: A comprehensive database search identified studies comparing magnesium sulfate with control in adults undergoing general anesthesia for general abdominal surgery. Using random-effects models, data were presented as mean ± Standard Deviation (SD) or Odds Ratios (OR) with corresponding 95% Confidence Intervals (95% CI). A two-sided p-value < 0.05 was considered statistically significant.

Results: In total, 31 studies involving 1762 participants met the inclusion criteria. The magnesium group showed significantly lower postoperative pain scores at both early (within six hours) and late (up to 24 hours) time points compared to the control group. The early mean score was 3.1 ± 1.4 vs. 4.2 ± 2.3, and the late mean score was 2.3 ± 1.1 vs. 2.7 ± 1.5, resulting in an overall Mean Difference (MD) of −0.72; 95% CI −0.99, −0.44; $p < 0.00001$. The magnesium group was associated with lower rates of postoperative opioid consumption and shivering and had a longer time to first analgesia administration compared to the saline control group.

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Conclusion: Magnesium sulfate administration was linked to reduced postoperative pain and opioid consumption following general abdominal surgery.
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Introduction

Effective pain management is a critical objective in both anesthesia and perioperative care. Magnesium modulates pain by inhibiting the N-methyl-D-aspartate receptor, impeding calcium entry into the cell.[1,2] Previous clinical trials have affirmed the efficacy of magnesium sulfate in diminishing postoperative pain when juxtaposed with saline control.[1,3,4] While using magnesium sulfate has demonstrated a reduction in postoperative opioid requirements, the optimal dosing regimen remains uncertain.[3,4]

Prior reviews exploring magnesium as an analgesic adjunct encompassed a spectrum of surgeries characterized by diverse anticipated postoperative pain severities. This systematic review focuses on evaluating the effectiveness of magnesium sulfate for perioperative analgesia in adults undergoing General Anesthesia (GA) for general abdominal surgery and comparing it with an inert control. The primary objective is to assess postoperative pain scores in the group administered magnesium sulfate compared to the control. Secondary outcomes encompass postoperative opioid consumption, intraoperative complications, time to rescue analgesia, and postoperative side effects.

Methods

This systematic review and meta-analysis followed a predefined protocol, registered with PROSPERO (CRD42022326263), and adhered to PRISMA reporting Guidelines.[5]

Study selection

We included Randomized Controlled Trials (RCTs) involving Intravenous (IV) magnesium sulfate administration (bolus, infusion, or combination) for perioperative analgesia in adults undergoing general abdominal surgeries under General Anesthesia (GA). Exclusions comprised cohort studies, meta-analyses, systematic reviews, case reports, case series, abstracts, conference proceedings, studies not in English, investigations with non-IV magnesium administration, and those lacking a separate magnesium study arm. Postoperative pain scores (Numerical Rating Scale — NRS) were assessed at early (within 6 hours) and late (up to 24 hours) time points. Side effects and complications related to magnesium sulfate, were recorded in the Operating Room (OR) and/or Postanesthetic Care Unit (PACU). Cumulative postoperative opioid consumption was converted to Morphine Milligram Equivalents (MME) and measured at early and late time points.

Search strategy

A comprehensive search across PubMed, Medline, Embase, Web of Science, and Cochrane databases used the National Center for Biotechnology Information Medical Subject Headings (NCBI MeSH) descriptors [magnesium (mh) or magnesium (tw) or magnesium sulfate (mh) or magnesium sulfate (tw) or magnesium sulphate (tw)] and [perioperative period (mh) or perioperative (tw) or intraoperative (tw) or intraoperative period (mh) or postoperative (tw) or postoperative period (mh)].

Executed in January 2022, the detailed literature search strategy is in Supplementary Table S1. Two independent authors (YS and NK) scrutinized titles and abstracts, and full texts were assessed by two reviewers (YS and MN). References in the included studies were manually searched. Trials were evaluated for bias using the Cochrane risk of bias tool, graded as “high risk”, “low risk”, or “unclear risk” of bias.[6,7] GRADE methodology assessed evidence.[8]

Data extraction

A standardized protocol guided a data collection form for study characteristics, patient demographics, and intraoperative and postoperative data. Study characteristics were recorded, including the author’s name and publication year. Preoperative data, such as age, sex, and Body Mass Index (BMI), were documented. Intraoperative and postoperative data included the type of surgery, duration, doses, and methods of administration of magnesium sulfate and the control, intraoperative complications (such as hypotension and bradycardia), postoperative pain scores (Numerical Rating Scale — NRS), postoperative opioid consumption, time to rescue analgesia, and the incidence of postoperative adverse effects (hypotension, bradycardia, shivering, and Postoperative Nausea and Vomiting [PONV]). Two investigators (YS and YA) extracted data and compiled the results. Any discrepancies in data collection were solved by discussion and dialogue among the team members and by consulting the expert author (MN). Whenever data was missing, we made a concerted effort to contact the corresponding author via email. Our analysis exclusively incorporates studies for which we received a response regarding missing data. YS, NK, and YA ensured data accuracy and completeness.

Outcome definition

Primary outcome: postoperative pain scores (Numerical Rating Scale — NRS) in magnesium sulfate vs. control groups. Secondary outcomes: postoperative opioid consumption, time to rescue analgesia, intraoperative complications (hypotension, bradycardia), and postoperative side effects (hypotension, bradycardia, shivering, PONV).

Statistical analysis

Continuous data were presented as mean and standard deviation (SD) and compared as Mean Differences (MD) and 95% Confidence Interval (95% CI); dichotomous data were

presented as Odds Ratios (ORs) and 95% CI; $p < 0.05$ was considered significant. A random-effects model accommodated inter-study variation. Egger's test, Begg's test, fail-safe N-test, and funnel plot inspection assessed publication bias. Statistical heterogeneity used the I^2 statistic and Chi-Square test ($I^2 > 50\%$, and $p < 0.05$ indicated significant heterogeneity).[9] Sensitivity and influence analysis was conducted to explore and address heterogeneity by excluding outliers and recalculating pooled estimates. Subgroup and meta-regression analysis was performed to adjust for patient baseline and clinical characteristics to confirm the outcome of the pooled estimate. Review Manager Software (RevMan, V.5.4.1) and comprehensive metanalysis software version 3.0 were used to conduct the analysis.

Results

Our initial search identified 2320 studies, which underwent screening by titles and abstracts, resulting in 248 studies for

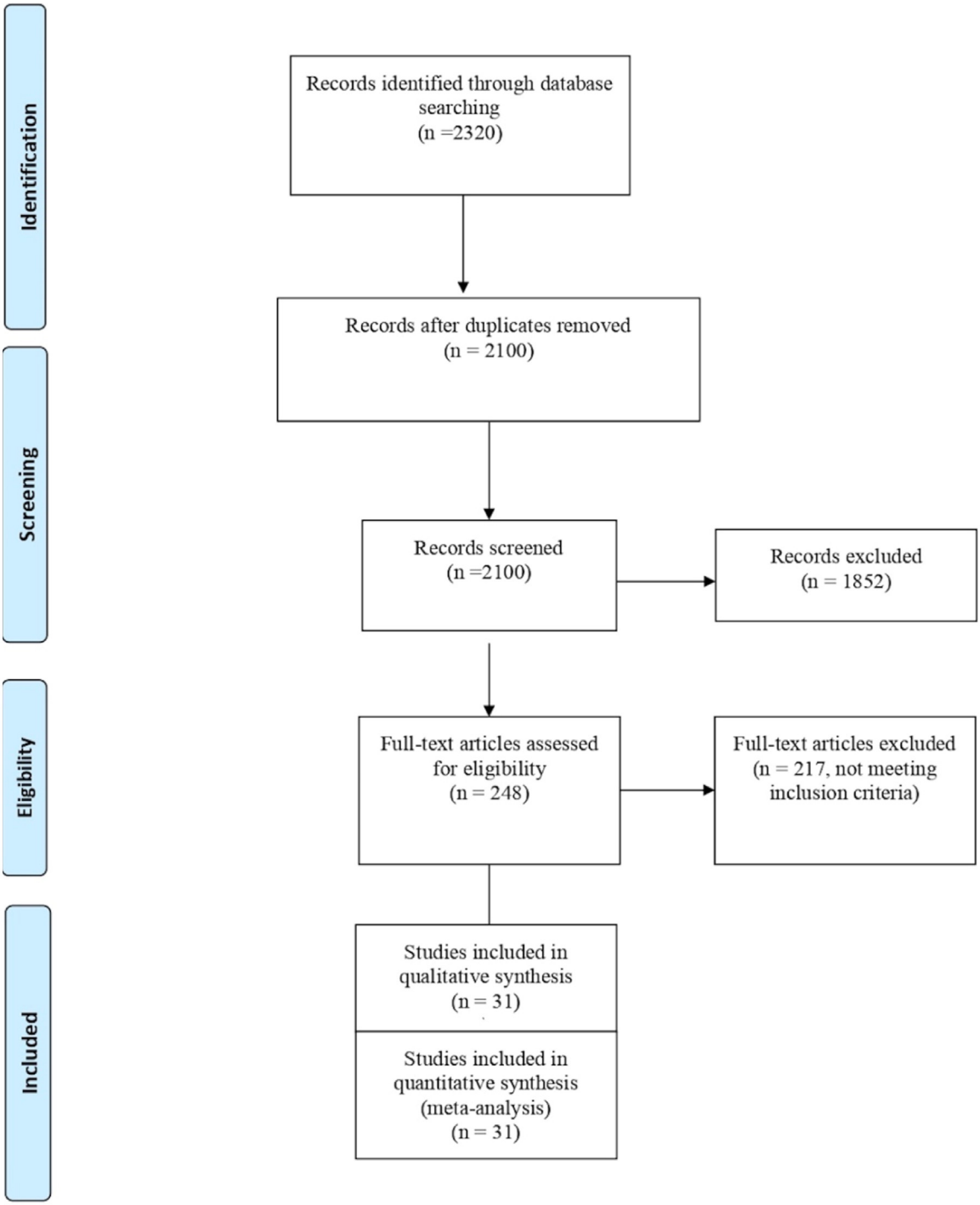


Figure 1 PRISMA flow diagram (n, number).

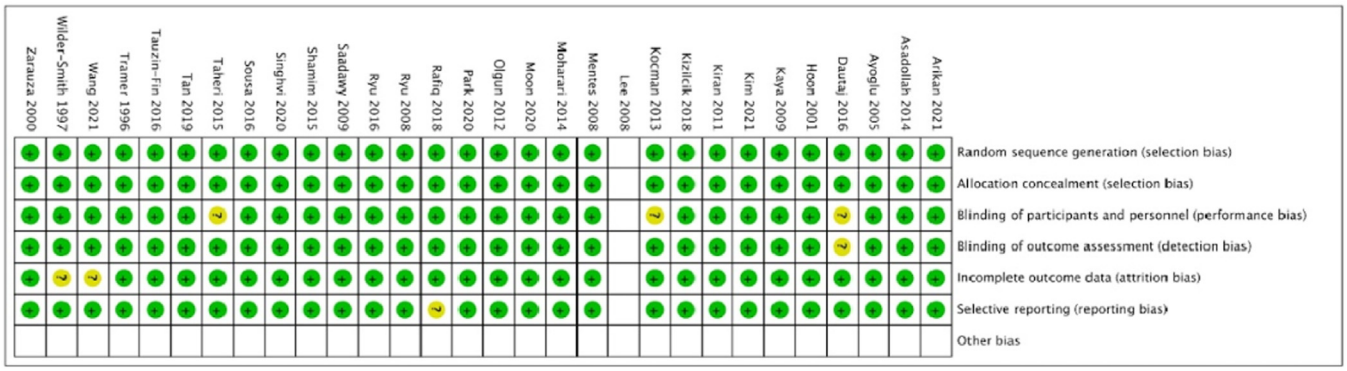


Figure 2 Cochrane risk of bias assessment. Green, Low risk; Yellow, Unclear risk; Red, High risk.

full-text eligibility review. Ultimately, 31 studies with 1762 participants (800 patients in the $MgSO_4$ group and 802 patients in the control group) met the inclusion criteria and were included in the analysis (Figure 1).[10-40] Participants in the included trials underwent various general abdominal surgeries under General Anesthesia (GA) and received either magnesium sulfate or a control perioperatively. Supplementary Table S2 summarizes the data on the baseline patient characteristics. The quality of the studies was assessed using the Cochrane risk of bias tool, revealing some risks of bias in at least one domain for all studies (Figure 2). The GRADE evidence is summarized in Table 1.

The baseline characteristics were similar between the magnesium and control groups across all individual trials, with no notable variances in patient age (800 vs. 802 patients, 49.4 ± 12.2 vs. 49.4 ± 12.9 years, $p = 0.93$), BMI (215 vs. 218 patients, 28.9 ± 9.3 vs. 28.8 ± 11.4 $kg.m^{-2}$, $p = 0.57$), or surgery duration (697 vs. 696 patients, 111 ± 71.8 vs. 114 ± 70.7 minutes, $p = 0.36$). Fifty-four percent of patients underwent open surgical procedures, while 46% underwent laparoscopic surgeries. The mean magnesium sulfate administered in the studies analyzed in our meta-analysis was 41.1 ± 14.6 $mg.kg^{-1}$ (ranging from 3 to 50 $mg.kg^{-1}$). Sixty-six percent of these studies continued with continuous magnesium infusion following the initial loading dose. The Systematic Review (SR) of the included studies is summarized in Supplementary Table S3.

Early postoperative pain score

Twenty-seven trials, consisting of 1525 patients, contributed to the analysis of early (up to 6 hours) postoperative pain scores, indicating a significantly lower mean score in the magnesium group (n = 762, 3.1 ± 2.5) compared to the control group (n = 763, 4.1 ± 2.8) (MD = -1.04; 95% CI: -1.52, -0.55; $p < 0.0001$; $I^2 = 94\%$) (Figure 3 A).[10-12,14-17,19-31,33,34,36-40] Publication bias was investigated using a funnel plot (Figure 4), Begg's test ($p = 0.774$), Egger's test ($p = 0.646$), and fail-safe N-test (1991) for each parameter, which was not significant (Figure 4). The funnel plot identified six studies as the major outliers contributing to the heterogeneity. When these studies were excluded and the pooled estimate recalculated, the MD decreased from -1.02 to -0.56, 95%CI narrowed (-0.81, -0.30), and heterogeneity decreased from 95% to 77% without impacting the final inference of our result ($p < 0.0001$).

Late postoperative pain score

Twenty-three trials, consisting of 1297 patients, were included in the analysis of late (up to 24 hours) postoperative pain scores, revealing a significantly lower mean score in the magnesium group (n = 657, 2.3 ± 2.0) compared to the control group (n = 640, 2.9 ± 2.4) (MD = -0.41; 95% CI: -0.67, -0.14; $p = 0.006$; $I^2 = 87\%$) (Figure 3 B).[10-12,14-16,19,20,22,24-27,29-31,33,34,36-40] No significant publication bias was observed (Figure 4). The funnel plot identified six studies as the major outliers contributing to the heterogeneity. When these studies were excluded and the pooled estimate recalculated, the MD decreased from -0.42 to -0.41, the 95% CI narrowed (-0.53, -0.29), and heterogeneity decreased from 87% to 11% without impacting the final inference of our result ($p < 0.00001$). The overall postoperative pain score data indicated MD = -0.72; 95% CI: -0.99, -0.44; $p < 0.00001$; $I^2 = 93\%$. Influence analysis confirmed the robustness of the results.

Early cumulative postoperative opioid consumption

Seventeen trials, consisting of 916 patients, contributed to the analysis of early (up to 6 hours) postoperative opioid consumption, demonstrating a significantly lower mean measurement in the magnesium group (n = 459, 9.7 ± 7.7 MME) compared to the control group (n = 457, 12.4 ± 8.4 MME) (MD = -2.75; 95% CI: -4.20, -1.29; $p = 0.0002$; $I^2 = 99\%$) (Figure 5).[10-12,15,17-22,25,26,28,30,32,34,38]

Late cumulative postoperative opioid consumption

Twenty-one trials, consisting of 991 patients, were included in the analysis of late (up to 24 hours) postoperative opioid consumption, indicating a significantly lower mean score in the magnesium group (n = 496, 19.4 ± 12.4 MME) compared to the control group (n = 496, 27.0 ± 16.2 MME) (MD = -8.46; 95% CI: -15.06, -1.87; $p = 0.01$; $I^2 = 100\%$) (Figure 5).[10-14,18-20,22,24-27,30-32,35-39] The overall postoperative opioid consumption data revealed MD = -5.81; 95% CI: -9.09, -2.52; $p = 0.0005$; $I^2 = 100\%$.

Time to rescue analgesia

Five trials with 268 patients contributed to the analysis of time to rescue analgesia, indicating significantly longer time

Table 1 GRADE Evidence.

			Quality assessment						
Outcome	n/ Design/ Sample size	Summary Estimate	Risk of Bias	Magnitude of effect	Inconsistency	Indirectness	Imprecision	Publication Bias?	Quality of Evidence?
Postoperative pain scores									
Early	27/RCT/1525	MD = -1.04 95% CI: -1.04, -0.55	Low	High	No	No	Yes	No	⊕⊕◯◯ Low
Late	23/RCT/1250	MD = -0.41 95% CI: -0.67, -0.14	Low	High	No	No	Yes	No	⊕⊕◯◯ Low
Postoperative opioid consumption									
Early	17/RCT/916	MD = -2.75 95% CI: -4.20, -1.29	Low	High	No	Yes	No	No	⊕◯◯◯ Very Low
Late	21/RCT/1907	MD = -8.46 95% CI: -15.06, -1.87	Low	Moderate	No	Yes	No	No	⊕◯◯◯ Very Low
Time to rescue analgesia	5/RCT/268	MD = 21.45 95% CI 6.62, 36.28	Serious	Moderate	No	No	No	No	⊕⊕⊕◯ Moderate
Intraoperative complications	7/RCT/820	OR = 1.27; [0.78, 2.08]	Low	Moderate	No	No	No	No	⊕⊕◯◯ Low
Postoperative shivering	5/RCT/264	OR = 0.19 95% CI: 0.09 — 0.44	Serious	High	Serious	No	No	Yes	⊕⊕◯◯ Low

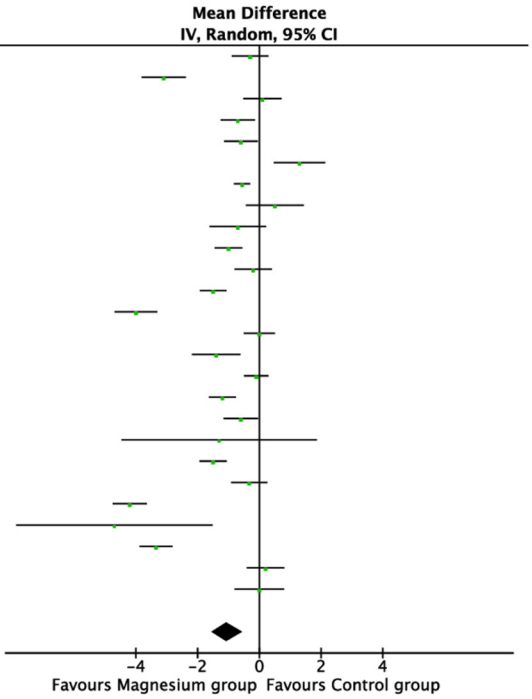
RCT, Randomized Controlled Trial; MD, Mean Difference; CI, Confidence Interval; OR, Odds Ratio.

A. Pain Score at 6h

Study or Subgroup	Magnesium Group Mean	SD	Total	Control Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Arikan, 2016	4.1	1.7	40	4.4	0.9	40	4.1%	−0.30 [−0.90, 0.30]
Asadollah, 2015	4	1	15	7.1	1	15	3.9%	−3.10 [−3.82, −2.38]
Ayoglu, 2005	2.1	1	20	2	1	20	4.0%	0.10 [−0.52, 0.72]
Bhatia, 2004	3.5	1	25	4.2	1	25	4.1%	−0.70 [−1.25, −0.15]
Dautaj, 2016	3.4	1	26	4	1	26	4.1%	−0.60 [−1.14, −0.06]
Kim, 2021	4.2	1.8	26	2.9	1.2	26	3.8%	1.30 [0.47, 2.13]
Kiran, 2011	1.32	0.84	50	1.88	0.44	50	4.3%	−0.56 [−0.82, −0.30]
Kocman, 2013	2.4	1.3	20	1.9	1.7	20	3.7%	0.50 [−0.44, 1.44]
Lee, 2008	6.3	2.3	35	7	1.54	35	3.7%	−0.70 [−1.62, 0.22]
Lu, 2021	2	1	37	3	1	40	4.2%	−1.00 [−1.45, −0.55]
Mavrommati, 2004	1.2	1	21	1.4	1	21	4.0%	−0.20 [−0.80, 0.40]
Mentes, 2008	3.4	1	41	4.9	1	42	4.2%	−1.50 [−1.93, −1.07]
Moharari, 2014	5	1	16	9	1	16	4.0%	−4.00 [−4.69, −3.31]
Moon, 2020	3	1	31	3	1	30	4.1%	0.00 [−0.50, 0.50]
Olgun, 2012	1.8	1.1	30	3.2	1.9	30	3.9%	−1.40 [−2.19, −0.61]
Park, 2020	1.2	1	60	1.3	1.2	60	4.2%	−0.10 [−0.50, 0.30]
Rafiq, 2018	2.9	1	40	4.1	1	40	4.2%	−1.20 [−1.64, −0.76]
Ryu, 2008	2.4	1	25	3	1	25	4.1%	−0.60 [−1.15, −0.05]
Ryu, 2016	5	7.7	37	6.3	6.1	37	1.5%	−1.30 [−4.47, 1.87]
Saadawy, 2009	3.8	1	40	5.3	1	40	4.2%	−1.50 [−1.94, −1.06]
Shamim, 2015	3.9	1.185	30	4.23	1.135	30	4.1%	−0.33 [−0.92, 0.26]
Singhvi, 2020	2.6	1	25	6.8	1	25	4.1%	−4.20 [−4.75, −3.65]
Sousa, 2016	1.6	3.2	18	6.3	6.1	18	1.5%	−4.70 [−7.88, −1.52]
Taheri, 2015	6.45	1.05	20	9.8	0.62	20	4.1%	−3.35 [−3.88, −2.82]
Tramer, 1996	3.7	1	21	3.5	1	21	4.0%	0.20 [−0.40, 0.80]
Wilder−Smith, 1997	1	1	13	1	1	11	3.9%	0.00 [−0.80, 0.80]
Total (95% CI)			**762**			**763**	**100.0%**	**−1.04 [−1.52, −0.55]**

Heterogeneity: $Tau^2 = 1.40$; $Chi^2 = 465.24$, df = 25 ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 4.21$ ($P < 0.0001$)

Magnesium vs. Control: 3.1 ± 1.4 vs. 4.2 ± 2.3
Predictive Interval: -3.534 to 1.459



B. Pain Score at 24h

Study or Subgroup	Magnesium Group Mean	SD	Total	Control Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Arikan, 2016	2.8	0.3	40	3.1	1	40	4.9%	−0.30 [−0.62, 0.02]
Asadollah, 2015	2.3	1	15	3.1	1	15	3.8%	−0.80 [−1.52, −0.08]
Ayoglu, 2005	1.1	1	20	0.3	1	20	4.1%	0.80 [0.18, 1.42]
Bhatia, 2004	3.6	1	25	3.2	1	25	4.3%	0.40 [−0.15, 0.95]
Dautaj, 2016	2.44	1	26	3.78	1	26	4.3%	−1.34 [−1.88, −0.80]
Kim, 2021	1.6	0.7	26	1.8	0.8	26	4.7%	−0.20 [−0.61, 0.21]
Kiran, 2011	0.78	0.68	50	1.3	0.46	50	5.1%	−0.52 [−0.75, −0.29]
Kocman, 2013	1.4	1.4	20	1.3	1.6	25	3.4%	0.10 [−0.78, 0.98]
Lee, 2008	2.6	0.7	35	3.3	0.7	35	4.9%	−0.70 [−1.03, −0.37]
Lu, 2021	2	1	37	2.6	0.76	40	4.7%	−0.60 [−1.00, −0.20]
Mentes, 2008	4.1	1	41	4.2	1	42	4.6%	−0.10 [−0.53, 0.33]
Moharari, 2014	1	1	16	1	1	16	3.9%	0.00 [−0.69, 0.69]
Moon, 2020	3	1	31	3	1	30	4.4%	0.00 [−0.50, 0.50]
Olgun, 2012	1	0.1	30	1.4	1	30	4.8%	−0.40 [−0.76, −0.04]
Ryu, 2008	1.1	1	25	1.5	1	25	4.3%	−0.40 [−0.95, 0.15]
Ryu, 2016	4	6.1	37	5.3	6.9	37	0.7%	−1.30 [−4.27, 1.67]
Saadawy, 2009	2.8	1	40	3.4	1	40	4.6%	−0.60 [−1.04, −0.16]
Singhvi, 2020	3.1	1	25	5.9	1	25	4.3%	−2.80 [−3.35, −2.25]
Sousa, 2016	1	1	18	1	1.6	18	3.4%	0.00 [−0.87, 0.87]
Taheri, 2015	4.6	0.94	20	5.9	0.45	20	4.6%	−1.30 [−1.76, −0.84]
Tramer, 1996	2.5	1	21	3	1	21	4.1%	−0.50 [−1.10, 0.10]
Wilder−Smith, 1997	1	1	13	1	1	11	3.6%	0.00 [−0.80, 0.80]
Zarauza, 2000	3	1	23	3.5	1	24	4.2%	−0.50 [−1.07, 0.07]
Zarauza, 2000	2	1	23	1	1	24	4.2%	1.00 [0.43, 1.57]
Total (95% CI)			**657**			**665**	**100.0%**	**−0.41 [−0.67, −0.14]**

Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 160.20$, df = 23 ($P < 0.00001$); $I^2 = 86\%$
Test for overall effect: $Z = 2.99$ ($P = 0.003$)

Magnesium vs. Control: 2.3 ± 1.1 vs. 2.7 ± 1.5
Predictive interval: -1.661 to 0.850

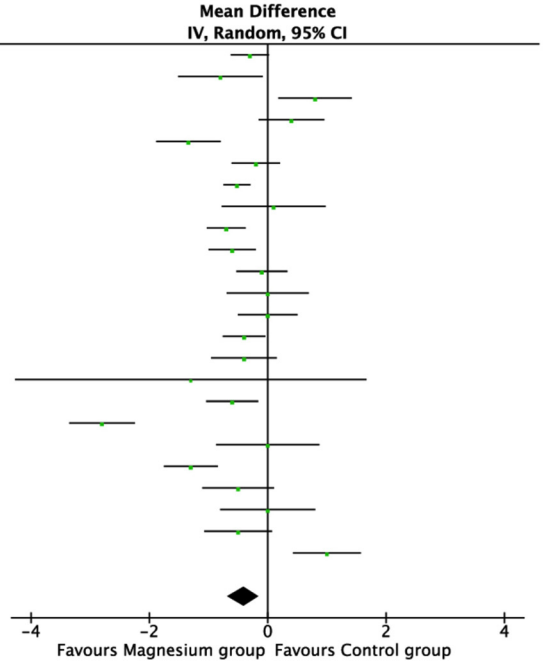


Figure 3 Meta-analysis of early (6 h) and late (24 h) postoperative pain in magnesium and control group patients undergoing surgery. The mean difference of each included study is plotted. Using the random effects model, a pooled estimate of overall mean difference (diamonds) and 95% Confidence Intervals (width of diamonds) summarizes the effect size. CI, Confidence Interval; IV, Inverse Variance.

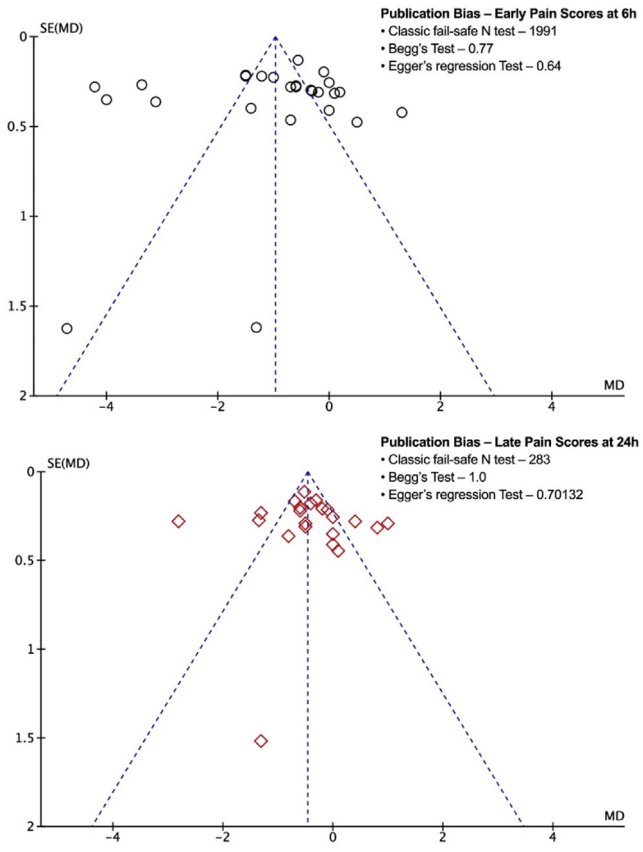


Figure 4 Funnel Plot for the association of early (6 h) and late (24 h) postoperative pain in patients belonging to the magnesium versus the control group. No evidence for substantial publication bias was found in Begg's or Egger's tests. According to classic fail-safe N, missing studies were required to bring the p-value to more than alpha, suggesting the absence of publication bias. SE(MD), Standard Error of Mean Difference.

in the magnesium group (n = 130, 196.0 ± 315.1 min) compared to the control group (n = 138, 121.0 ± 252.3 min) (MD = 21.45; 95% CI: 6.62, 36.28; p = 0.005; I^2 = 96%) (Supplementary Fig. 1).[13,15,17,21,30]

Intraoperative complications

For intraoperative hypotension (n = 375 patients) and bradycardia (n = 445 patients), six[12,18,20,28,29,33] and seven trials,[12,18,20,24,29,33,34] respectively, were included in the meta-analysis, which showed no significant differences between the magnesium and control groups (OR = 1.52; 95% CI: 0.79–2.92; p = 0.90; I^2 = 0% and OR = 0.91; 95% CI: 0.38–2.17; p = 0.82; I^2 = 48%, respectively) (Supplementary Fig. 2).

Postoperative side effects: hypotension, bradycardia, PONV, shivering

Ten (n = 629 patients),[10,14,16,18,23,28,30,33,35,40] seven (n = 427 patients),[10,16,18,30,33,35,40] twenty (n = 1134 patients),[10-16,19,20,22,23,25,27,29-31,35,37,38,40] and five trials (n = 264 patients)[12,22,30,34,37] respectively were included in the analysis of postoperative hypotension, bradycardia, PONV, and shivering, indicating no significant differences between the magnesium and control groups (OR = 0.90; 95% CI: 0.47–1.72; p = 0.75; I^2 = 0%; OR = 0.91; 95% CI: 0.38–2.17; p = 0.82; I^2 = 48%; OR = 0.78; 95% CI: 0.59–1.09; p = 0.08; I^2 = 56%, and OR = 0.19; 95% CI: 0.09–0.44; p < 0.0001; I^2 = 0%, respectively) (Supplementary Fig. 3).

Sensitivity, subgroup and meta-regression analysis

We performed subgroup analysis regarding surgical type (laparotomy vs. laparoscopy: 14 studies vs. 12 studies: MD [95% CI]: -1.20 [-1.34, -1.06] vs. -0.63 [-0.79, -0.46]) and magnesium continuous infusion (yes vs. no: 17 studies vs. 9 studies: -0.85 [-1.43, -0.27] vs. -1.34 [-2.19, -0.48]). No significant differences were observed between these subgroups. In addressing baseline patient and clinical characteristic variations, we conducted a meta-regression analysis, considering factors such as age, gender, BMI, surgical duration, postoperative opioid use, and magnesium dosage as continuous variables. Moreover, we categorized surgical type (laparotomy versus laparoscopy) and magnesium continuous infusion (yes vs. no) to assess their impact on outcomes. Although these variables slightly affected the mean difference, they did not substantially influence the overall estimation of pain scores at 6 and 24 hours (refer to Supplementary Table S3). Additionally, we evaluated the stability of aggregated pain scores through influence analyses by systematically excluding each study from the dataset and recalculating aggregated pain scores based on the remaining studies (see Supplementary Fig. 4A and 4B).

Discussion

Effective postoperative pain management is crucial as it correlates with adverse clinical outcomes and patient dissatisfaction, potentially leading to chronic pain.[41] Our findings underscore the beneficial impact of perioperative magnesium sulfate on postoperative pain outcomes, encompassing pain scores, opioid consumption, and adverse effects such as postoperative shivering in adults undergoing General Anesthesia (GA) for general abdominal surgery. Notably, the time to the first analgesic administration was prolonged in the magnesium group compared to the saline control. Importantly, no significant disparities were observed between the two groups concerning intraoperative complications and postoperative side effects, including hypotension, bradycardia, shivering, and Postoperative Nausea and Vomiting (PONV).

This study is distinctive as it represents the first systematic review and meta-analysis consolidating evidence from randomized control trials that specifically focus on the analgesic effects of magnesium sulfate for abdominal surgery. Previous systematic reviews have explored the relationship between magnesium and postoperative analgesia across various surgical disciplines, including orthopedic and cardiac surgery, alongside abdominal surgeries.[1,3,42-44] An earlier systematic review and meta-analysis on perioperative intravenous magnesium sulfate administration for postoperative pain also demonstrated a reduction in postoperative opioid

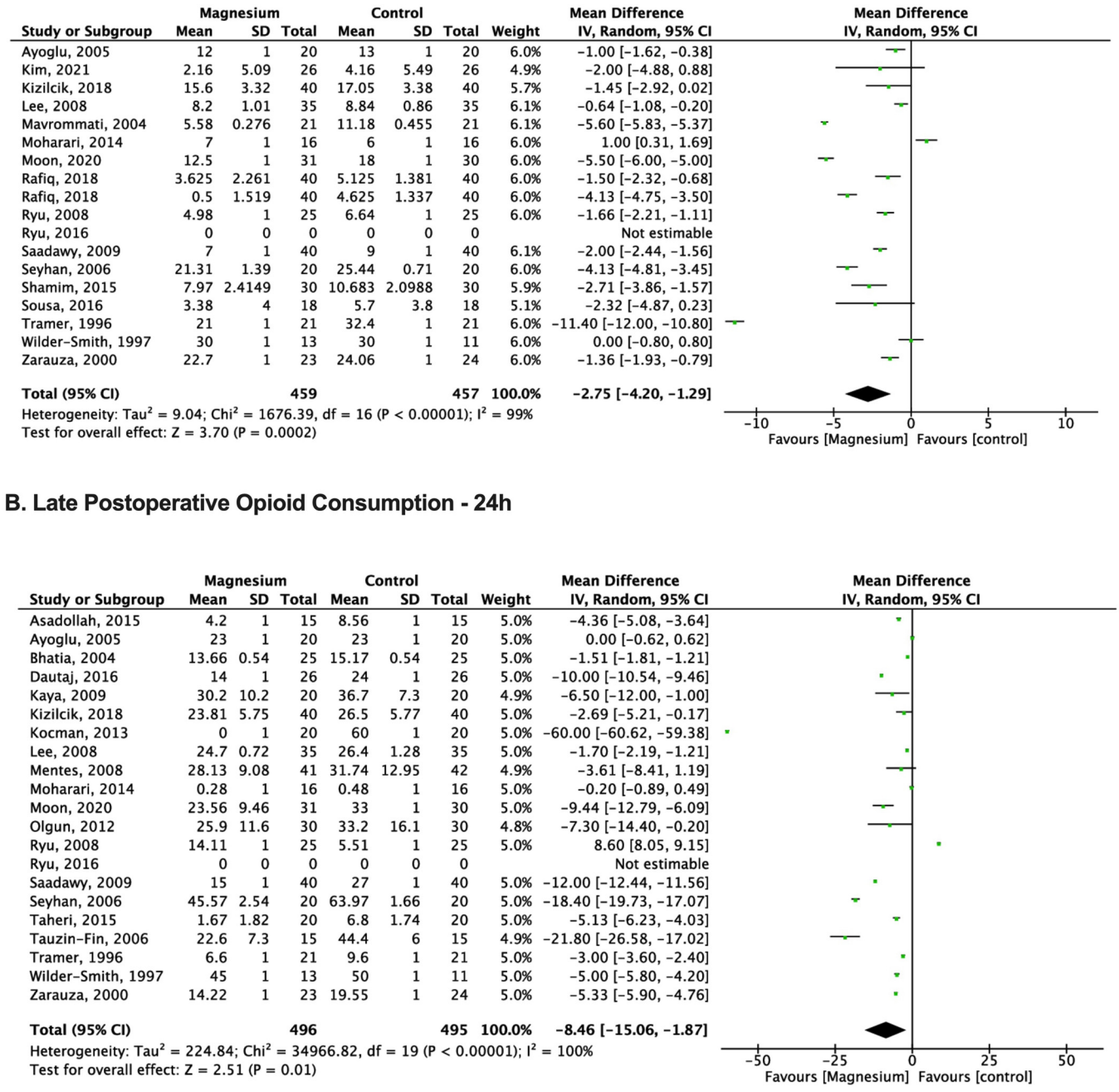


Figure 5 Meta-analysis of early (6 h) and late (24 h) postoperative opioid consumption in magnesium and control group patients undergoing surgery. The mean difference of each included study is plotted. Using the random effects model, a pooled estimate of overall mean difference (diamonds) and 95% Confidence Intervals (width of diamonds) summarizes the effect size. CI, Confidence Interval; IV, Inverse Variance.

consumption compared to control groups, indicating lower postoperative pain. Interestingly, the mode of delivery (bolus, bolus administration, or infusion) did not significantly impact outcomes, and the total magnesium dose administered did not correlate with 24 hour postoperative morphine requirements. Notably, a single bolus administration between 40 and 50 $mg.kg^{-1}$ reduced postoperative morphine consumption.[3] This aligns with a randomized controlled trial, which suggested that a higher intravenous magnesium dose (50 $mg.kg^{-1}$ bolus + 30 $mg.kg^{-1}.h^{-1}$ infusion compared to 30 $mg.kg^{-1}$ + 15 $mg.kg^{-1}.h^{-1}$) not only decreased postoperative pain scores but also effectively mitigated pneumoperitoneum-related hemodynamic instability during gastrointestinal laparoscopy.[45] However, high-dose magnesium administration has been acknowledged to lead to more frequent bradycardia and hypotension likely.[3]

Most trials in our review employed a 40–50 mg.kg^{-1} bolus dose of magnesium.[13,14,16-27,30,33,34,37-40] Interestingly, two trials in our review utilized much lower magnesium doses, with Kocman et al. prescribing one group at 5 mg.kg^{-1} and another at 7.5 mg.kg^{-1} for laparoscopic cholecystectomy, and Dautaj et al. prescribing 3 mg.kg^{-1} for open cholecystectomy.[31,36] Even at lower doses, both trials found that the magnesium groups exhibited significantly better postoperative pain control with no difference in side effects compared to the control group.[31,36] Kocman et al. noted that a magnesium dose of 7.5 mg.kg^{-1} was more effective in preventing postoperative pain than the control and magnesium sulfate dose of 5 mg.kg^{-1}.[31] A meta-analysis by De Oliveira et al. also demonstrated that systemic magnesium reduced postoperative pain and opioid consumption after various surgical procedures under GA, with a reduction in postoperative shivering also noted.[42] Another systematic review by Guo et al. in 2015 confirmed that magnesium administration during GA decreased analgesic consumption and postoperative pain scores without increasing adverse events.[44] It is worth noting that Lysakowski et al. in 2007 did not agree with the effectiveness of perioperative magnesium on postoperative pain intensity and analgesic requirements.[1] De Oliveira et al. suggested that this discrepancy could be attributed to the fewer subjects in their observed studies, the inclusion of pediatric populations, and the allowance of various regional anesthesia methods. In contrast, our study was limited to adults and only included those undergoing GA to reduce clinical heterogeneity.[42]

Kawakami et al. conducted a systematic review on magnesium and postoperative shivering, including 64 trials and 4303 patients. They also demonstrated that intravenous magnesium prevented postoperative shivering without resulting in increased adverse events.[46] The biological mechanism underlying this effect remains uncertain. Shivering can persist despite efforts to avoid hypothermia and may occur even in normothermic conditions. The resulting increase in oxygen demand, leading to heightened carbon dioxide production, may induce myocardial ischemia.[46] As magnesium exerts a calcium inhibitory effect, causing central arteriolar vasodilation and inducing the production of vasodilator prostaglandins, it possesses anticonvulsant properties and may slightly lower the shivering threshold in patients.[47,48]

Magnesium sulfate could be an effective adjunct for perioperative analgesia in adults undergoing GA for abdominal surgery. However, our results are constrained by the available evidence in published studies and may have happened by chance. We sought to minimize heterogeneity by restricting our inclusion criteria to general abdominal surgery procedures performed under GA. Despite these constraints, there might still be variability in expected pain severities and pain scores across the studies, even within general surgical procedures such as laparotomy versus laparoscopy. Heterogeneity could stem from differences in baseline chronic pain and opioid tolerance within the patient population, variations in specific surgical procedures, and diverse study designs across the included trials. The varied dosing and administration protocols for magnesium sulfate across studies limit the ability to draw definitive conclusions about the optimal regimen for analgesia in abdominal surgery. Future studies exploring the pharmacokinetics and pharmacodynamics of magnesium in more controlled temperature conditions to measure the impact on postoperative analgesia and shivering may offer valuable insights into its mechanism of action, aiding in identifying optimal dosing strategies for clinicians.

Conclusion

The findings of the present comprehensive analysis support magnesium sulphate's efficacy in providing perioperative analgesia for adults undergoing general abdominal surgery under general anesthesia. The observed reductions in postoperative pain scores, decreased opioid consumption, lower incidence of shivering, and prolonged time to rescue analgesia administration in the magnesium group highlight its potential as a valuable adjunct in pain management strategies. The results suggest incorporating magnesium sulfate into perioperative protocols may improve patient comfort and outcomes following surgery. Further research, including large-scale clinical trials, may be warranted to confirm these findings and elucidate the optimal dosing regimens and administration protocols for maximizing the analgesic benefits of magnesium sulfate in this context.

Declaration of competing interest

The authors declare no conflicts of interest.

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None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844524.

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SHORT COMMUNICATION

Determination of ED_{50} and ED_{95} of remimazolam besylate combined with alfentanil for adult gastroscopy: a prospective dose-finding study

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KEYWORDS
Alfentanil;
Dose;
Gastroscopy;
Remimazolam besylate;
Sequential method

Abstract
Background: To explore the median effective dose (ED50) and 95% effective dose (ED95) of remimazolam besylate combined with alfentanil for adult gastroscopy.
Methods: This prospective studyenrolled 31 patients scheduled to painless gastroscopy at Anhui No. 2 Provincial People's Hospital between April and May, 2022. 5 μg.kg^{-1} of alfentanil hydrochloride was used for pre-analgesia. The initial single loading dose of remimazolam besylate was 0.12 mg.kg^{-1}, increased or reduced by 0.01 mg.kg^{-1} for the next patient with modified Dixon sequential method. The modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) was used to assess sedation.
Results: Combined with alfentanil, the ED50 of remimazolam besylate was 0.147 mg.kg^{-1} (95% CI: 0.138-0.160 mg.kg^{-1}) and ED95 0.171 mg.kg^{-1} (95% CI: 0.159-0.245 mg.kg^{-1}). The induction time after injection of remimazolam besylate was 70 $\pm$ 25 s, with the anesthesia recovery time and the observation time in resuscitation room 5.13 $\pm$ 2.13 min and 2.32 $\pm$ 1.6 min, respectively. Twenty nine patients' vital signs were within acceptable limits during gastroscopy.
Conclusions: The ED50 of remimazolam besylate combined with alfentanil for painless gastroscopy was 0.147 mg.kg^{-1}, and the ED95 was 0.171 mg.kg^{-1}.
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Introduction

An increasing number of patients currently undergo gastroscopy under anesthesia, providing conditions for a thorough examination. It has been reported that painless gastroscopy has a much lower incidence of intraoperative and postoperative adverse reactions like nausea and vomiting, minimizing the risk of physical injury during examination.

Remimazolam besylate is a new type of water-soluble ultra-short-acting benzodiazepine for sedation and anesthesia.[1] Previous studies have suggested that it can safely and quickly induce sleep in patients undergoing painless colonoscopy and shorten anesthesia induction time. It also avoids

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adverse events like low Saturation of Peripheral Oxygen (SpO_2) and injection pain.[2] Due to its late application, phase III clinical studies were conducted mainly in painless colonoscopy, with a recommended loading dose of 7.5 mg and an additional dose of 2.5 mg.[1] However, this did not achieve effective sedation in painless gastroscopy, with a majority of patients exhibiting failure of sedation, significant body movement, and choking and coughing when the endoscope was inserted.[3,4] Alfentanil is a short-acting opioid widely used for intraoperative analgesia, including endoscopy.[5] The effective dose of remimazolam besylate combined with alfentanil in painless gastroscopy remains unknown.

Herein, we aimed to explore the ED_{50} and ED_{95} of the initial loading of remimazolam besylate combined with alfentanil for adult painless gastroscopy.

Methods

Study design and participants

This study was designed with up-and-down sequential allocation, enrolling patients scheduled to undergo painless gastroscopy at Anhui n° 2 Provincial People's Hospital between April and May 2022. The study was approved by the Ethics Committee of Anhui n° 2 Provincial People's Hospital and registered in the Chinese Clinical Trial Registry (ChiCTR2200060354). All patients voluntarily signed the informed consent.

Interventions

Patients were fasted for 6—8 hours and abstained from water for 2—4 hours before anesthesia. All drugs were avoided. Heart Rate (HR), Systolic Bblood Pressure (SBP), Mean Arterial Pressure (MAP) and SPO_2 were routinely monitored. In the left decubitus position, patients received a slow intravenous injection of alfentanil hydrochloride of 5 $\mu g.kg^{-1}$ (Yichang Humanwell Pharmaceutical Co., Ltd., 50 $\mu g.mL^{-1}$ in saline) for analgesic pretreatment. About one minute later, remimazolam besylate (Yichang Humanwell Pharmaceutical Co., Ltd., 25 mg by $C_{21}H_{19}BrN_4O_2$) was single-injected. As reported, the initial loading dose of remimazolam besylate was set at 0.12 $mg.kg^{-1}$, which was increased or reduced by 0.01 $mg.kg^{-1}$ for the next patient with the modified Dixon sequential method. The initial loading dose would be increased in the next patient as positive reactions were observed in the patient during endoscopy; otherwise, the initial loading dose would be reduced. In the event of a suspicious effect of sedation such as obvious swallowing, the next patient would receive a similar dosage. The formal study started when the dose reduction was altered to increase or vice versa, and the previous case of this patient was considered the first. The experiments were performed sequentially and terminated after seven negative-positive response crossovers (Supplementary Table 1).

Each patient was scored with MOAA/S (Supplementary Table 2)[6] at 30 s (t1), 1 min (t2), and 2 min (t3) after the injection of an initial loading dose of remimazolam besylate. Patients with a score higher than 2 after 2 minutes would be deemed to have sedation failure and receive remimazolam besylate of 2.5 mg until successful placement of the gastroscope. Otherwise, patients would be considered as effective sedation. Besides, patients without such deep sedation at any time during the gastroscopy would receive additional remimazolam besylate of 2.5 mg until the gastroscopy was completed, which would be no more than five times within 15 minutes, with a maximum bolus of 19.5 mg. Timely measures would be taken for the treatment of any adverse events during the study.

Data collection

The initial loading dose of remimazolam besylate, use of the first remedial sedation, MOAA/S scores at t1, t2, and t3, the induction time of sedation, the anesthesia recovery time, the observation time in the resuscitation room, and the adverse reactions were recorded. MAP, HR, and SPO_2 after entering the operating room (T0), endoscope placement (T1), end of gastroscopy (T2) and when patients left the resuscitation room (T3) were also collected.

Statistics analysis

SPSS 26.0 statistical software (IBM, Armonk, NY, USA) was used. The Probit regression model was used to calculate ED_{50}/ED_{95} and 95% Confidence Interval (95% CI). Data presentation and statistical tests were performed as reported. A two-sided $p < 0.05$ was considered as statistically significant.

Results

A total of 31 patients were eventually included including 13 (41.9%) males and 18 (58.1%) females. Age and body mass index of all participants were 43.7 ± 12.2 years old and 23.4 ± 3.3 $kg.m^{-2}$, respectively. Eight (25.8%), 15 (48.4%), and 8 (25.8%) patients were classified as ASA I, II or III.

Twenty nine patients' vital signs were within acceptable limits during gastroscopy. The induction time after injection of remimazolam besylate was 70 ± 25 s, with anesthesia recovery time and observation time in the resuscitation room 5.1 ± 2.1 min and 2.3 ± 1.6 min, respectively.

ED_{50} of the initial loading dose of remimazolam besylate combined with alfentanil was 0.147 $mg.kg^{-1}$ (95% CI 0.138–0.160 $mg.kg^{-1}$), and ED_{95} was 0.171 $mg.kg^{-1}$ (95% CI 0.159–0.245 $mg.kg^{-1}$). Fourteen patients had effective sedation and successful gastroscope placement after the initial loading dose administration, and 5 and 12 patients succeeded with an additional 2.5 mg due to sedation failure and positive reactions, respectively (Fig. 1). With the increase in the dosage, the depth of sedation increased, while the positive gastroscopic reactions decreased (Fig. 2).

No significant changes in vital signs were seen except for MAP, which fell significantly at T1 and T2 (both $p < 0.05$ vs. T0) and rose significantly at T3 ($p < 0.05$ vs. T2).

Discussion

This study showed that the ED_{50} of the initial loading dose of remimazolam besylate combined with alfentanil was 0.147 $mg.kg^{-1}$ and the ED_{95} was 0.171 $mg.kg^{-1}$, which could

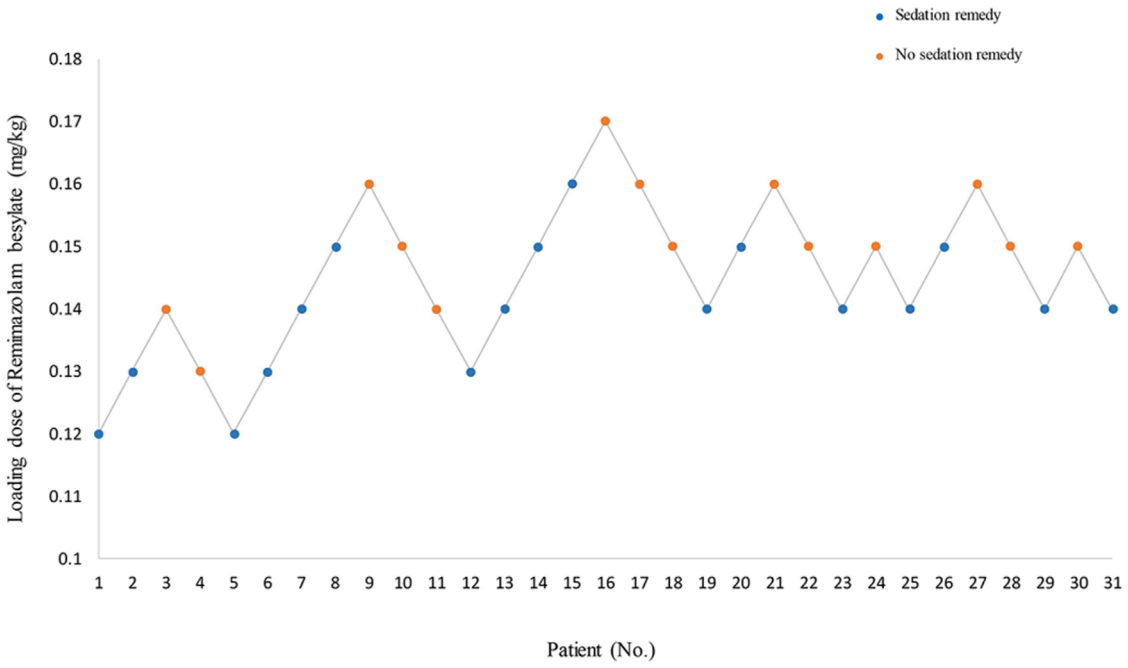

Figure 1 Sequential Experiment Chart. Sequential anesthesia results of remimazolam in anesthesia for gastroscopy.

assist clinical practice of remimazolam besylate during painless gastroscopy.

Endoscopic sedation is widely used in routine practice to relieve anxiety and discomfort, resulting in a successful procedure, and this is also the reason why we focused on this population.[7,8] Remimazolam besylate is a new type of benzodiazepine and ultra-short-acting γ-Aminobutyric Acid type A (GABAA) receptor agonist characterized by quick onset, short half-life, thorough removal, quick loss of sedation effect and fast recovery. It is metabolized into inactive products by tissue esterase and excreted through the kidney.[9] Alfentanil, a new type of opiate, has been widely used for anesthesia in short operations and outside operating rooms for its characteristics of quick onset, high antalgic intensity, short maintenance time, quick metabolism, elevated safety, and awakening quality. Yang et al found that, compared to propofol, remimazolam besylate might have reduced the incidence of delirium in patients who underwent cardiac surgery. In this study, patients were given remimazolam besylate combined with alfentanil before the gastroscopy. We found that the vital signs of most patients were within acceptable limits during gastroscopy except for one who developed hypotension, and one with obvious respiratory depression. The Dixon sequential method is the method most widely used in studies on the dose of anesthetic drugs and has the advantage of saving samples.[10] Therefore, it was used to determine the initial effective dose of remimazolam besylate for painless gastroscopy in this study.

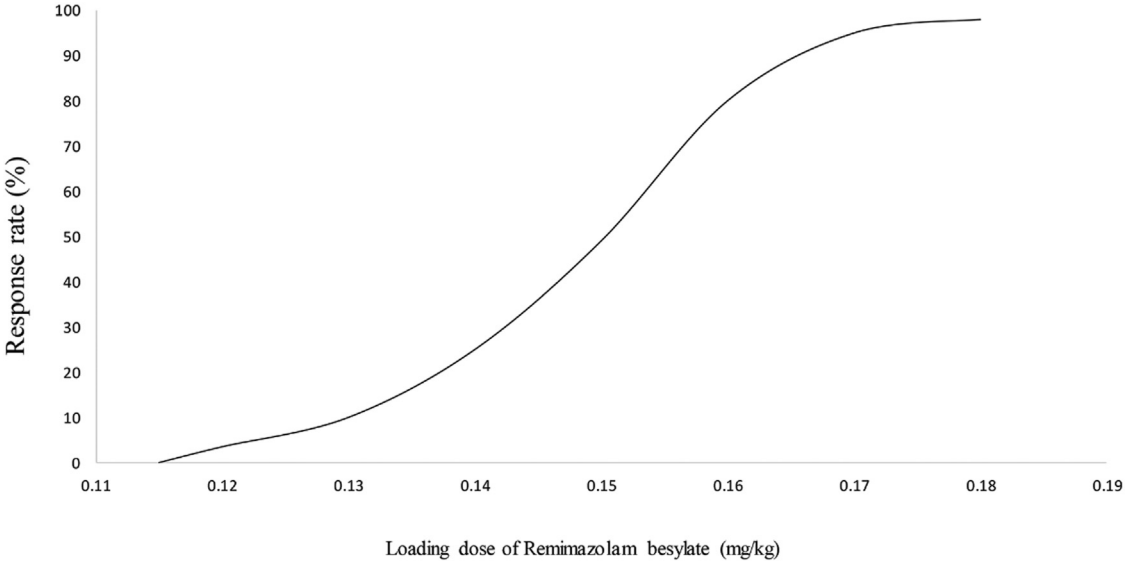

Figure 2 Dose-response curve. Dose-response relationship of remimazolam in anesthesia for gastroscopy.

Gradient increase or decrease of remimazolam besylate provides an accurate indication for ED_{50}. We further found that the ED_{50} of remimazolam besylate combined with alfentanil for painless gastroscopy was 0.147 $mg.kg^{-1}$, and the ED_{95} was 0.171 $mg.kg^{-1}$.

This study had some limitations. The study was a single-centered study. Besides, no serum assays of remimazolam besylate and alfentanil were detected.

Conclusions

In conclusion, the ED_{50} of remimazolam besylate combined with alfentanil for adult gastroscopy was 0.147 $mg.kg^{-1}$, and the ED_{95} was 0.171 $mg.kg^{-1}$.

Ethics approval statement

This study was approved by the Ethics Committee of Anhui n° 2 Provincial People's Hospital.

Patient consent statement

All patients had voluntarily signed the informed consent.

Funding

None.

Data availability

The data set supporting the results of this article are included within the article.

Declaration of competing interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844518.

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LETTER TO THE EDITOR

Enhancing surgical outcomes in dengue patients: strategic approaches to anesthetic management and timing of elective surgery

Dear Editor,

Dengue fever remains a significant global health concern, particularly in tropical and subtropical regions where it manifests as a cyclical outbreak, affecting millions annually. The recent revisions to the WHO case classification in 2009 aimed to streamline diagnosis and management, yet challenges persist, especially concerning surgical interventions in dengue patients.[1]

Dengue can be detected in its early stages (less than five days) by virus isolation, RNA detection, or by looking for antigens like NS1. After this time (more than five days after infection), the viremia has decreased and antibody responses have developed, making dengue virus RNA and antigens potentially undetectable. At this point, serological techniques for specific antibody identification (IgM or IgG detection) are appropriate.[1]

Despite advancements in diagnostic techniques enabling early identification, the optimal timing for elective surgery post-dengue infection remains ambiguous. Furthermore, there is a notable absence of consensus on anesthetic management strategies tailored to dengue patients undergoing surgery. This critical gap underscores the urgent need for standardized protocols and guidelines in this domain to ensure optimal patient outcomes.[2,3]

Dengue's pathophysiology presents complexities for surgical interventions, particularly concerning coagulopathy and microvascular alterations observed in severe cases. Thromboelastographic (TEG) analyses of dengue patients have shown coagulation factor deficiency as the major abnormality followed by platelet dysfunction, primary fibrinolysis but sustained fibrinogen levels.[4] Despite extensive search, it is important to note that the existing literature lacks definitive guidelines or recommendations regarding the optimal timing for elective surgery following dengue virus infection. Additionally, there is a paucity of guidance on the most effective anesthetic management during surgery in patients with dengue fever. This gap underscores the necessity for further research and the development of standardized protocols in these critical areas of patient care.[2]

Microvascular alterations and coagulopathy brought on by severe dengue may make surgical interventions dangerous and surgical management difficult. The gastrointestinal, hepatic, renal, hematological, neurological, respiratory, and cardiac systems are becoming more frequently involved in disease patterns. One recognizable symptom of dengue hemorrhagic fever during its crucial period is abdominal pain. While some dengue patients may simulate an acute abdomen without any real issues, others may present with surgical complications such as gastrointestinal hemorrhage, acute pancreatitis, and splenic rupture.[2]

Diagnosis of an acute abdomen can be difficult in a critically ill dengue patient and should be considered. Dengue infections may be associated with true or apparent surgical acute abdomen because of several reasons. A true acute abdomen may occur as a complication of dengue fever (ruptured splenic hematomas, upper and lower gastrointestinal bleeding, and abdominal wall hematomas). Dual pathologies may occur and can be related to dengue, for example, acute acalculous cholecystitis and appendicitis. Dengue infections may occur with other simultaneous surgical conditions unrelated to dengue (e.g., bowel obstruction). The pathophysiological mechanisms for acute abdomen in dengue are poorly understood. It may be because of direct viral invasion of the abdominal organs such as the appendix, gallbladder wall, pancreas, or spleen leading to inflammation and edema.

A systemic inflammatory response may be another reason. As most patients who presented acute abdomen had features of dengue hemorrhagic fever or dengue shock syndrome, the systemic inflammatory response and plasma leakage may have led to the edematous and inflammatory changes within organs. An edematous appendix with luminal obstruction may precipitate a secondary bacterial infection and cause appendicitis. The pathogenesis of acute acalculous cholecystitis may be multifactorial. The systemic inflammatory response, endotoxemia, cholestasis, secondary bacterial translocation, microangiopathic changes, and ischemia reperfusion injury may contribute.[2] Edema of splenic parenchyma due to fluid leakage or bleeding with expansion of a hematoma within a non-yielding splenic capsule may cause spontaneous splenic rupture. The systemic inflammatory response with coagulopathy can lead to spontaneous bleeding or increased bleeding during minor

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trauma, especially when there is an underlying pathology such as mucosal ulceration.[2]

Anesthetic management in dengue patients poses unique challenges, primarily due to severe thrombocytopenia, coagulopathy, and vasculopathy, which heighten the risk of major bleeding and mortality during surgery. Noninvasive and invasive monitoring techniques are essential for maintaining hemodynamic stability, while special precautions are warranted during induction and intubation to minimize complications.[3]

Prophylactic platelet transfusions are discouraged due to associated risks, while alternative interventions such as cryoprecipitate and recombinant activated Factor VII may be considered in cases of life-threatening bleeding. Fluid resuscitation protocols must be tailored to address plasma leakage and shock, with emphasis placed on goal-directed therapy to optimize cardiac preload and organ perfusion.[4]

The current literature lacks definitive guidelines on the ideal interval for elective surgery post-dengue infection, with few centers adopting protocols based on disease severity and surgical complexity. A prior study has identified the optimal timeframe for renal transplant surgery in both donors and recipients who test positive for dengue. Patients with positive dengue screening should undergo a waiting period averaging 6 weeks and must test negative for NS1.[5]

Complete clinical and laboratory recovery, including normalization of blood counts, liver function, renal parameters, and coagulation profiles, should precede elective procedures.

Prospective, randomized-controlled trials exploring anesthetic management during surgery in dengue patients and preoperative protocols for those with prior dengue virus infection are urgently needed. Although multicentric studies with robust follow-up mechanisms hold promise for elucidating optimal practices in this complex clinical scenario and represent the gold standard of evidence, it appears that they may not be currently feasible, particularly given the small number of dengue fever patients who will require surgical procedures.

The literature on anesthesia management in patients with dengue fever is mainly in the form of case reports or case series. Such studies could help establish evidence-based guidelines, improve surgical outcomes in this complex clinical scenario, and investigate the impact of different anesthetic approaches or tailored preoperative protocols. That could offer valuable insights into enhancing outcomes for dengue patients undergoing surgery.

For instance, Joshi et al highlight the challenges of managing anesthesia in pregnant dengue patients for emergency cesarean section and underscore the need for tailored strategies.[6] Additionally, Hariyanto et al emphasize the importance of TEG as a point-of-care test, which may clearly identify the coagulation abnormalities in dengue fever patients with hemorrhagic complications. The authors suggest a TEG-based therapeutic strategy, in order to avoid potential complications related to unnecessary transfusions in these patients.[7]

Delving deeper into these interventions and rationales is crucial. Future research, such as multicentric studies with robust follow-ups mechanisms to track the long-term outcomes of dengue patients undergoing surgery, could focus on elucidating the optimal timing and dosage of anesthesia in these patients, as well as developing standardized preoperative protocols tailored to their unique needs. The efforts would not only improve patient outcomes, but also contribute significantly to the existing body of knowledge on surgical management in dengue patients.

In conclusion, addressing the challenges associated with surgical interventions in dengue patients requires interdisciplinary collaboration and evidence-based protocols. By prioritizing research efforts in this domain, we can enhance patient care and minimize perioperative complications in this vulnerable population.

Conflicts of interest

The authors declare no conflicts of interest.

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LETTER TO THE EDITOR

ICERA: Increasing accessibility to medical education through structured international collaboration

Dear Editor,

The COVID-19 pandemic triggered sudden and significant adjustments to anesthesia residency training programs worldwide. Initially, the most pressing issues focused on concerns of reduced clinical exposure provided to trainees, largely due to the widespread cancellation of elective surgeries.[1-4] However, reduction of educational activities and networking opportunities, especially those across institutions, also played a large role in degrading the quality of the residency experience.[5] Initial stages of the pandemic caused an abrupt discontinuation of in-person learning opportunities such as didactic lectures and grand rounds. With efforts to adhere to social distancing guidelines and reduction of the spread of the disease, such gatherings were temporarily paused and substituted with virtual learning modalities.[6] Once established, the shift to virtual learning platforms became a flexible option for presenting educational material. Virtual platforms gave trainees the ability to maintain a regular attendance schedule while minimizing the risk of infection. Virtual sessions were recorded and archived, increasing the accessibility of educational material. Trainees could easily catch up on missed sessions or revisit key material at a later date, enhancing their learning experience. Furthermore, virtual platforms have fostered real-time interactions and discussions, even across geographical boundaries, regardless of where different parties are physically located.[5]

While largely beneficial, these virtual shifts brought to light an uneven access to quality virtual learning across anesthesia residency programs. This disparity was especially apparent in low- and middle-income countries, where resource limitations often hindered effective implementation.[7] That being said, significant distinctions prevail among European nations, particularly evident in the divergent educational standards, structures and resources within residency programs.[8] These variations contribute to inconsistent progress in developing core competencies and implementing best practices to ensure patient safety. For example, in Denmark, clinical experience and completion of the anesthesia residency training program is prioritized over the successful passing of a national written examination. In Switzerland, there is an emphasis on theoretical knowledge and the successful completion of a board certification test. Both approaches differ in ensuring optimal patient safety. The identification of such inconsistent standards in postgraduate medical education across the European Union, including Italy, Portugal, France, and Spain, suggest a larger gap in the need for a more standardized program.[9]

Recognizing these differences in didactic education and the increasing accessibility of virtual learning, a unique collaboration emerged between the faculty in the Departments of Anesthesiology at Boston University, in the United States, and Sapienza University, in Italy. Virtual platforms have allowed these physicians to eliminate the ocean of distance that otherwise served as a barrier to collaboration, fostering a seamless exchange of knowledge, ideas and expertise. The initial series of lectures targeted at advancing anesthesia education and training worldwide sparked a global initiative. Creating a global network of established anesthesiologists, they formed the International Collaboration for Education and Research in Anesthesia (ICERA).

Impact

From initial lectures to virtual classrooms, ICERA has morphed in a year. Spanning 20 countries and attracting over 400 participants (as shown in Table 1 and Figs. 1 and 2), ICERA has fostered a vibrant international connection between anesthesia trainees and attending physicians, solidifying its impact beyond the challenges posed by the COVID-19 pandemic.

Empowering anesthesiology residents worldwide, ICERA provides free access to high-quality virtual courses on crucial topics. These courses, expertly designed by dedicated anesthesiologists worldwide, and vetted by ICERA's executive board, directly address the learning needs mandated by the various residency programs and stay at the forefront of global advancements. ICERA lectures are currently a freely accessible resource to the public, thus eliminating any potential financial barriers. They offer the advantage of recorded sessions accessible virtually anywhere, and with the ability to revisit key content or explore new topics at the resident's own pace.

Lectures are conducted via videoconferencing software, providing attendees real-time opportunities for interactive learning. Notably, dedicated time is allocated afterwards for further discussion, allowing trainees to directly engage with international experts outside of their institutional

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Table 1 List of participating countries.

Italy	Greece	Turkey	Argentina
Montenegro	United Kingdom	Kenya	Portugal
Spain	Kosovo	Uganda	Cyprus
Greece	Albania	Romania	Brazil
Tanzania	Colombia	Switzerland	Canada
Moldova	Argentina	Poland	Germany

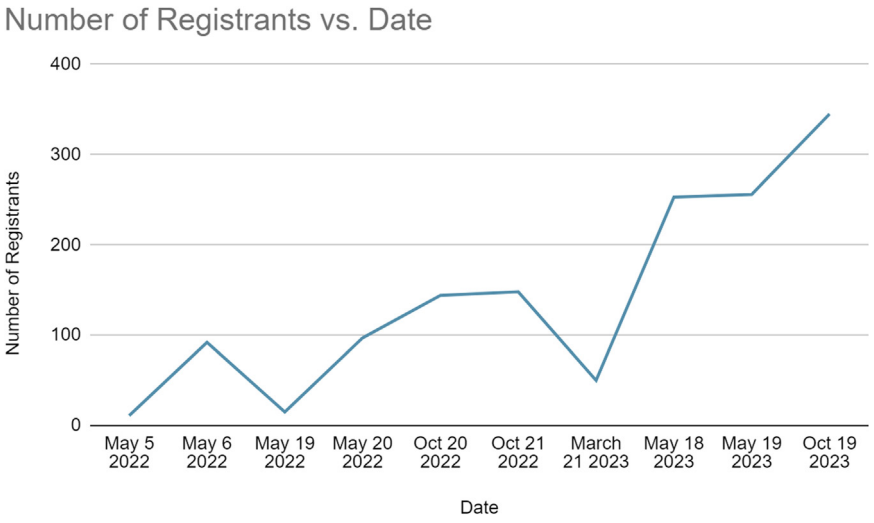

Fig 1 Number of registrants over time.

network. This intentional collaborative design fosters a shared understanding of emerging challenges in the ever-expanding field of anesthesia.

ICERA's collaborative reach extends beyond the classroom and the latest trends in perioperative medicine. ICERA aims to broaden the education, research, and scholarly opportunities for anesthesiology trainees worldwide. Recognizing the unique landscape of residency programs across the globe, there are opportunities to harmonize the educational framework for anesthesia didactics. This focus on standardization, particularly in regions with limited resources, holds the potential to empower future anesthesiologists and propel our field's collective expertise to new heights. Moreover, ICERA's commitment is sustained by mentoring initiatives that cater to anesthesiologists at any stage of their careers. ICERA provides a pivotal platform for participants to expand their professional networks, connecting them with experts and individuals with diverse interests beyond their immediate institutions. Additionally, the sharing of best practices in anesthesia care through ICERA contributes to a continuous enhancement in patient outcomes, reflecting a commitment to ongoing quality improvement in the field of anesthesiology.

ICERA's effects extend beyond knowledge sharing to sparking international research. Clinicians can now design

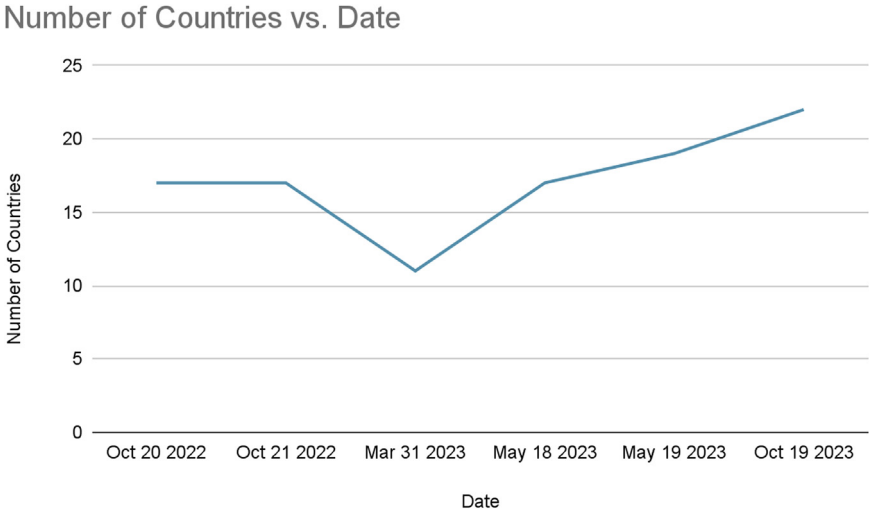

Fig 2 Number of countries over time. *Country data not collected before Oct 20, 2022.

multicenter studies with diverse participants, a stark contrast to the typical regional single-center projects.[10] This shift promises not only valuable insights into regional healthcare variations, but also a groundbreaking platform for drawing broader conclusions applicable to global perioperative medicine.

ICERA keeps its global community informed with a triannual newsletter, bursting with updates, lecture highlights, and insights into evolving topics in anesthesia. The newsletter features highlights of recent and upcoming lectures, offering valuable insights into evolving topics, as well as keeping members informed of evolving best practices, with updates on consensus guidelines and anesthesia recommendations. Launched in September 2023, it is a valuable source of ongoing information for the ICERA global community.

Conclusion

According to the World Federation of Societies of Anaesthesiologists, a critical concern within the global anesthesia community is the shortage of adequately-trained anesthesiologists in developing countries.[11] This shortage impacts the safe and effective delivery of anesthesia services, as these are contingent on the expertise and proficiency of anesthesiologists, emphasizing the pivotal role played by comprehensive training. The situation underscores the importance of ongoing efforts to enhance access to education and mentorship in the field of anesthesia.

Addressing this challenge requires sustained international collaboration to develop effective solutions. A key aspect of this collaboration is the creation of platforms for sharing knowledge and best practices. This is where ICERA plays a significant role. ICERA offers a valuable resource for anesthesiologists at various states of their careers. ICERA provides opportunities for trainees to enhance their clinical skills and for faculty members to advance in research and professional development. This collaborative global environment is instrumental in pursuing shared goals and fostering collective, meaningful change in the field of anesthesia.

Conflicts of interest

The authors declare no have conflicts of interest.

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