

Shivering Management in Spinal Anesthesia: Evaluating the Role of Ketamine: A Narrative Review

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ARTICLE INFO

Article history:

Received 22 May 2024

Revised 12 June 2024

Accepted 28 June 2024

Keywords:

Intravenous Ketamine;
Shivering;
Spinal Anesthesia;
Shivering Management

ABSTRACT

Background: Shivering is one of the most prevalent known complications due to dysregulation in the thermoregulatory system following regional anesthesia, with an incidence of 65%, leading to unpleasant outcomes and decreased patient satisfaction. Ketamine, a weak analgesic, affects the thermoregulatory center.

Methods: The authors conducted a search and selection of articles using reputable scientific databases. The search keywords included Shivering, Ketamine, and Spinal Anesthesia. The selected articles summarized the literature findings related to ketamine and shivering after spinal anesthesia.

Results: This narrative review synthesizes findings from multiple studies examining the role of ketamine in managing shivering following spinal anesthesia. Based on the results obtained, 10 areas were examined: Definition of shivering, Epidemiology of postoperative shivering, Pathophysiology of shivering, Risk factors for post-spinal anesthesia shivering, Spinal anesthesia, its benefits, and its impact on shivering, Post-anesthetic shivering (PAS) complications, Risk factors for postoperative shivering, Control and management of post-anesthetic shivering (PAS) dosage, Effective timing and benefits of ketamine administration in postoperative shivering.

Conclusions: The effectiveness of ketamine in preventing shivering after spinal anesthesia is evident from the mixed results of studies. Ketamine, regardless of dosage, can be effective in reducing shivering after spinal anesthesia based on the mentioned criteria. Standardized research with precise methods to determine optimal dosages and ensure safety is necessary.

Introduction

Spinal anesthesia is one of the most common and reliable methods of anesthesia used in various lower surgeries [1], providing sympathetic blockade that helps vasodilation and redistributes heat, potentially leading to hypothermia [2]. Postoperative shivering, due to dysregulation in the thermoregulatory system, affects approximately 60% of patients

undergoing regional anesthesia [3-4], and despite its role in combating hypothermia, it is considered a detrimental outcome. Pharmacological treatments remain the preferred method for managing shivering [5]. Ketamine is a competitive antagonist of the NMDA receptor. Its administration in patients at risk of hypothermia has been rationalized, and multiple studies have shown intravenous ketamine to be suitable for preventing postoperative shivering [6-7]. However, selecting the appropriate drug for preventing shivering during spinal

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anesthesia with minimal adverse effects is crucial [1]. Circumstances may arise where meperidine is unavailable, shivering is not adequately treated with meperidine, or patients have underlying issues such as bradycardia, respiratory depression, and nausea-vomiting, which may interfere with meperidine's effects. Therefore, considering the high prevalence of shivering following spinal anesthesia, its adverse effects, reduced patient satisfaction, increased patient disability, as well as

the financial and economic burden on hospitals, coupled with the conflicting perspectives on the effectiveness of ketamine and low prophylactic doses shown in various studies [8-10], this narrative review aims to explore post-spinal anesthesia shivering and the impact of ketamine on its occurrence, drawing on published articles in this field. Graphical Abstract of this review article is depicted in (Figure 1).

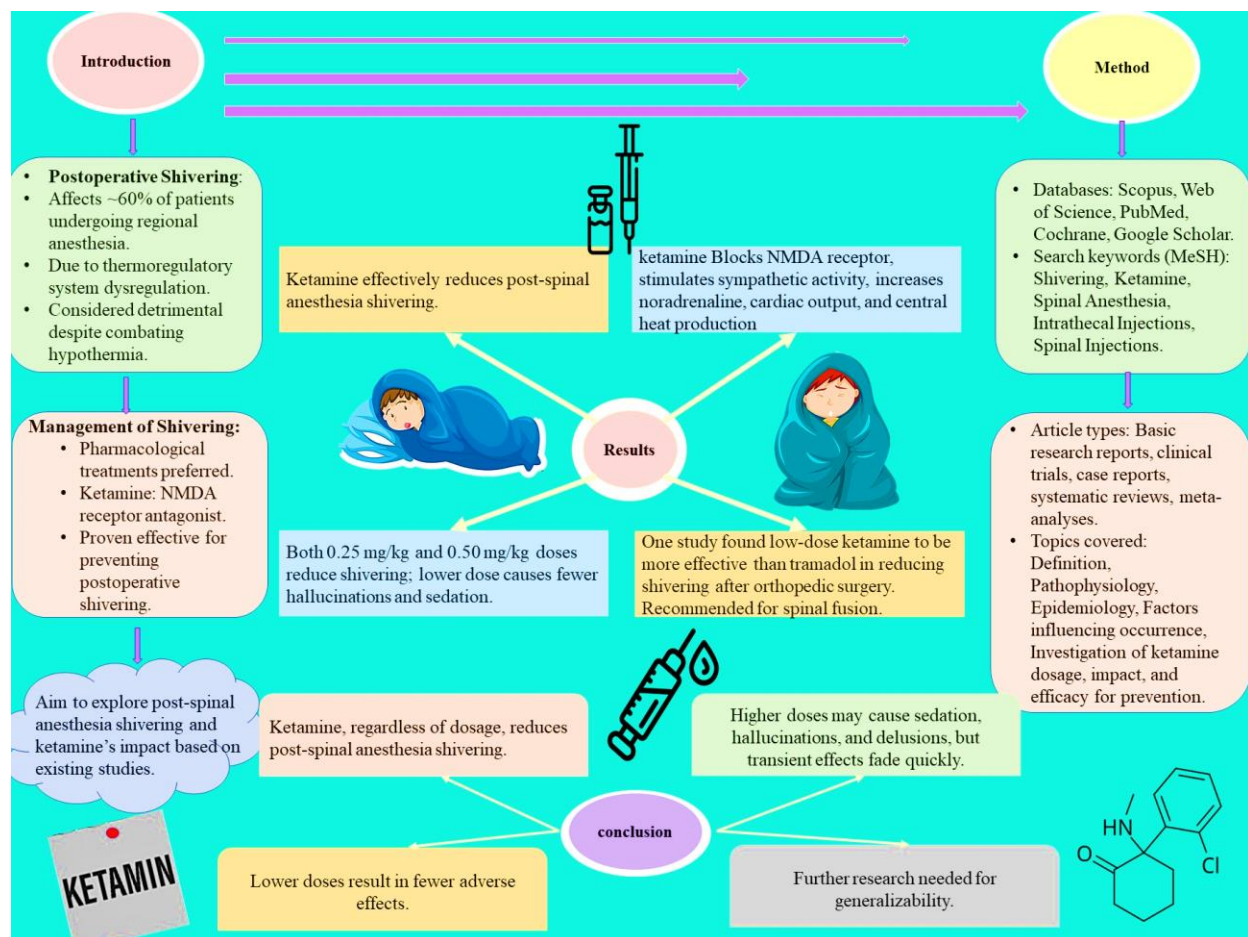


Figure 1- Graphical Abstract of this review article

Methods

Search Strategy

The authors searched and selected articles using reputable databases such as Scopus, Web of Science, PubMed, Cochrane, and the Google Scholar search engine. The search keywords, based on Medical Subject Headings (MeSH), included terms such as Shivering, Ketamine, Spinal Anesthesia, Intrathecal Injections, and Spinal Injections. The selected articles for review encompassed basic research reports, clinical trials, case reports, and systematic reviews and meta-analyses, as

necessary. Sources were meticulously chosen to establish connections, prioritize clinical evidence hierarchy, and refine study design. The narrative review succinctly summarizes the literature findings related to post-spinal anesthesia shivering, including its definition, pathophysiology, epidemiology, factors influencing its occurrence, and the investigation of ketamine dosage, impact, and efficacy for shivering prevention.

Study Selection

The screening process was conducted by pairs of authors (SS, MM, SM, MA, PM, AS) who independently reviewed titles, abstracts, and full texts. Predetermined inclusion and exclusion criteria guided study selection.

Inclusion criteria comprised studies relevant to the research questions, randomized controlled trials, cohort studies, studies published in both Persian and English within the past five years, patients experiencing post-anesthetic shivering under spinal anesthesia, and the use of intravenous ketamine as part of the shivering treatment protocol.

Data Extraction

Data extraction was performed by four researchers. Extracted data from each article encompassed pertinent study particulars (including primary authorship and publication year) Characteristics of the study (objective, study country, and patient group sizes), patient demographics (mean age range), intervention (timing of ketamine use, dosage administered, mode of administration), assessment tools, comparison with placebo or other prescribed drugs. The collected data were analyzed and prepared for presentation. Existing gaps in the studies were identified.

Results

Spinal Anesthesia: Benefits and Its Impact on Shivering

Spinal anesthesia, due to its ease of administration, rapid onset, and predictable duration of action, is a widely used technique for lower limb surgeries performed under either median or paramedian approaches by anesthesia specialists(11, 12). Compared to general anesthesia, spinal anesthesia leads to higher patient satisfaction, a higher rate of recovery without the use of sedative drugs, and minimal post-anesthesia pain scores in the post-anesthesia care unit. Spinal anesthesia is associated with reduced incidence of venous thrombosis and pulmonary embolism, decreased need for blood transfusion, and is often preferred in short-term surgeries due to its cost-effectiveness, high success rate, and facilitating early mobilization and feeding [11, 13-15]. However, post-spinal anesthesia shivering is one of the complications of this method, which may be related to changes in thermoregulatory mechanisms and an increase in body temperature [16].

Definition of Shivering

Shivering, according to the Oxford English Dictionary, is defined as uncontrollable trembling resulting from cold, fear, or excitement. The root of this word is "shiver," which is used both as a verb, meaning to tremble, and as a noun, meaning trembling. In colloquial terms, it refers to muscle twitching due to cold, fear, or excitement [17-18]. Thus, besides health issues, emotional factors can also contribute to this problem. Moreover, shivering, as an involuntary oscillatory

muscular hyperactivity, occurs in the upper and lower extremities, neck, and jaw for more than 15 seconds, ranging from mild (hair bristling) to severe (continuous skeletal muscle contraction) [19-20]. Furthermore, this term is entirely different from "tremor" because tremor refers to involuntary and pathological movements in body muscles that have a relatively rhythmic and oscillatory (forward and backward) pattern. It is the most common form of involuntary movement and can occur in the hands, arms, head, face, vocal cords, trunk, and legs, with most tremors occurring in the hands. In many individuals, shivering is a symptom or sign of a neurological disorder, such as Parkinson's disease. All tremors cease during sleep. Physiological tremors exist in normal individuals and are asymptomatic. Tremors are considered pathological when they disrupt the patient's function. Clinically, pathological tremors can be classified as prominent physiological, Parkinson's, essential, and cerebellar tremors [17, 21].

Epidemiology of Shivering

The administration of anesthesia is recognized as a particularly critical phase for patients undergoing surgical procedures, due to the high potential for significant clinical errors that can lead to irreversible outcomes [22-23]. Post-anesthesia shivering (PAS) is one of the most commonly recognized complications due to disruption in the thermoregulatory system following general anesthesia and regional anesthesia [5]. The prevalence of shivering varies widely, reported between 5 to 65 percent in general anesthesia and approximately 60 percent in regional anesthesia. Moreover, up to 65 percent of patients experience shivering during the postoperative recovery phase. Thus, it seems that both general anesthesia and regional anesthesia disrupt the body's thermoregulatory mechanisms and compromise the effectiveness of the homeostatic system [3, 24]. Administration of the spinal block reduces the body's set point for temperature regulation by 0.5 degrees Celsius, resulting in vasoconstriction and shivering above the injection site. This reduction is directly related to the level of spinal block and increases with age, reaching 85 percent in women undergoing spinal anesthesia for cesarean section [25-26]. The high incidence of shivering after cesarean section may be due to a tendency to protect their children when perceiving nerve block as paralysis, which increases the sense of danger in women. This leads to the continued secretion of nervous hormones. The nervous system can override this activation with shivering [26]. Additionally, urological surgeries are highly sensitive and complex procedures that require appropriate techniques and medications tailored to the patient's clinical condition. Especially in two surgeries, transurethral resection of the prostate (TURP) and percutaneous nephrolithotomy (PCNL), absorption of a

large volume of irrigation fluid may increase the risk of injury to the urethra, bladder, and rectum [27-28].

Pathophysiology and Causes of Shivering

Clarifying the pathophysiology of shivering requires an intricate exploration of the physiological mechanisms governing this involuntary response. A differentiating factor in the electromyographic recordings between patients with post-anesthesia shivering and those who are fully awake is the presence of clonus similar to that seen in patients with spinal cord injury. The primary cause of post-anesthesia shivering is surgical hypothermia, resulting from the suppression of thermal autoregulation by anesthesia [18]. Shivering is a complex physiological process primarily regulated by the central nervous system, especially the hypothalamus, acting as a vital mechanism to maintain thermal balance. Located in the preoptic area of the hypothalamus, near the wall of the third ventricle, the thermoregulatory center regulates body temperature. When the central body temperature drops below a certain threshold, shivering occurs, serving as a vital mechanism in both humans and warm-blooded animals [29-30]. The cause of shivering is primarily a response to central hypothermia and also a response to fever because the body tries to raise its temperature to a new set point [31]. Factors such as hypothermia, age, anesthesia methods and drugs, and the extent and duration of surgery, play a significant role in its occurrence. Moreover, the factors affecting the prevalence of this complication differ between men and women, which may be related to hormonal changes in women. A better understanding of the clinical factors associated with postoperative shivering can assist anesthesiologists in the treatment or prevention of this unpleasant complication [31-32]. The complex neural pathways involved in shivering include a spectrum of neurotransmitters, including noradrenaline and serotonin, which modulate the activity of motor neurons and ultimately lead to rhythmic muscle contractions characteristic of shivering. Additionally, shivering is influenced by various factors such as environmental temperature, metabolic rate, and hormonal regulation [18, 31]. Medical conditions or medications can disrupt the body's thermoregulatory mechanisms and consequently increase susceptibility to shivering. Its occurrence during surgical procedures is common and influenced by factors such as anxiety levels, body temperature fluctuations, and anesthesia administration methods [31]. Additionally, factors such as uncontrolled spinal reflexes, postoperative pain, decreased sympathetic activity, suppression of adrenal glands, metabolic alkalosis, cytokine release during surgery, and response to hypothermia contribute to shivering [33-34].

Risk Factors for Postoperative Shivering

Past analyses of data from over 2595 patients have identified multiple factors that significantly influence the occurrence of post-anesthesia shivering. These factors include variables such as duration of surgery, gender, use of anticholinergic drugs, spontaneous breathing during anesthesia, physical status based mostly on the ASA scale, type of surgery, and blood transfusion. Additionally, older age and prescription of certain medications have been recognized as protective factors [35]. Recent research has also identified risk factors for the occurrence of postoperative shivering, including younger age, type of surgery, and low central body temperature. Certain drugs and medical conditions can also stimulate body temperature regulatory mechanisms and increase susceptibility to shivering. These findings provide valuable information to medical professionals to analyze the risk of postoperative shivering and implement necessary improvements in the pre-and post-operative stages [32].

Consequences of Post-Anesthesia Shivering

Central body temperature is considered one of the most important and stable variables in maintaining human body physiology. Any disturbance in this variable, including hypothermia during surgery, can lead to issues such as postoperative shivering, coagulation disorders, nitrogen balance insufficiency, and changes in drug effects on the body [36]. Studies have shown that even mild hypothermia can significantly increase the risk of postoperative shivering, so preventing hypothermia, even mildly, is crucially important [37]. Postoperative shivering, like other complications of anesthesia and analgesia, increases patient dissatisfaction, morbidity during and after surgery, and oxygen consumption by up to 600 percent. Therefore, efforts to reduce its incidence with appropriate measures during and after surgery are essential. The physiological consequences of shivering include increased oxygen consumption, minute ventilation, risk of myocardial ischemia due to increased oxygen consumption, interference with electrocardiographic and blood pressure monitoring, increased intracranial and intraocular pressure, increased carbon dioxide and catecholamine production, increased cardiac workload, patient discomfort, intensified pain at the surgical site, exacerbation of lactic acidosis, and basal metabolic rate [2, 9, 25]. Venous blood oxygen saturation reduction is also a potential consequence of postoperative shivering, which may pose problems in patients with coronary artery involvement and limited pulmonary reserves. Understanding the pathophysiology of shivering is of great importance in clinical practice, as this level of knowledge helps physicians and paramedics effectively diagnose conditions related to thermoregulatory dysfunction and implement necessary improvements [38-39]. Additionally, knowledge of the

underlying mechanisms of shivering helps in developing therapeutic interventions aimed at reducing shivering and increasing patient comfort and outcomes, especially in critical care settings and during surgical procedures where the risk of shivering is higher.

Control and Treatment of Post-Anesthesia Shivering

Given the issues mentioned above, the importance of treating and preventing postoperative shivering is paramount. Currently, various pharmacological and non-pharmacological methods for preventing hypothermia and shivering are suggested and used. Among these methods, maintaining patient warmth before and during surgery and preventing operating room cooling are among the most important non-pharmacological methods [26]. Actions such as oxygen administration, patient warming, and control of spinal reflexes have a significant impact on shivering control [26, 40]. However, since the entire skin surface contributes to body temperature regulation by 20 percent, non-pharmacological methods alone may not be sufficient, and the use of pharmacological methods is necessary [26, 38]. Various drugs such as meperidine, tramadol, hydrocortisone, nefopam, clonidine, ketamine, and magnesium sulfate have been used to treat postoperative shivering, each with a different mechanism of action [38, 41]. For example, meperidine controls shivering by affecting kappa receptors or directly affecting the thermoregulatory center [5]. Tramadol inhibits the reuptake of 5-hydroxytryptamine norepinephrine and dopamine, also inhibiting shivering [42]. Clonidine and dexmedetomidine are alpha-2 receptor agonists and reduce shivering by inhibiting norepinephrine reuptake [43-44]. Magnesium sulfate is also known as a muscle relaxant and is used to prevent shivering [27]. Studies have shown that some drugs such as meperidine are effective in treating postoperative shivering at all doses. However, due to the potential side effects such as respiratory depression and central nervous system depression, selecting alternative drugs for the prevention and treatment of shivering has always been important [34, 45]. Additionally, the issue of choosing the appropriate pharmacological method for postoperative patients is still a subject of discussion, as the importance of controlling postoperative shivering and the necessity of selecting a drug that does not have adverse effects on patient status are essential. Therefore, further research in this area is essential.

Ketamine

Initially developed in 1964, the safety profile of ketamine transformed it into a vital anesthetic drug for wounded American soldiers during the Vietnam War. Today, ketamine remains the premier anesthetic drug in veterinary medicine. Ketamine's psychotomimetic effects

have led to its use as a "model" drug for schizophrenia. These effects have also contributed to its recreational use. However, ketamine currently serves a medical role in pain management, and its potential antidepressant effects are under investigation [46]. Ketamine is an anesthetic drug that provides analgesic, hypnotic, and profound amnesic effects. In clinical doses, ketamine causes less respiratory depression compared to other intravenous anesthetics and has sympathomimetic properties [47].

Mechanism of Ketamine

Pharmacologically, ketamine's primary effect is on glutamate, the main excitatory neurotransmitter in the brain. It acts as a non-competitive antagonist at one of three glutamate receptors: The N-methyl-D-aspartate (NMDA) receptor. Ketamine also has lesser effects at other receptor sites. The drug may enhance gamma-aminobutyric acid (GABA) synaptic inhibition and stimulate dopamine release. Ketamine has two isomers, both of which have similar pharmacokinetic profiles [46]. However, the S (+) isomer is more potent. Most commercial preparations contain a racemic mixture of this drug. The S (+) and R (-) isomers have similar pharmacodynamic properties. When injected intravenously, its effects are rapid, occurring within approximately 30 seconds [47]. (S)-ketamine has shown neurorestorative effects, increasing the synthesis of growth-associated proteins related to plasticity and repair in hippocampal neurons. Additionally, ketamine plays a role in moderating the inflammatory response to ischemia, reducing the severity of brain damage. Laboratory studies have shown that ketamine suppresses the production of inflammatory cytokines and prevents neutrophil adherence to the endothelium. Further animal studies have shown that racemic ketamine improves neurological outcomes and reduces the volume of hemorrhagic necrosis without altering brain edema in traumatic brain injury models. The primary intravenous effect of ketamine on post-anesthetic shivering, according to recent studies, is direct stimulation of the central sympathetic system, by blocking the NMDA receptor, which modulates noradrenergic and serotonergic neurons in the locus coeruleus. NMDA agonists increase neuronal secretions in the preoptic hypothalamic area [48-49].

Effect of Ketamine on Post-Anesthetic Shivering

This narrative review, following an examination of numerous studies, discusses the impact, effective dose, and efficacy of ketamine in reducing post-spinal anesthesia shivering. Studies on the use of ketamine to reduce shivering post-surgery have provided insights into its prescription. Ketamine, by blocking this receptor, stimulates sympathetic activity, leading to increased peripheral noradrenaline release and cardiac output and

intensifying central heat production, thus reducing the redistribution of heat from the core to the periphery. Therefore, administering intravenous ketamine to patients at risk of hypothermia may be logical. Ketamine achieves this by increasing plasma noradrenaline and constricting peripheral arteries. Several studies have shown that ketamine is effective as a preventive drug for postoperative shivering [50-51]. In a randomized clinical trial, the first group received 0.25 mg/kg intravenous ketamine, while the second group received 0.50 mg/kg intravenous ketamine. This study showed that patients in both ketamine-receiving groups experienced less shivering at 5, 10, and 20 minutes post-surgery. Patients receiving lower doses of ketamine (0.25 mg/kg compared to 0.50 mg/kg) experienced less hallucinations and sedation [33]. A study by Khan and colleagues in 2022, a future-focused cohort, comparing the effects of two ketamine drugs with tramadol on post-orthopedic surgery shivering, found that after spinal anesthesia, low-dose ketamine was more effective in reducing the frequency and intensity of shivering. This study recommended the use of low-dose ketamine as a preventive measure against shivering after spinal fusion [3]. Additionally, meta-analysis and several intervention studies have demonstrated that, aside from the beneficial prevention of post-spinal anesthesia shivering, ketamine recipients experienced fewer adverse effects such as nausea and vomiting, hypotension, and bradycardia compared to recipients of other sedative drugs [38].

Included studies suggest that ketamine may be a more effective anti-shivering drug than various analgesic drugs because it has higher sedation scores in the ketamine group, which may be crucial for maintaining optimal surgical conditions and reducing patient pain after spinal anesthesia [8, 52]. However, since there are differences in the types and doses of local anesthetics used for spinal anesthesia, as well as the types and durations of interventions performed in existing RCTs, the findings may be very heterogeneous. The main limitation of this narrative review study may be the relatively small sample size for generalization; therefore, further studies are needed.

Conclusions

Research endeavors in the field of ketamine use as a preventive option for post-spinal anesthesia shivering indicate that this article intends to investigate the effectiveness of this drug in reducing shivering and its benefits and drawbacks by reviewing published studies. Based on the reviewed studies in this research, ketamine, regardless of dosage, can be effective in reducing post-spinal anesthesia shivering based on the mentioned criteria and demonstrates a significant reduction in shivering after spinal anesthesia. However, the crucial

point is the dosage of this drug in the process of reducing shivering. In most studies on shivering reduction, doses of 0.25 and 0.50 mg/kg ketamine are used, but this dose of half a milligram per kilogram may lead to sedation, hallucinations, and delusions. Transient side effects disappear within an hour. Patients receiving lower doses of ketamine at 0.25 mg/kg experience less hallucination and sedation compared to 0.50 mg/kg [33]. Ultimately, this review highlights the significant impact of ketamine on reducing shivering post-spinal anesthesia, but further research and standardization of doses are essential to ensure its effectiveness and safety. The findings underscore ketamine's potential as a preferable pharmacological option due to its effectiveness and minimal adverse effects compared to other agents. The main purpose of interpreting the obtained information is to provide a comprehensive understanding of ketamine's role in managing postoperative shivering, thereby aiding in the selection of appropriate therapeutic interventions for patients undergoing spinal anesthesia. The generalizability of these results is supported by the consistent findings across various studies, although further research with larger sample sizes and standardized methodologies is necessary to confirm these conclusions and refine clinical guidelines.

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