Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol.(8) Issue(11) (2023), (1-11) **online : ISSN 2356–976x**
http://bjas.bu.edu.eg

New Approach in Prevention of Shivering with Spinal Anesthesia

Taghreed.M.El-Maghrabey, Ehab.E.Afify and Marwa.M.Abouseeda
Anesthesia and Intensive Care Dept., Faculty of medicine, Benha University
E-mail: princesstoty26@gmail.com

Abstract
Background: Shivering during spinal anesthesia is a multifactorial challenge triggered by factors such as cold environments and vasodilation, leading to discomfort, increased oxygen consumption, and potential surgical complications. Effective prevention and management strategies are essential to ensure patient well-being. This review article explores a range of methods, including non-pharmacological and pharmacological approaches, for shivering prevention during spinal anesthesia, considering patient-specific factors and potential side effects, while also highlighting recent advancements in this field and their clinical implications. **Objective:** The aim of this review article is to provide a comprehensive overview of recent advancements and approaches in the prevention of shivering during spinal anesthesia. It explores the mechanisms underlying shivering, discusses a wide range of pharmacological interventions, highlights non-pharmacological strategies, and offers insights into clinical considerations. **Conclusions:** Shivering during spinal anesthesia remains a significant concern, but recent developments in both non-pharmacological and pharmacological methods offer promising avenues for prevention and management.

Keywords: Shivering; Spinal Anesthesia; Prevention; Pharmacological Methods; Non-Pharmacological Methods; Clinical Considerations.

1. Introduction

Shivering is an involuntary somatic motor response triggered by exposure to cold environments or fever. It serves to generate heat and involves the contraction of skeletal muscles [1]. This response is controlled by brain mechanisms, particularly the median preoptic nucleus (MnPO), as evidenced by experiments monitoring parameters like brown adipose tissue (BAT) temperature, arterial pressure, and heart rate. Acute skin cooling consistently increases EMG, BAT temperature, and heart rate, all of which can be inhibited by muscimol nano-injection into the MnPO [2, 3].

The most common causes of shivering include fever, shivering with spinal anesthesia, movement disorders, postanesthetic shivering, fear, excitement, stress, tremors, low blood sugar, anxiety, and shivering. Shivering with spinal anesthesia is an involuntary, oscillatory muscular activity that significantly increases metabolic heat production, potentially reaching up to 600% above the basal metabolic level [4]. The exact mechanisms underlying post-spinal shivering are not fully understood but may involve thermoregulatory responses to hypothermia, affecting neurons in specific brain regions.

To prevent shivering during spinal anesthesia, various methods can be employed: Non-pharmacological methods: For non-hypothermic patients, monitoring vital signs may be sufficient. Hypothermic patients can benefit from passive or active warming procedures performed at least 30 minutes before the operation. Passive methods involve external thermal insulation or warm blanket application, while active methods include the use of heat transfer mechanisms, such as warm air or water-based systems, as well as warm intravenous or irrigation fluids [5].

Pharmacological methods: Several medications can be used to prevent shivering during spinal anesthesia, including Ketamine, Phenylephrine, Ondansetron, Tramadol, Pethidine, Granisetron, Dexmedetomidine, Nalbuphine, Clonidine, Magnesium sulfate, Propofol and Dexamethasone [6, 7].

The aim of this study is to discuss the recent methods to prevent shivering with spinal anesthesia.

2. Shivering with Spinal Anesthesia

Shivering frequently occurs as a complication of anesthesia, especially following spinal anesthesia, with reported incidence rates of up to 50-65%. The mechanism underlying shivering during spinal anesthesia is primarily vasodilatation, leading to rapid heat loss and a shift of body heat from the core to peripheral tissues, resulting in hypothermia and subsequent shivering. This phenomenon can increase oxygen consumption, posing risks of hypoxemia and complications in the postoperative phase [8].

Pathophysiology

Shivering serves as a physiological response to cold exposure, triggered as a means of preserving heat after peripheral vasoconstriction. It often presents as an involuntary, oscillatory muscular activity during early post-anesthetic recovery. Shivering can vary in intensity, ranging from isolated facial or muscle group fasciculations to full-body involvement. Its incidence varies across different anesthesia procedures. The pathophysiology of shivering involves cooling

of the preoptic region of the hypothalamus, with efferent signals traveling through the medial forebrain bundle and spinal alpha motor neurons. Cold stimulation recruits motor neurons in a specific sequence, leading to the observed rhythmic pattern of electromyographic discharges during shivering [9].

Etiology

The etiology of shivering is multifactorial, with various causes including thermoregulatory impairment due to anesthesia, exposure to a cool environment, pain, disinhibited spinal reflexes, decreased sympathetic activity, and respiratory alkalosis. Despite being often associated with hypothermia, shivering can also occur in normothermic patients during the perioperative period. Shivering has both thermoregulatory benefits and adverse effects [10]. While it helps raise core body temperature, it also places the body under increased physiological stress, potentially doubling oxygen consumption and leading to increased catecholamine release, cardiac output, heart rate, and arterial pressure. It can interfere with monitoring during anesthesia and postoperative care, affecting patient comfort and satisfaction [11].

Grading and mechanisms

Shivering can be graded to assess its severity and impact on patient well-being. Various scales have been proposed, ranging from assessing muscle activity to interference with monitoring or causing patient distress. The neurophysiology of shivering involves complex mechanisms, including thermosensors, neural pathways, and central integration in the hypothalamus. The efferent shivering pathway originates in the hypothalamus and ends at motor neurons [12].

3. New Approach in Shivering Prevention (Non-Pharmacological and Pharmacological Methods)

Shivering with spinal anesthesia is a common and distressing complication of surgery, often caused by postoperative pain and hypothermia. Recognizing the importance of maintaining normal body temperature during and after anesthesia, effective treatment strategies have become essential. While various therapeutic approaches exist, most are empirical, and the overall quality of antishivering guidelines is limited. Shivering occurs in diverse settings and with varying durations and intensities, necessitating tailored treatment algorithms. The American Society of Anesthesiologists recommends forced-air warming devices and meperidine as effective strategies, leading to two main approaches: pharmacological and nonpharmacological methods [13].

A. Non-pharmacological therapy

Non-pharmacological therapy is often favored over medications for managing shivering due to the potential adverse effects of drugs in clinical settings. These methods aim to maintain or elevate body temperature above the shivering threshold or suppress the central shivering reflex by providing warm sensory input through the skin. Active cutaneous warming, including electric heating, water-circulating garments, forced-air, and radiant heating, is particularly effective in perioperative and induced hypothermia scenarios. Passive cutaneous warming and core warming methods, such as heated fluids and heated air, offer limited benefits [14]. Active cutaneous warming, by increasing body heat content and minimizing heat redistribution, interferes with cutaneous thermoreceptors and effectively controls thermoregulatory shivering. Upper body forced-air warming has shown efficacy in caesarean deliveries, emphasizing the need for preoperative warming before sympathetic-mediated vasodilation and core-periphery redistribution [15].

B. Pharmacological therapy

Opioids, 2-agonists, anticholinergics, central nervous system stimulants, and corticosteroids are only some of the pharmacological treatments available for avoiding and managing shivering during spinal anaesthesia. Thermal receptors, the spinal cord, brainstem, anterior hypothalamus, and the cerebral cortex are all involved in the complicated thermoregulatory control loop that these drugs aim to modulate. Centrally acting analgesics (tramadol), opioid receptor agonists (meperidine, fentanyl), cholinesterase inhibitors (physostigmine), and N-methyl-D-aspartate receptor antagonists (ketamine, magnesium sulphate) are all very effective drug groups [15]. Clonidine and dexmedetomidine, both 2-central agonists, are more effective than ondansetron and dexamethasone, both anti-inflammatory medications. Some drugs, like clonidine, which may cause bradycardia, hypotension, and drowsiness, or ondansetron, which is used to reduce postoperative nausea and vomiting, can come with possible adverse effects. Although most studies have improved, comprehensive monitoring of drug side effects is still inadequate [16].

Opioid receptor agonists

Meperidine

The opioid receptor agonist meperidine has shown therapeutic efficacy in the prevention and treatment of shivering during spinal anaesthesia. It reduces the threshold for

shivering and causes the body temperature to drop by activating and -opioid receptors in the central nervous system, in particular the receptor [17]. Meperidine's greater equi-analgesic dosage compared to other opioids like fentanyl, alfentanil, sufentanil, or morphine makes it a popular choice for intravenous administration in the therapy of shivering. Use of this drug, however, has been linked to negative outcomes such nausea, vomiting, and slowed breathing. While intrathecal pethidine is useful for lowering shivering during spinal anaesthesia for a caesarean section, it has been linked to an increase in nausea and vomiting [18]. There is a need for more research to determine the best strategy for managing shivering with spinal anaesthesia, particularly in the context of different dose levels and their impact on shivering and side effects [19], as different studies have explored the optimal dose of intrathecal pethidine for shivering prevention, with varying results and considerations of side effects.

Tramadol

Tramadol, a unique analgesic with dual mechanisms involving the inhibition of noradrenaline and 5-HT3 reuptake, has been explored for its potential in shivering control. It is a racemic mixture of (+) dextro and (-) levo enantiomers and is considered safer than other opioid analgesics in terms of respiratory depression and addiction [20, 21]. Tramadol's analgesic action is mediated through its weak μ-opioid receptor agonism, synergizing with its influence on serotonergic and noradrenergic receptors. The racemic mixture of enantiomers offers a synergistic analgesic effect, with the (+) enantiomer acting as a μ-opioid receptor agonist and the (-) enantiomer inhibiting noradrenaline reuptake. It is used mainly to treat muscle, joint, and wound pain, with some limitations regarding patient medical history. Tramadol's metabolism involves O- and N-demethylation, forming metabolites, of which O-desmethyl tramadol (M1) is particularly potent [22]. Despite its advantages, tramadol is not without side effects, including serotonin syndrome, seizures, hyperalgesia, and various central nervous system, gastrointestinal, dermatologic, genitourinary, cardiovascular, metabolic, and musculoskeletal disturbances [23].

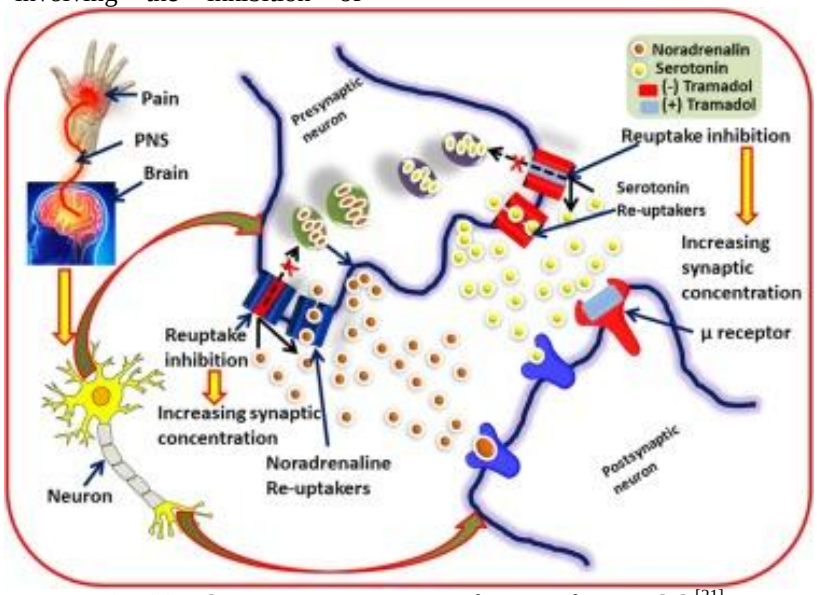

Fig. (1) Schematic representation of MOA of Tramadol [21]

The mechanism of tramadol's action in shivering control is multifaceted, involving its effect on central neurotransmission. Its modulation of 5-HT3 and noradrenergic receptors, impacting the nucleus raphe magnus and inhibitory pathways, contributes to its antishivering efficacy [24]. The racemic mixture's synergistic effect on analgesia and temperature regulation, along with its ability to inhibit serotonin and noradrenaline reuptake, further supports its potential in shivering management. Tramadol's clinical utility in controlling post-anesthetic shivering has been compared favorably to pethidine, particularly within the first 30 minutes post-administration, with tramadol showing a lower recurrence rate. Core temperature may influence response rates, as lower core temperatures were associated with reduced efficacy. Overall, tramadol's antishivering effect, combined with its safety profile, makes it a promising option in managing shivering during anesthesia [25].

Nalbuphine

Nalbuphine is widely employed in clinical surgery for its analgesic properties, but its high dosage has been linked to an increased risk of normeperidine toxicity, prompting the exploration of new drugs for post-anesthetic shivering management. Nalbuphine exerts its anti-shivering effect through its κ-receptor and α2-receptor activities, possessing both μ-antagonist and κ-agonist characteristics. This synthetic opioid demonstrates a high affinity for κ-opioid receptors in the central nervous system. Studies have shown that intravenous nalbuphine effectively treats shivering, exhibiting a higher success rate and faster cessation of shivering compared to dexmedetomidine. Furthermore, nalbuphine has a lower incidence of bradycardia and excessive sedation following treatment, making it a valuable option for managing shivering without causing respiratory depression, particularly in spinal anesthesia settings [26, 27].

Antiserotonergic agents

5-HT3 receptor antagonists, a relatively recent addition in the realm of shivering prevention, have gained prominence due to the potential side effects associated with both opioid and non-opioid drugs used for shivering management. These antagonists have demonstrated efficacy in preventing shivering, with meta-analysis findings suggesting comparable effectiveness to meperidine. The mechanism of action involves inhibiting the reuptake of 5-HT in the preoptic area of the hypothalamus, where 5-HT3 is released to activate heat production pathways and raise body temperature. Consequently, 5-HT3 receptor antagonists prove effective in preventing shivering following both general anesthesia and spinal anesthesia [28].

Ondansetron

Ondansetron, a 5-HT3 (serotonin) antagonist primarily used as an antiemetic, has been a subject of controversy regarding its effectiveness and safety in preventing shivering with spinal anesthesia. its mechanism of action may involve inhibiting 5-ht reuptake in the preoptic anterior hypothalamic region, influencing both heat production and heat loss pathways. studies have shown that both 4 mg and 8 mg of ondansetron administered at the end of surgery significantly reduce the risk of shivering with spinal anesthesia [29]. Furthermore, ondansetron exhibits similar antishivering effects to meperidine but with a lower risk of bradycardia and a significant association with a decreased risk of hypotension, as supported by meta-analysis findings, suggesting its safe and potentially shiver-reducing use [30].

In contrast to ondansetron, palonosetron, a newer 5-HT3 antagonist, has not been found to influence perioperative hypothermia or postanesthetic shivering significantly, indicating differences in efficacy compared to ondansetron in this context. Additionally, research highlights the potential of low-dose ketamine and ondansetron in preventing shivering during spinal anesthesia, although comparative studies evaluating their use are limited [31]. The relative preservation of temperature observed in ketamine groups may be attributed to the vasoconstrictive action of ketamine, while the difference in ondansetron's effectiveness between studies could be attributed to variations in dosage [32, 33].

Granisetrone

Granisetron, a potent 5HT3 receptor antagonist, has gained attention for its minimal adverse effects compared to other antiemetic drugs and its potential in preventing post-spinal anesthesia shivering [34]. Research suggests that serotonin antagonism, influenced by Granisetron, can lower the human thermal set-range, thereby reducing metabolic cold defenses and discomfort associated with post-operative hypothermia [28]. Studies have shown the effectiveness of Granisetron in preventing shivering, with various doses such as 3 mg, 1 mg, or 40 μg/kg proving to be effective. Additionally, Granisetron has demonstrated effectiveness in preventing emetic symptoms during regional anesthesia [34].

Comparative studies have shown that Granisetron can effectively reduce the incidence and severity of perioperative shivering in a dose-dependent manner. It has also been associated with a reduced incidence of postoperative nausea and vomiting (PONV) and pruritus, with no significant difference observed between different doses of Granisetron [35]. Meta-analyses have further supported the efficacy of 5-HT3 receptor antagonists, including Granisetron, in preventing post-operative shivering, with comparable effectiveness to meperidine. However, more high-quality randomized controlled trials with larger sample sizes are still needed to draw definitive conclusions about the preventive efficacy of 5-HT3 receptor antagonists in perioperative shivering prevention [36, 37].

The same dose that we used in our study. Also, it was reported that dexmedetomidine infusion during surgery was effective in the prevention of post-anesthetic shivering in patients undergoing elective abdominal hysterectomy. It was found the incidence of shivering as 15% with dexmedetomidine and 55% with placebo following general anesthesia. A previous study

results are similar to their study with the incidences being 10% and 56.7%, respectively. The lower incidence of shivering in the dexmedetomidine group may be related to the depression of the thermoregulation threshold [38].

In a study observed that dexmedetomidine effectiveness in suppressing postanesthesia shivering in patients who had undergone laparoscopic surgery during general anesthesia. They administered intravenous dexmedetomidine 1 μg/kg during the perioperative period. They noted that the incidence of shivering was significantly lower in the dexmedetomidine group and concluded that intravenous Antishivering effects of dexmedetomidine may lessen the frequency of shivering [39].

Another research found that SA with strong bupivacaine (0.5%) + 5 g intrathecal dexmedetomidine for lower abdominal operations resulted in a significantly reduced incidence of shivering than the control group (12 of 31). Factors that enhance the likelihood of feeling cold during SA are likely contributors to these variations. Age, sensory-block intensity, intrathecal local anaesthetic temperature, intravenous fluid temperature, and operating room environment are all contributors. Temperatures of intrathecal medicines and intravenous solutions (room temperature) were similar across the two groups in another research [40], as was the age distribution of patients undergoing spinal anathesthia.

Meds That Reduce Inflammation

Dexamethasone

Dexamethasone is an anti-inflammatory and immunosuppressant medication belonging to the synthetic glucocorticoid family of steroids. It is around 25-30 times as strong as hydrocortisone, making it one of the most active glucocorticoids. It inhibits the central thermoregulatory system, preventing shivering related to temperature regulation, and it blocks the activation of inflammatory reactions and cytokine release in surgical patients, preventing nonthermoregulatory shivering [41].

Cholinesterase inhibitors

They are a class of medications that play a crucial role in medicine, particularly in the context of anesthesia and the treatment of specific medical conditions. These drugs primarily work by inhibiting the breakdown of acetylcholine, a neurotransmitter, leading to increased acetylcholine levels in the body. Physostigmine is one of the prominent cholinesterase inhibitors used for its therapeutic properties [42].

Uses:

Physostigmine is commonly employed in clinical settings to reverse the toxic effects of drugs or substances that have anticholinergic properties. Anticholinergic agents can cause a range of symptoms, including dry mouth, blurred vision, confusion, and delirium. Physostigmine's ability to increase acetylcholine levels counteracts these symptoms by restoring normal cholinergic function in the body. It is especially useful in the treatment of anticholinergic toxicity caused by medications or plants. Myasthenia gravis is an autoimmune disorder characterized by muscle weakness and fatigue. Cholinesterase inhibitors like physostigmine are used to improve muscle strength and neuromuscular function by increasing acetylcholine availability at the neuromuscular junction. This helps alleviate the symptoms of the condition and enhances muscle contractions [43].

Side Effects:

While physostigmine can be highly beneficial in certain situations, it is not without potential side effects. Common side effects may include: Physostigmine can slow down the heart rate, leading to bradycardia. This effect should be closely monitored in patients with pre-existing heart conditions. Gastrointestinal disturbances, such as nausea and vomiting, are possible side effects of physostigmine. Increased acetylcholine levels may result in excessive salivation or drooling. Some individuals may experience profuse sweating as a result of increased cholinergic activity. In rare cases, excessive cholinergic stimulation can lead to muscle weakness or twitching. While uncommon, in high doses, physostigmine can potentially trigger seizures [44].

Role in shivering with spinal anaesthesia

Physostigmine, a cholinesterase inhibitor, has been explored for its potential role in addressing shivering that occurs during spinal anesthesia, although it is not as commonly used for this purpose as some other medications like ketamine or magnesium sulfate. The rationale behind using physostigmine for shivering with spinal anesthesia lies in its ability to increase the levels of acetylcholine, a neurotransmitter, in the body. Acetylcholine is involved in the transmission of nerve signals, including those related to muscle contractions and temperature regulation. By inhibiting the breakdown of acetylcholine, physostigmine can enhance cholinergic activity, potentially influencing the body's response to temperature changes and muscle tone [45].

However, it's important to note that the use of physostigmine for shivering with spinal

anesthesia is not considered a first-line treatment. Other medications, such as opioids, N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., ketamine), and centrally acting analgesics, are often preferred for this purpose due to their more established efficacy [45].

NMDA Receptor Antagonist

Ketamine

Ketamine, a noncompetitive Because of its influence on body temperature, the NMDA receptor antagonist is a useful medicine for the prevention and treatment of shivering during spinal anaesthesia. In order to lessen the pain and dangers associated with shivering during surgery, ketamine blocks NMDA receptors, making the body less sensitive to variations in temperature. However, if you take too much ketamine, you might experience sleepiness, hallucinations, and delirium. To maximise its therapeutic advantages while limiting its side effects, close monitoring and titration of the dosage are required. Combining it with ondansetron has shown positive results in preventing shivering in recent trials, but the risk of sedation and other adverse effects prevents it from being widely used in this setting [45-47].

Sulfate of magnesium

Magnesium sulphate, or "mag sulphate," has several medical uses and is often used to prevent or control shivering during spinal anaesthesia. Like ketamine, it acts as an N-methyl-D-aspartate (NMDA) receptor antagonist, lowering the chance of shivering during surgical operations by regulating the body's reaction to temperature fluctuations [48]. Magnesium sulphate is also used in obstetrics to treat and prevent eclampsia, a seizure disorder that may occur in pregnant women. Seizures brought on by eclampsia may be better managed with the use of this CNS depressant and muscle relaxant. Muscle weakness, respiratory depression, and low blood pressure are all possible adverse effects, particularly at larger dosages, therefore doctors need to keep an eye on their patients [49].

Magnesium sulphate has a dual action as a calcium antagonist and NMDA receptor antagonist, perhaps decreasing the degree of shivering via centrally controlling temperature responses. Shivering caused by spinal anaesthesia may be significantly reduced with the infusion of magnesium sulphate during surgery. Especially in postoperative patients whose core temperatures are close to the typical shivering threshold, even a little reduction in the shivering threshold is frequently enough to decrease shivering. When given under general anaesthesia, magnesium sulphate has been shown to lessen cases of nausea and vomiting after surgery (PONV). However, dose and monitoring considerations are important for minimising adverse effects [50].

2-receptor agonist

Shivering has been treated with medicines that target alpha2 adrenergic agonist receptors, which may decrease sympathetic activity and centrally regulate vasoconstrictor tone. Patients administered dexmedetomidine may be more sedated, but the Cochrane review found that both clonidine and dexmedetomidine were effective in reducing shivering. This evidence, however, is of extremely poor quality. Oral or intravenous, during or before surgery, the dosing and administration options are flexible [51].

A meta-analysis revealed that dexmedetomidine is more effective than placebo in preventing shivering, but not more effective than other anti-shivering medications. Injections into the spinal canal (epidural) or the veins (intravenous) may provide the desired effect. However, the half-life of dexmedetomidine is around two hours, thus the period between the last dosage and the conclusion of operation should be shorter than that. Although 1 mg/kg bolus is the standard, 0.5 mg/kg i.v. may be all that's needed for prophylaxis [52].

Dexmedetomidine inhibits neuronal excitability, reduces central thermosensitivity, and lowers the temperature at which vasoconstriction and shivering become physiologically significant. Sedation, bradycardia, hypotension, and dry mouth are some of the unwanted side effects. However, dexmedetomidine is not advised for use exclusively in the prevention of shivering owing to its relatively expensive price and probable adverse effects [52].

Dexmedetomidine

Shivering during regional anaesthesia may be efficiently reduced by dexmedetomidine, a highly selective 2-adrenergic receptor agonist, without causing serious side effects [53]. Although the precise process of shivering under regional anaesthesia is not well known [45], it is assumed that its mode of action in suppressing shivering is centrally mediated. Dexmedetomidine's sedative properties complement its distinctive profile as an anti-shivering drug, making it a useful choice for preventing shivering without producing severe sedation, respiratory depression, or hemodynamic instability. Besides raising the threshold at which shivering begins, it also dampens the neuroendocrine and

hemodynamic responses to anaesthesia and surgery [38].

Dexmedetomidine has been utilised for pain relief and avoidance of shivering in a variety of trials, often in conjunction with other agonists. Dexmedetomidine is versatile, as shown by the fact that it may be used to treat postoperative pain when combined with remifentanil, as well as to prevent shivering when given at a lower dosage (0.05 g/kg/hour) [54].

Clonidine

Clonidine, a 2 receptor agonist, significantly decreases the need for oxygen and the frequency of shivering in postoperative patients. Three different systems [55] are involved in its anti-shivering mechanism: the hypothalamus, the locus coeruleus, and the spinal cord. As a result of these processes, the body's thermoregulatory threshold for vasoconstriction shifts, 2 receptors are activated in the spinal cord, and norepinephrine and other mediators are released. Prophylactic use of clonidine vs tramadol for the treatment of shivering during spinal anaesthesia has been studied [56], with clonidine demonstrating a greater response rate and decreased recurrence of shivering. Clonidine is often preferred over tramadol for shivering control because to its effectiveness and superior tolerability [55]. However, tramadol is associated with a greater risk of nausea and vomiting, limiting its usage.

A paralysis of the muscles caused by blocking nerve impulses

As a last resort, several TTM regimens recommend using an NMB to calm trembling. Because it has not been demonstrated to increase myocardial work and is linked with fewer problems [58], a research by Dupuis et al.29 concluded that vecuronium is superior than pancuronium for the decrease of shivering. Neuromuscular blocking drugs are linked to increased time spent on mechanical ventilation, longer stays in the neurointensive care unit, and a higher risk of ventilator-associated infections. Because hypothermia modifies the typical peripheral response to a train-of-four evaluation, its use may confound clinical monitoring of NMB. The chances of long-term deleterious effects from NMBs are increased by the agents' decreased responsiveness to monitoring and longer duration of impact during hypothermia [58].

There are more medicines that may be used to treat and prevent spinal anathesia-related shivering. Physostigmine prevents the release of acetylcholine in the brain, but it also has negative side effects include making you sick to your stomach and speeding up your heart rate and blood pressure. However, there was a clear adverse impact on hemodynamics when the stimulant doxapram was administered to treat the trembling associated with spinal anathesthia. Shivering may be prevented in patients having general anaesthesia for a knee arthroscopy on an outpatient basis by administering hydrocortisone (1-2 mgkg1 i.v.). One of the most researched effective antishivering medications is nefopam [59], a centrally acting analgesic that inhibits synaptosomal reuptake of many neurotransmitters, including dopamine, NE, and serotonin.

Parecoxib has anti-shivering and postoperative analgesic benefits when given prophylactically. These findings suggest that the cyclooxygenase 2-prostaglandin E2 pathways have a role in the control of shivering [45].

Phenylephrine

When injected intravenously or topically applied to mucosal membranes, phenylephrine, an alpha-1 adrenergic agonist, causes significant constriction of blood vessels. Numerous parameters, such as dosage strategy, volume status, heart rate, autonomic tone, and preexisting cardiac diseases, impact its effects on cardiac output and end perfusion, leading to nuanced and diverse results [60]. Reflex bradycardia may counteract its effect on cardiac output, despite its ability to briefly increase preload owing to venoconstriction and enhance systemic vascular resistance and afterload through artery constriction. Patients who are hypotensive and bradycardic may need to reevaluate the usage of phenylephrine because activation of alpha-1 receptors may cause baroreceptor-mediated reflex bradycardia. In ocular uses, it dilates the pupil, which is useful for a variety of diagnostic and therapeutic purposes [61].

Dexamethasone

Dexamethasone, a potent steroid medication, possesses anti-inflammatory and immunosuppressant properties, exerting effects 25 times more potent than cortisol in its glucocorticoid function while having minimal mineralocorticoid impact. It can reduce the temperature gradient between the core and skin by regulating the immune response and decreasing the release of vasoconstrictors and pyrogenic cytokines. Studies have shown that dexamethasone can significantly decrease the incidence of shivering during spinal anesthesia, often outperforming other medications like pethidine, with a reduced shivering rate of 10% compared to 37.5% in the pethidine group. Various studies using different doses of dexamethasone have consistently shown its effectiveness in reducing shivering incidence,

even at very low doses, making it a valuable option in managing this complication during surgical procedures [62].

4. Future Prospectives:

First, the development of more precise patient risk assessment tools can enhance our ability to tailor prevention strategies. Personalized medicine, taking into account individual patient characteristics and genetic factors, may guide the selection of the most effective interventions. Furthermore, ongoing research into novel pharmacological agents and delivery methods holds promise for improved shivering management with fewer side effects. Combining the power of artificial intelligence and real-time monitoring could lead to predictive models that anticipate and preempt shivering events. Additionally, advancements in medical technology may offer innovative approaches, such as targeted temperature management devices and drug delivery systems. Collaborative efforts among anesthesiologists, surgeons, pharmacologists, and engineers are essential to further refine and optimize shivering prevention strategies, ultimately enhancing patient care and surgical outcomes in the context of spinal anesthesia.

5. Conclusions

In conclusion, shivering remains a challenging and multifaceted concern during spinal anesthesia, impacting patient comfort, surgical outcomes, and healthcare resource utilization. This review article has provided a comprehensive overview of the mechanisms, risk factors, and an extensive array of prevention strategies, both non-pharmacological and pharmacological. While significant progress has been made in shivering prevention, there is no one-size-fits-all solution. Careful consideration of patient characteristics, surgical context, and potential side effects is paramount in selecting the most appropriate prevention method. The future holds promise for even more refined and personalized approaches, driven by advancements in medicine and technology. Through continued research and collaboration, the medical community can look forward to a future where shivering during spinal anesthesia becomes an increasingly manageable and rare occurrence, ensuring improved patient comfort and safety.

References

[1] G.V. Allen, D.F. Cechetto. Serotoninergic and nonserotoninergic neurons in the medullary raphe system have axon collateral projections to autonomic and somatic cell groups in the medulla and spinal cord. J Comp Neurol;350:357-66. 1994

[2] K. Nakamura, S.F. Morrison. A thermosensory pathway that controls body temperature. Nat Neurosci;11:62-71. 2008

[3] K. Nakamura, S.F. Morrison. Central efferent pathways for cold-defensive and febrile shivering. J Physiol;589:3641-58. 2011

[4] G.G. Giesbrecht, D.I. Sessler, I.B. Mekjavic, M. Schroeder, G.K. Bristow. Treatment of mild immersion hypothermia by direct body-to-body contact. J Appl Physiol;76:2373-9. 1994

[5] G.D. Simegn, S.D. Bayable, M.B. Fetene. Prevention and management of perioperative hypothermia in adult elective surgical patients: A systematic review. Ann Med Surg (Lond);72:103-15. 2021

[6] A. Ghazi, F.J. Nia, K.I.Z. Far. Comparison of Low-Dose Ketamine and Propofol Effects on Preventing Shivering in Cesarean Section under Spinal Anesthesia. J Hunan Univ Nat Sci;48:25-35. 2021

[7] B. Destaw, E. Melese, S. Jemal. Effects of prophylactic intravenous dexamethasone versus pethidine for prevention of post-spinal anesthesia shivering for patients who underwent transurethral resection of the prostate under spinal anesthesia: Prospective cohort study. Int J Surg;26:137-44. 2020

[8] Y.A. Ferede, H.A. Aytolign, A.T. Mersha. "The magnitude and associated factors of intraoperative shivering after cesarean section delivery under Spinal anesthesia'': A cross sectional study. Ann Med Surg;72:103-15. 2021

[9] A.A. Romanovsky. The thermoregulation system and how it works. Handbook of clinical neurology. 1562018. p. 3-43.

[10] R. Corso, D. Cattano. Hypothermia and Its Management. Improving Anesthesia Technical Staff's Skills: Springer; 2022. p. 197-203.

[11] T. Lulic, J. El-Sayes, H.J. Fassett, A.J. Nelson. Physical activity levels determine exercise-induced changes in brain excitability. PLoS One;12:173-7. 2017

[12] C.L. Tan, Z.A. Knight. Regulation of body temperature by the nervous system. Neuron;98:31-48. 2018

[13] F. Haman, D.P. Blondin. Shivering thermogenesis in humans: Origin, contribution and metabolic requirement. Temperature;4:217-26. 2017

[14] J.L. Apfelbaum, J.H. Silverstein, F.F. Chung, R.T. Connis, R.B. Fillmore, S.E. Hunt, et al. Practice guidelines for postanesthetic care: an updated report by the American Society of Anesthesiologists

Task Force on Postanesthetic Care. Anesthesiology;118:291-307. 2013

[15] B. Park, T. Lee, K. Berger, S.M. Park, K.E. Choi, T.M. Goodsell, et al. Efficacy of Nonpharmacological Antishivering Interventions: A Systematic Analysis. Crit Care Med;43:1757-66. 2015

[16] S.M. Park, H.S. Mangat, K. Berger, A.J. Rosengart. Efficacy spectrum of antishivering medications: meta-analysis of randomized controlled trials. Crit Care Med;40:3070-82. 2012

[17] S. Shami, K. Nasseri, M. Shirmohammadi, F. Sarshivi, N. Ghadami, E. Ghaderi, et al. Effect of low dose of intrathecal pethidine on the incidence and intensity of shivering during cesarean section under spinal anesthesia: a randomized, placebo-controlled, double-blind clinical trial. Drug Des Devel Ther;10:3005-12. 2016

[18] S.S. Mohammadi, S. Jabbarzadeh, A. Movafegh. Efficacy of granisetron on prevention of shivering, nausea and vomiting during cesarean delivery under spinal anesthesia: A randomized double-blinded clinical trial. J Obstet Anaesth Crit Care;5:22-9. 2015

[19] Y.C. Lin, C.Y. Chen, Y.M. Liao, A.H. Liao, P.C. Lin, C.C. Chang. Preventing shivering with adjuvant low dose intrathecal meperidine: A meta-analysis of randomized controlled trials with trial sequential analysis. Sci Rep;7:153-9. 2017

[20] J. Shah, A.B. Nair, H. Shah, S. Jacob, T.M. Shehata, M.A. Morsy. Enhancement in antinociceptive and anti-inflammatory effects of tramadol by transdermal proniosome gel. Asian J Pharm Sci;15:786-96. 2020

[21] S. Nakhaee, C. Hoyte, R.C. Dart, M. Askari, R.J. Lamarine, O. Mehrpour. A review on tramadol toxicity: mechanism of action, clinical presentation, and treatment. Forensic Toxicol;39:293-310. 2021

[22] L.M. Bigal, K. Bibeau, S. Dunbar. Tramadol prescription over a 4-year period in the USA. Curr Pain Headache Rep;23:1-7. 2019

[23] A. Domínguez-Oliva, A. Casas-Alvarado, A.E. Miranda-Cortés, I. Hernández-Avalos. Clinical pharmacology of tramadol and tapentadol, and their therapeutic efficacy in different models of acute and chronic pain in dogs and cats. J Adv Vet Anim Res;8:404-10. 2021

[24] M. Subedi, S. Bajaj, M.S. Kumar, Y. Mayur. An overview of tramadol and its usage in pain management and future perspective. Biomed Pharmacother;111:443-51. 2019

[25] S.A. Sheweita, Y.A. El-Dafrawi, O.A. El-Ghalid, A.A. Ghoneim, A. Wahid. Antioxidants (selenium and garlic) alleviated the adverse effects of tramadol on the reproductive system and oxidative stress markers in male rabbits. Sci Rep;12:13958-66. 2022

[26] H. Teymourian, S.A. Mohajerani, P. Bagheri, A. Seddighi, A.S. Seddighi, I. Razavian. Effect of Ondansetron on Postoperative Shivering After Craniotomy. World Neurosurg;84:1923-8. 2015

[27] G. Yu, S. Jin, J. Chen, W. Yao, X. Song. The effects of novel α(2)-adrenoreceptor agonist dexmedetomidine on shivering in patients underwent caesarean section. Biosci Rep;39. 2019

[28] C. Zhou, Y. Zhu, Z. Liu, L. Ruan. 5-HT3 receptor antagonists for the prevention of postoperative shivering: a meta-analysis. J Int Med Res;44:1174-81. 2016

[29] K. He, H. Zhao, H.C. Zhou. Efficiency and safety of ondansetron in preventing postanaesthesia shivering. Ann R Coll Surg Engl;98:358-66. 2016

[30] M. Li, X. Hu, Y. Tan, B. Yang, K. Li, Z. Tang. Meta-analysis of randomized controlled trials on the efficacy and safety of ondansetron in preventing postanesthesia shivering. Int J Surg;35:34-43. 2016

[31] R. Ramanathan, R. Sethi, S. Singh, M. Varshney, D. Das, D. Nandagopalou, et al. Efficacy of Prophylactic Ketamine, Ondansetron, and Pethidine in Preventing Perioperative Shivering in Patients Undergoing Elective Knee Replacement Surgery Under Spinal Anaesthesia. Turk J Anaesthesiol Reanim;50:44-51. 2022

[32] S. Shakya, A. Chaturvedi, B.P. Sah. Prophylactic low dose ketamine and ondansetron for prevention of shivering during spinal anaesthesia. J Anaesthesiol Clin Pharmacol;26:465-9. 2010

[33] Y.Y. Jo, Y.B. Kim, D. Lee, Y.J. Chang, H.J. Kwak. Implications of palonosetron in elderly patients undergoing laparoscopic cholecystectomy with respect to its anti-shivering effect. Aging Clin Exp Res;28:83-8. 2016

[34] W. Wang, X. Song, T. Wang, C. Zhang, L. Sun. 5-HT(3) Receptor Antagonists for the Prevention of Perioperative Shivering: A Meta-Analysis. J Clin Pharmacol;57:428-39. 2017

[35] S.D. Kabade, Y. Venkatesh, S. Karthik, V. Kumar. Comparative study of granisetron

versus pethidine for the prevention of perioperative shivering under spinal Anesthesia. Karnataka Anaesth J;2:14-8. 2016
[36] M. Dasgupta, B.N. Biswas, S. Chatterjee, P. Mazumder, M. Bhanja Chowdhury. Randomized, placebo-controlled trial of granisetron for control of nausea and vomiting during cesarean delivery under spinal anesthesia. J Obstet Gynaecol India;62:419-23. 2012
[37] A.A. Gugale, P.M. Bhalerao. Palonosetron and granisetron in postoperative nausea vomiting: A randomized double-blind prospective study. Anesth Essays Res;10:402-7. 2016
[38] B. Usta, M. Gozdemir, R.I. Demircioglu, B. Muslu, H. Sert, A. Yaldiz. Dexmedetomidine for the prevention of shivering during spinal anesthesia. Clinics (Sao Paulo);66:1187-91. 2011
[39] S.J. Bajwa, S. Gupta, J. Kaur, A. Singh, S. Parmar. Reduction in the incidence of shivering with perioperative dexmedetomidine: A randomized prospective study. J Anaesthesiol Clin Pharmacol;28:86-91. 2012
[40] K. Nasseri, N. Ghadami, B. Nouri. Effects of intrathecal dexmedetomidine on shivering after spinal anesthesia for cesarean section: a double-blind randomized clinical trial. Drug Des Devel Ther;11:1107-13. 2017
[41] S. Noreen, I. Maqbool, A. Madni. Dexamethasone: Therapeutic potential, risks, and future projection during COVID-19 pandemic. Eur J Pharmacol;894:173-9. 2021
[42] T. Bui, H. Duong. Muscarinic Agonists. 2020
[43] A.M. Arens, T. Kearney. Adverse Effects of Physostigmine. J Med Toxicol;15:184-91. 2019
[44] O.A. Andrade, Z. Gondal. Physostigmine. 2019
[45] M.B. Lopez. Postanaesthetic shivering - from pathophysiology to prevention. Rom J Anaesth Intensive Care;25:73-81. 2018
[46] H. Ahmed, A. Haider, S.M. Ametamey. N-Methyl-D-Aspartate (NMDA) receptor modulators: a patent review (2015-present). Expert Opin Ther Pat;30:743-67. 2020
[47] A. Garcia-Romeu, B. Kersgaard, P.H. Addy. Clinical applications of hallucinogens: A review. Exp Clin Psychopharmacol;24:229-68. 2016
[48] M.A. Hicks, A. Tyagi. Magnesium sulfate. 2020
[49] R.A. Elsharkawy, T.E. Farahat, M.S. Abdelhafez. Analgesic effect of adding magnesium sulfate to epidural levobupivacaine in patients with pre-eclampsia undergoing elective cesarean section. J Anaesthesiol Clin Pharmacol;34:328-34. 2018
[50] H. Omar, W.A. Aboella, M.M. Hassan, A. Hassan, P. Hassan, A. Elshall, et al. Comparative study between intrathecal dexmedetomidine and intrathecal magnesium sulfate for the prevention of post-spinal anaesthesia shivering in uroscopic surgery;(RCT). BMC anesthesiology;19:1-10. 2019
[51] S.R. Lewis, A. Nicholson, A.F. Smith, P. Alderson. Alpha-2 adrenergic agonists for the prevention of shivering following general anaesthesia. Cochrane Database Syst Rev;2015:111-9. 2015
[52] Z.X. Liu, F.Y. Xu, X. Liang, M. Zhou, L. Wu, J.R. Wu, et al. Efficacy of dexmedetomidine on postoperative shivering: a meta-analysis of clinical trials. Can J Anaesth;62:816-29. 2015
[53] S. Lee. Dexmedetomidine: present and future directions. Korean J Anesthesiol;72:323-30. 2019
[54] R. Venkatraman, K. Karthik, A. Pushparani, A. Mahalakshmi. [A prospective, randomized, double-blinded control study on comparison of tramadol, clonidine and dexmedetomidine for post spinal anesthesia shivering]. Braz J Anesthesiol;68:42-8. 2018
[55] A.M. Eskandr, A.M. Ebeid. Role of intrathecal nalbuphine on prevention of postspinal shivering after knee arthroscopy. Egypt J Anaesth 32:371-4. 2016
[56] N.K. Verma, M. Kumar. Comparison of clonidine, dexmedetomidine and tramadol for control of post spinal shivering: A randomized double blind clinical study. Int J Life Sci Scienti Res;2:658-64. 2016
[57] T.S. Kundra, G. Kuthiala, A. Shrivastava, P. Kaur. A comparative study on the efficacy of dexmedetomidine and tramadol on post-spinal anesthesia shivering. Saudi J Anaesth;11:2-8. 2017
[58] A. Jain, M. Gray, S. Slisz, J. Haymore, N. Badjatia, E. Kulstad. Shivering Treatments for Targeted Temperature Management: A Review. J Neurosci Nurs;50:63-7. 2018
[59] Z.U. Khan, U. Naz, M. Durrani, A. Zeb. Treatment of Post Operative Shivering in Head Trauma, Comparison of Ketamine & Pethidine. Ophthalmol Update;18:71-8. 2020

[60] M. Al-Khrasani, D.A. Karadi, A.R. Galambos, B. Sperlagh, E.S. Vizi. The Pharmacological Effects of Phenylephrine are Indirect, Mediated by Noradrenaline Release from the Cytoplasm. Neurochemical Research;47:3272-84. 2022

[61] M.J. Chua, N. Varshney, T. Eke. Intracameral phenylephrine for surgical mydriasis and intra-operative floppy iris syndrome: systemic adverse effects and optimal dose. Journal of Cataract & Refractive Surgery:10.1097. 2022

[62] M. Entezariasl, K. Isazadehfar. Dexamethasone for prevention of postoperative shivering: a randomized double-blind comparison with pethidine. Int J Prev Med;4:818-24. 2013