Review • DOI: 10.2478/rjaic-2022-0006 • RJAIC 2022;29(1):41-46

Romanian Journal of Anesthaesia and Intensive Care

NARRATIVE REVIEW ON PERIOPERATIVE SHIVERING DURING CAESAREAN SECTION UNDER NEURAXIAL ANAESTHESIA

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Abstract

Perioperative shivering is a well-known complication reported in 29 to 54% of patients undergoing a caesarean section under regional anaesthesia. It interferes with pulse oximetry, blood pressure (BP), and electrocardiographic monitoring (ECG). Moreover, it gives the patient a distressing and unpleasant experience. This review aims to examine the mechanism of shivering during the caesarean section under neuraxial anaesthesia and to explore available information for preventing and managing this clinically significant complication.
A literature search of PubMed, MedLine, Science Direct, and Google Scholar was done. The search results were limited to randomised controlled trials (RCT) and systematic reviews.
This review studied the efficacy of various nonpharmacological and pharmacological methods to manage perioperative shivering. We found that pre-warming and intraoperative warming are simple and effective interventions, although the effect seems to depend on the duration of treatment. Multiple pharmacological interventions, including opioids, NMDA receptor antagonists, and alpha-2 adrenergic agonists, have been studied and found to reduce the incidence and severity of perioperative shivering during caesarean section under neuraxial anaesthesia.

Keywords

Neuraxial anaesthesia • caesarean section • perioperative shivering

Introduction

Lower segment caesarean section is one of the most common surgical procedures performed worldwide. Neuraxial anaesthesia is the preferred technique in elective surgeries and in many emergency operations because it is rapid in onset, creates minimal fetal and maternal drug exposure, and has a high success rate.

Perioperative shivering is a common complication, reported in up to 54% of patients undergoing caesarian sections under regional anaesthesia [1]. It is a protective reflex characterised by the involuntary oscillatory activity of the skeletal muscles of the upper limbs, neck, and jaw to raise metabolic heat production. It is a distressing and unpleasant feeling which ultimately affects the overall patient experience [2]. The exact mechanism of shivering during a caesarean section under neuraxial anaesthesia is unknown. The suggested contributing mechanisms include heat redistribution resulting from vasodilation as the result of spinal anaesthesia and the use of oxytocin and intrathecal morphine, all of which are associated with hypothermia [3]. Other contributing factors are the cold ambient temperature in the operating room, rapid infusion of unwarmed intravenous solutions, and choice of neuraxial technique.

The incidents of perioperative shivering during the caesarean section are less with spinal than with epidural anaesthesia [3]. The increased block density of a spinal anaesthesia impairs the thermoregulatory control more than the less extensive blockade resulting from an epidural. The reduction in the shivering threshold with spinal anaesthesia is also proportional to spinal block height [3]. Very little is known about the best way to prevent shivering during spinal anaesthesia. This review examines the shivering mechanism and explores the available evidence for its prevention and management.

Consequences of shivering

Perioperative shivering causes an adrenergic stimulation and an associated increase in plasma catecholamine level, which precipitates tachycardia and increased cardiac output.

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It also causes a two- to three-fold increase in metabolic rate and oxygen consumption, leading to hypoxemia with increased carbon dioxide production [4]. Some studies show that babies born to hypothermic mothers may be at risk of lower temperature, lower Apgar score, and lower umbilical pH at birth. Other concerns raised by perioperative shivering are interference with pulse oximetry, blood pressure, and electrocardiographic monitoring. It also causes an increase in intraocular pressure and intracranial pressure [4, 5].

Pathogenesis behind temperature dysregulation

The temperature regulating system is comprised of three components: afferent thermal sensors, central regulation, and efferent responses [5]. These components work together to maintain a normal core body temperature between 36.5 and 37.5 °C. Afferent delta and c-fibres carry cold and warm thermal inputs through the lateral spinothalamic tract and the inputs are integrated at the anterior hypothalamus. The hypothalamus, connected with the hippocampus, limbic system, pons, and midbrain, compares peripheral information with the thermal set-point and initiates an appropriate autonomic and behavioural response to cool or warm the body [4,5]. Neuraxial anaesthesia alters the thermoregulatory mechanism by impairing sensory input, decreasing the central shivering threshold and inhibiting efferent response. Furthermore, neuraxial anaesthesia causes sympatholysis and vasodilatation, which leads to an internal redistribution of heat from the core to the peripheral compartment. Loss of thermoregulatory vasoconstriction below the block's level, along with increased cutaneous blood flow, contributes to heat loss from the body surface. This resultant continued heat loss leads to more shivering in the remaining unblocked dermatomes [6].

Prevention and management

Prevention and treatment of perioperative shivering during a caesarian section under neuraxial anaesthesia are clinically challenging. Both nonpharmacological and pharmacological methods have been studied, showing varying degrees of efficacy. Nonpharmacological methods are used throughout the peripartum period. However, pharmacological treatments for shivering are limited in the parturient due to placental drug transfer to the fetus and the potential of such treatments to affect the immediate peripartum experience adversely. As such, pharmacological treatments are generally reserved for the postpartum period or administered neuraxially to reduce systemic effect.

Nonpharmacological Interventions

Nonpharmacological methods (Table 1) including prewarming, warmed intravenous crystalloid solutions, the use of warming devices, and maintaining a controlled operating room temperature have shown promising results in preventing perioperative shivering.

Prewarming

Redistribution of body heat is the primary cause of hypothermia in patients undergoing neuraxial anaesthesia. With sympatholysis, blood vessels in peripheral tissues dilate, allowing warm-core blood to rapidly redistribute to high-surface-area cutaneous tissues exposed directly to ambient temperature. Pre-anaesthetic cutaneous warming mitigates heat loss from redistribution by increasing peripheral tissue heat content and reducing the core-to-peripheral tissue temperature gradient [3]. Studies have shown that even a brief 15-minute period of prewarming, when combined with intraoperative warming techniques, prevents hypothermia and shivering in patients undergoing elective caesarean delivery under neuraxial anaesthesia [4,5,6].

Intraoperative Warming

Forced-air warming, warm intravenous fluids, and ambient operating room temperature control are the most commonly used methods to prevent intraoperative hypothermia. Forced-air warming units work by distributing heated air to the covered body surface. Air warming acts through peripheral conduction and convection to increase skin temperature and reduce the core-to-peripheral tissue temperature gradient. It provides the dual benefit of transferring heat to the body and reducing heat losses from the skin under the air warmer. The performance of forced-air warming depends on the duration of the application and the surface area covered. Theoretically, the greater the area covered by the warming blanket, the less redistributive heat loss. Many studies from the non-obstetric patient population have compared the efficacy of lower body versus upper body forced-air warming for patients undergoing neuraxial anaesthesia [4,5,6]. They

Table 1: Nonpharmacological methods of preventing perioperative shivering

	Example	Mechanism	Remark
Prewarming	Blanket, forced-air warmer, warmed IV fluids	Increases body surface heat content and reduces heat loss from redistribution	Active warming is more effective than passive warming
Intraoperative warming	Forced-air warmer, warmed IV fluids	Reduces core-to-surface heat loss	Lower body forced-air warmer is more effective than upper body

Abbreviations: IV, intravenous

suggested that heat transfer with forced-air warming over the lower body is more effective than the upper body. However, the only study investigating lower body warming on obstetric patients did not show a benefit, likely as a result of insufficient duration of application [7]. Studies have shown that warming blankets must be applied for a sufficient period preoperatively to be effective. Given its virtual lack of side effects, we recommend the use of prewarming and intraoperative warming methods. These include a comfortable surgical preparatory area and operating room temperature, warm blanket or forced-air warmer, applied as early as possible and throughout the perioperative period, and administering warm IV fluids.

Pharmacological Interventions

Pharmacological intervention (Table 2) does not raise body temperature, but rather resets the shivering threshold to a lower level. Various pharmacological therapies via intravenous and intrathecal routes have been studied as prevention or treatment options for shivering during the caesarian section. However, no ideal treatment exists. The theoretical disadvantage of the intravenous route is the potential for drugs to cross the uteroplacental barrier. Intrathecal medications tend to have a localised effect with small doses and negligible systemic uptake. Many drugs such as meperidine, fentanyl, sufentanil, tramadol, ondansetron, granisetron, clonidine, ketamine, and magnesium sulphate have been studied for the management of perioperative shivering during cesarean section with varying degrees of efficacy.

Opioids

Meperidine is a synthetic opioid and is widely used for the treatment of shivering. Its antishivering effect is thought to be mediated through its κ-opioid receptor activity, anticholinergic action, monoamine reuptake inhibition, N-methyl-d-aspartate (NMDA) receptor antagonism, and stimulation of adrenergic receptors. Many obstetric and non-obstetric studies have demonstrated its efficacy. It has been used through both intravenous and intrathecal routes. IV Meperidine is much more effective in treating shivering than equianalgesic doses of other opioids [8,9]. However, its popularity in the obstetric population has waned due to the possible sedative effect on the mother, placental transfer to the fetus, and an increased incidence of nausea and vomiting. Studies have shown that 10 mg is the minimum effective intrathecal dose, which can reduce the severity of perioperative shivering without increasing the rate of adverse events [10]. Other intrathecal opioids such as fentanyl, sufentanil, and tramadol have also been studied for the prevention of perioperative shivering during caesarian section under neuraxial anaesthesia with positive results. In various randomised controlled trials, intrathecal fentanyl doses in the range of 20 to 25 µg have been shown to reduce the incidence and severity of shivering without increasing other side effects [8,11]. The actions of these lipophilic µ-receptor agonists on the thermoregulatory and spinal afferent thermal inputs at the spinal cord level have been attributed to the antishivering effect of fentanyl and sufentanil. However, a recent meta-analysis found that intrathecal sufentanil does not reduce the incidence of postoperative shivering [12]. Intrathecal tramadol inhibits the reuptake of 5-hydroxytryptamine (5-HT) and norepinephrine in the spinal cord [13] which facilitates 5-hydroxytryptamine release and accelerates descending spinal inhibitory pathways and ultimately modifies thermoregulatory control and shivering. Studies have concluded that the anti-shivering effect of intrathecal tramadol at 10 mg significantly reduces the incidence of shivering in parturients at the cost of higher incidences of nausea and vomiting, which were amenable to treatment with antiemetic drugs [13].

Table 2: Pharmacological methods of preventing perioperative shivering

	Mechanism	Remark
Opioid Meperidine 10 mg IT Fentanyl 20 – 25 µg IT Tramadol 10 mg IT	Mu and Kappa receptor agonism, anticholinergic action, monoamine reuptake inhibition	Effective at reducing the incidence and severity of perioperative shivering
5-HT3 Antagonist Ondansetron 8 mg IV	Inhibit serotonin reuptake at the pre-optic anterior hypothalamic region	May be effective when compared to inactive placebo but not when compared to intrathecal fentanyl
NMDA Antagonist Ketamine 0.25 – 0.5 mg/kg IV Magnesium Sulphate 50 mg Epid	Modulate noradrenergic and serotonergic neurons in the locus coeruleus	Ketamine appears effective while evidence on magnesium is limited
Alpha-2 Agonist Dexmedetomidine 5 – 10 µg IT Dexmedetomidine 1 µg/kg Epid Dexmedetomidine 30 mcg IV	Alpha-2 receptor stimulation decreases the thermoregulatory threshold for shivering at the hypothalamus level, and modulate cutaneous thermal inputs via descending inhibition, thus inhibiting shivering at the spinal cord level	Dexmedetomidine is effective at reducing shivering but can lead to bradycardia

Abbreviations: IT, intrathecal; IV, intravenous; Epid, epidural

In summary, intrathecal opioids are effective in reducing the incidence and the severity of perioperative shivering during caesarean section under neuraxial anaesthesia. Meperidine, although the most effective at treating shivering, is becoming obsolete due to potential neurotoxicity. Administering spinal anaesthesia with intrathecal fentanyl and local anaesthetics for caesarean section is a common practice for elective and urgent surgery. This has been shown to be a safe technique to both the mother and the fetus and side effects are minimal even in doses up to 25 µg. Sufentanil is another commonly used intrathecal opioid for caesarean section but its efficacy in reducing perioperative shivering in this setting is less clear. Intrathecal tramadol is effective against postoperative shivering, but such use remains off-label and its safety may be unclear. Additionally, it appeared to increase the incidence of postoperative nausea and vomiting. Cautions should be exercised in utilising intrathecal tramadol for the purpose of preventing shivering.

5-HT3 antagonists

5-HT3 antagonists have been widely used as antiemetics in anaesthesia practice. Few randomised controlled trials and meta-analyses have investigated their effectiveness in preventing perioperative shivering, [14-18] but the results remain inconsistent. The mechanism of 5-HT3 antagonists as antishivering agents is not clear. These are postulated to act centrally at the level of the pre-optic anterior hypothalamic region by inhibition of serotonin reuptake.

5-HT3 antagonists are widely used in the peripartum population due to their low maternal and neonatal risk. Few studies have investigated their efficacy in reducing post-spinal anaesthesia shivering, but the results were mixed [14-18]. Browning et al. [14] did a double-blinded randomised, placebo-controlled trial on 120 parturients undergoing elective caesarean under combined spinal-epidural anaesthesia. Every women received either intravenous ondansetron 8 mg (n = 58) or saline (n = 60) before CSE anesthesia (intrathecal hyperbaric bupivacaine 0.5% 2.2-2.5 ml plus fentanyl 15 µg). They concluded that prophylactic ondansetron does not prevent shivering [14]. Later these results were criticised by Gu and Liu, for the scoring system utilised in the study and the concomitant use of intrathecal fentanyl in both groups, which would have decreased the incidence and severity of shivering [15]. Subsequently, Badawy and Mokhtar conducted a double-blinded, prospective, randomised trial, including 80 parturients undergoing elective caesarean section under spinal anaesthesia. Patients were randomised into two groups receiving either ondansetron 8 mg IV or saline placebo before a local anaesthetic only spinal anaesthesia. In this trial, the shivering scoring scale used by Browning et al. was modified, and intrathecal fentanyl was not used for either group. They concluded that ondansetron effectively reduced post-spinal shivering in parturients undergoing elective caesarean delivery [16].

At the present time, very few studies have investigated the efficacy of 5-HT3 antagonists in managing perioperative shivering during caesarean section under neuraxial anaesthesia, and their results are conflicting [14-18]. Based on the current evidence, we would not recommend the use of 5-HT3 antagonists for the sole purpose of reducing perioperative shivering. On the other hand, 5-HT3 antagonists are proven safe in the peripartum period and are useful in reducing the risk of nausea and vomiting associated with opioids used for caesarean section.

NMDA receptor antagonists

N-methyl-d-aspartate (NMDA) receptor antagonists are known to modulate central thermoregulatory control mechanisms. Ketamine and magnesium sulphate have been studied for their antishivering properties in both obstetric and non-obstetric populations. Ketamine, a competitive NMDA receptor antagonist, plays a role in thermoregulation through a variety of mechanisms [19,20]. NMDA receptors modulate noradrenergic and serotonergic neurons in the locus coeruleus and consequently, the NMDA receptors in the dorsal horn of the spinal cord . Ketamine also causes central sympathetic stimulation and inhibition of norepinephrine uptake in postganglionic sympathetic nerve endings, causing vasoconstriction and ultimately decreased core-to-peripheral redistribution of heat [19].

Only two randomised controlled trials studying the effect of ketamine on preoperative shivering in the obstetric population were found [19,20]. Kose et al. compared the efficacy and safety of intravenous ketamine 0.25 mg/kg with ketamine 0.5 mg/kg to prevent shivering in patients undergoing caesarean delivery under spinal anaesthesia. They concluded that intravenous ketamine 0.25 mg/kg was as effective as 0.5 mg/kg in preventing shivering and lacked severe adverse effects [19]. Zabetian et al. did a comparative study on different doses of pethidine and ketamine for the prevention of shivering during and after spinal anaesthesia at caesarean section [20]. They concluded that 0.3 mg/kg of ketamine is more effective than 0.15 mg/kg of ketamine for controlling postoperative shivering.

Magnesium sulfate ($MgSO_4$) is a calcium antagonist and a noncompetitive antagonist of NMDA receptors. It is thought to act centrally to reduce the shivering threshold. Intrathecal $MgSO_4$ is primarily utilised to provide perioperative analgesia and to prolong the period of anaesthesia and sensory blockade without any additional side effects. Two RCTs evaluated its perioperative antishivering effect during caesarean section under neuraxial anaesthesia [21,22]. Faiz et al. in their RCT used 25 mg intrathecal $MgSO_4$ along with bupivacaine for the prevention of shivering during caesarean section under spinal anaesthesia [21]. They concluded that intrathecal

injection of $MgSO_4$ improved perioperative shivering within 10 to 20 minutes after block administration, but this effect did not persist. Furthermore, a reduction in core temperature was found 30 minutes following the neuraxial administration of $MgSO_4$. The authors concluded that an insufficient dose of $MgSO_4$ was used in this trial, and they recommend future research should record core temperature simultaneously with measures of shivering.

Yousef et al. studied the effects of adding magnesium sulphate 50 mg to epidural bupivacaine in patients undergoing elective caesarean section using combined spinal-epidural anaesthesia [22] and in the results it was found that the incidences of perioperative shivering were 6.6% vs. 20%. They concluded that adding magnesium sulphate improved intraoperative shivering as well as the quality of postoperative analgesia.

Overall, the small number of available studies show ketamine effective in reducing the incidence of shivering. However, ketamine has the potential to cause amnesia, which may be highly undesirable in the peripartum period. Additionally, it may also cause nausea, vomiting, and a dissociative mental state that may be distressing to some parturients. Neuraxial $MgSO_4$ is an off-label use and the current evidence of it reducing shivering remains undetermined. Taken together, NMDA antagonists should not be used for the sole purpose of reducing perioperative shivering.

Alpha-2 adrenergic agonists

Alpha-2 adrenergic agonists are widely used in clinical anaesthesia practice. Both clonidine and dexmedetomidine are being extensively utilised for their sedative, analgesic, sympatholytic, and antishivering properties. Studies in both the obstetric and non-obstetric populations have explored the antishivering efficacy of alpha-2 adrenergic agents. Alpha-2 adrenergic receptors are widely distributed in the hypothalamus, and they play a vital role in thermoregulation. At the hypothalamic level, alpha-2 receptor stimulation decreases the thermoregulatory threshold for shivering, and at the spinal cord level, they modulate cutaneous thermal inputs via descending inhibition, thus inhibiting shivering.

Zhang et al. did a meta-analysis studying dexmedetomidine as a neuraxial adjuvant for preventing perioperative shivering [23]. This study identified three trials utilising intrathecal dexmedetomidine of 5 to 10 µg, and two trials using 1 µg/kg epidurally. All these trials have concluded that neuraxial dexmedetomidine is effective in lowering the incidence and intensity of shivering in parturients undergoing caesarean section without significant adverse effects. In the subgroup analysis of these five obstetric studies, Zhang et al. concluded that intrathecal dexmedetomidine in the dosage of 5 to10 µg significantly reduced the incidence of perioperative shivering during caesarean section [23]. Many trials have also studied intravenous dexmedetomidine in obstetric patients for the management of shivering during caesarean section. A meta-analysis by Bao et al. [24] on intravenous dexmedetomidine during spinal anaesthesia for caesarean section concluded that dexmedetomidine can decrease the incidence of nausea, vomiting, and shivering after spinal anaesthesia during caesarean section, but at the cost of a higher incidence of maternal bradycardia and hypotension. Lamontagne et al. [25] conducted a clinical trial to treat shivering in parturients during caesarean delivery. They used a single IV bolus of 30 µg of dexmedetomidine in 80 healthy parturients who showed significant shivering during delivery. They concluded that a single intravenous bolus of dexmedetomidine decreased the duration of shivering for up to 15 min during caesarean delivery under neuraxial anaesthesia.

Overall, both neuraxial and systemic administration of dexmedetomidine appear effective in reducing the incidence and severity of perioperative shivering in caesarean section. Several undesirable side effects may prevent its wide adoption. Dexmedetomidine can cause maternal bradycardia and hypotension, which can impact fetal well-being. Further, there is a potential amnestic effect associated with systemic dexmedetomidine, even at low doses. As with many other agents mentioned in this review, neuraxial dexmedetomidine is an off-label use. We caution the use of intrathecal dexmedetomidine in preventing shivering, and systemic use may be considered after the baby's delivery, given its potential to cause maternal hypotension and amnesia.

Conclusion

Perioperative shivering in parturients undergoing lower segment caesarean section is a well-known and common complication of neuraxial anaesthesia. In our literature review, we studied the efficacy of various nonpharmacological and pharmacological techniques of prevention of shivering in the perioperative period. Prewarming and intraoperative warming are simple and effective interventions, although the effect seems to depend on the duration of treatment. Given the virtual lack of side effects, prewarming and intraoperative warming measures should be implemented whenever appropriate. Multiple pharmacological interventions, including opioids, 5-HT3 antagonists, NMDA receptor antagonists, and alpha-2 adrenergic agonists, have been studied. We recommend the use of an intrathecal opioid such as fentanyl to reduce the incidence and severity of shivering, as it is effective, safe, and associated with minimal side effects. Dexmedetomidine has also shown promising results, but at the cost of risk of amnesia and maternal bradycardia and hypotension; it thus may be better reserved for the postpartum period. Using

5-HT3 receptor antagonists and NMDA receptor antagonists for the sole purpose of treating perioperative shivering is not recommended, given the insufficient evidence supporting their use in the current literature.

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