Effectiveness of Ondansetron in controlling Post Spinal Anesthesia Shivering Induced By Hypothermia

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Abstract
Background: Shivering can be caused by neuraxial as well as general anaesthetics. Because of the heterogeneity of the studies, estimating the incidence of shivering secondary to neuraxial block is tricky, however it is estimated to be around 55%. Spinal anaesthesia lowers core body temperature faster than epidural anaesthesia in the first 30 minutes following the block. Both strategies cause the temperature to drop at the same rate after 30 minutes. the recovery unit. Shivering not only causes psychological stress in the patient, but it also causes physiological changes such as increased oxygen consumption by 200–600%, increased carbon dioxide production, increased blood pressure, increased risk of myocardial ischaemia, infection, and bleeding, and increased minute ventilation. It also causes hypoxaemia, lactic acidosis, increased intraocular pressure, and intracranial pressure, as well as impeding patient monitoring tools like the electrocardiogram (ECG), non-invasive blood pressure (NIBP), and peripheral oxygen saturation (SpO2). Temperature monitoring is required for patients receiving anaesthesia, but due to the unavailability of an accurate non-invasive core temperature monitor, core temperature is frequently under-monitored during spinal anaesthesia, and significant hypothermia often goes unnoticed in these patients. For monitoring core temperature, disposable thermocouple and thermistor probes are utilized. They are a reasonably accurate (±0.5°C), low-cost, and dependable method. Infrared monitors detect the heat emitted by radiation and can measure the temperature of the tympanic membrane and forehead skin, however they are less accurate
Keywords: hypothermia, Shivering, anaesthesia

Introduction

Shivering can be caused by neuraxial as well as general anaesthetics. Because of the heterogeneity of the studies, estimating the incidence of shivering secondary to neuraxial block is tricky, however it is estimated to be around 55%. Spinal anaesthesia lowers core body temperature faster than epidural anaesthesia in the first 30 minutes following the block. Both strategies cause the temperature to drop at the same rate after 30 minutes

Shivering may be attributed to a variety of causes, including modulation of thermoregulatory thresholds, changes in body heat distribution, reduction in body core temperature, and the cooling action of fluids injected into the neuraxis **[1]**.

Post-spinal shivering (PSS) is one of the most common reasons of patient discomfort inside the OR and in the recovery unit. Shivering not only causes psychological stress in the patient, but it also causes physiological changes such as increased oxygen consumption by 200–600%, increased carbon dioxide production, increased blood pressure, increased risk of myocardial ischaemia, infection, and bleeding, and increased minute ventilation. It also causes hypoxaemia, lactic acidosis, increased intraocular pressure, and intracranial pressure, as well as impeding patient monitoring tools like the electrocardiogram (ECG), non-invasive blood pressure (NIBP), and peripheral oxygen saturation (SpO_2) **[2]**.

Shivering during Neuraxial Anaesthesia

Shivering-like tremor is a frequent mishap throughout neuraxial anaesthesia, and it can be caused by one of four things: (1) normal thermoregulatory shivering responding to core hypothermia, (2) normal shivering in normothermic or even hyperthermic patients who are feverish, (3) direct stimulation of cold receptors in the neuraxis by administered local anaesthetic, and (4) non-thermoregulatory muscular activity that resembles shivering.

Other aetiologies, however, are still feasible. For example, until now there is not any established credible explanation for the severe shivering that frequently happens shortly after induction of spinal or epidural anaesthesia.

The majority of shivering accompanied with neuraxial anaesthesia appears to be typical shivering as a result of hypothermia. Shivering almost always follows core hypothermia and vasoconstriction (above the block level) in patients given neuraxial anaesthesia **[1]**.

Moreover, electromyographic studies reveal that the tremor is waxing and waning at a rate of 4 to 8 cycles per minute, which is consistent with typical shivering. Even in normothermic people, fever is characterised by a regulated increase in thermoregulatory response thresholds, which can cause shivering. Perioperative fever, on the other hand, is presumably a rather uncommon cause of shivering **[3]** .

Thermoreceptors in the spinal cord are found in all mammals and birds. Therefore, a neuraxial injection of a comparatively cool (i.e. room temperature) local anaesthetic may theoretically trigger shivering by activating local temperature sensors.

Shivering-like tremor isn't always thermoregulatory. Low-intensity shivering-like muscle activity can be detected in surgical patients and during labour. Although the reason of this muscular activity is uncertain, it is linked to pain and hence could be the product of sympathetic nervous system stimulation **[4]**.

Surface temperature influences thermoregulatory responses; therefore, any sort of shivering can be alleviated by warming the skin surface. This is also why, even when the core temperature did not have the time to change, shivering often stops in a matter of a few seconds when a person enters a warm room **[5]**.

Sentient skin warming, on the other hand, is expected to only compensate for slight losses in core temperature because the entire skin surface contributes 20% to thermoregulatory control while the lower body contributes around 10%. As one might assume, skin warming is only successful in a small percentage of people **[4]**.

Shivering must be treated quickly and efficiently since it is exceedingly unpleasant for the patient, increases oxygen consumption and metabolic rate, and has many of the negative effects listed above **[6]**.

Shivering that is moderate or severe will almost always necessitate pharmacologic intervention. Shivering during neuraxial anaesthesia can be treated with the same medications that are useful for shivering after general anaesthesia by lowering the threshold temperature even further. Meperidine, tramadol, ketamine, and magnesium sulphate are among them **[3]**.

Management of inadvertent hypothermia & Shivering during anaesthesia

Temperature Monitoring

Temperature monitoring is required for patients receiving anaesthesia, but due to the unavailability of an accurate non-invasive core temperature monitor, core temperature is frequently under-monitored during spinal anaesthesia, and significant hypothermia often goes unnoticed in these patients **[7]**.

For monitoring core temperature, disposable thermocouple and thermistor probes are utilized. They are a reasonably accurate (±0.5°C), low-cost, and dependable method. Infrared monitors detect the heat emitted by radiation and can measure the temperature of the tympanic membrane and forehead skin, however they are less accurate **[8]**.

The tympanic membrane, oesophagus, nasopharynx, and rectum are all preferred sites. These regions are anatomical areas of highly perfused tissues with a uniform and high temperature in relation to the rest of the body. Because of its higher fluctuations and that it is less representative of core temperature, skin surface monitoring is not regarded accurate or dependable **[9]**.

➢ Avoiding hypothermia during anaesthesia

Evaporation, conduction, radiation, and convection are the four main mechanisms that contribute to perioperative heat loss. To avoid unintentional perioperative hypothermia, several approaches have been devised. The most popular method is cutaneous warming, which can be accomplished through passive insulation or active warming **[10]**.

The simplest technique of cutaneous warming is passive insulation, although it is insufficient on its own. Cotton blankets, surgical drapes, plastic sheets and reflective composites are among the materials utilised. The layer of still air trapped beneath the device acts as an insulator. A single layer reduces heat loss by around 30%; adding more layers reduces heat loss only slightly more **[11]**.

Circulating-water mattresses/garments, forced air warming devices, resistive heating devices, negative pressure water warming systems, and radiant heaters are examples of active warming equipment. For intraoperative warming, forced air warming devices are the most often tested, recommended, and used technologies **[12]**.

In contrast, warming intravenous fluids does not warm patients, but contributes to prevent fluid-induced hypothermia in patients given large volumes of fluid as Administration of large quantity of cold fluids causes significant heat loss. One unit of refrigerated blood or one-litre crystalloid at room temperature can reduce mean body temperature by 0.25°C **[12]**.

The temperature of the operating room has the greatest impact on heat loss from skin radiation and convection, as well as evaporation from large surgical incisions. During induction and while the patient is prepped and draped, the operating room should be warmed to at least 24°C. If the room temperature drops below 21°C, all patients become hypothermic. The room temperature can be adjusted to a suitable level for the staff once warming devices have been applied to the patient **[13]**.

Device	Mechanism of action	Advantage	Disadvantage	Remarks
Circulating water mattresses	Conduction	No ambience warming	Take 2-3 times longer than forced air warmers, nearly ineffective, cover only posterior surface, need unimpeded high thermal contact with well-perfused skin, pressure point ischemia, limited warming capacity in lateral or lithotomy positions	Heated water is passed within a mattress, more effective and safer when placed over patients rather than under them
Circulating water garments	Conduction	Can transfer large amounts of heat, outperform forced air warmers, low risk of burns, no ambience warming	Bulky, risk of water leakage	Access both anterior and posterior surfaces of body
Forced air warmers	Convection	Readily available, completely eliminate heat loss, remarkably safe, reduce convective and radiant heat losses, fast warm up time, high warming capacity, do not cause burns, useful for rewarming	Can disrupt laminar air flow patterns, may harbor microbial pathogens, can contaminate surgical site, costly, warm ambience	Heated air is distributed through a specially designed blanket that circulates warm air around body, efficacy depends on blanket properties and surface area covered
Resistive heating devices	Conduction	Reusable, energy efficient, easy to clean, cost effective, good alternative to forced air warmers, do not interfere with surgical site	Can cause burns, long warm up time	Low voltage electric current is passed through semiconductive polymer or carbon fiber systems to generate heat
Negative pressure water warming systems			Can cause burns, role in intraoperative setting questionable since already vasodilated	Apply subatmospheric pressure with a thermal load improving subcutaneous perfusion and opening AV shunts, promote periphery to core transfer of heat
Radiant heaters	Radiation	Fast warm-up time, good warming capacity	Bulky, warm ambience, risk of burns	Used in postanesthesia recovery room

AV=Arteriovenous

Figure 1: *Comparison of various cutaneous active warming devices*[45]

Pharmacological methods of PSS prophylaxis:

Opioids, α2-agonists, anticholinergics, central nervous system stimulants, and corticosteroids have all been demonstrated to be beneficial in the prevention and treatment of PSS. Owing to temperature modulation, it is strictly regulated by a complex and multilevel control loop including thermal receptors, the spinal cord, brain stem, anterior hypothalamus, and cerebral cortex; targeted antishivering therapy is complicated and comprises a wide variety of drugs **[14]**.

Centrally acting analgesics (tramadol), opioid agonists (pethidine, fentanyl), cholinesterase inhibitors (physostigmine), and NMDA antagonists (ketamine, magnesium sulphate) were all highly effective antishivering medications However, due to varied adverse effects, only a handful of them were suggested for the prevention of PSS **[15]**.

- **Opioid receptor agonists:**

Pethidine has a therapeutic impact on PSS, and its mechanism is most likely linked to the activation of the κ and μ-opioid receptors, which act primarily on the central nervous system. It is the only opioid that acts as an agonist at both receptors, which are linked to the pathophysiology of shivering by lowering the shivering threshold and causing a drop in core temperature, resulting in an anti-shivering action. The most frequent intravenous medication used to treat and prevent shivering is pethidine. Taking the side effects into account, findings of the research showed that pethidine might cause nausea and vomiting, as well as respiratory depression **[16]**.

Tramadol is a synthetic opioid that works in a variety of ways. It is a weak agonist for μ-opioid receptors, with little activity for κ- or σ-receptors. It's also a partial norepinephrine (NE) and 5-hydroxytryptamine (5HT) inhibitor. At therapeutically relevant concentrations, tramadol is said to block the N-Methyl-D-Aspartate (NMDA) receptor **[14]**.

N-Methyl-D-aspartate receptor antagonist:

Ketamine is a non-competitive NMDA receptor antagonist that inhibits postganglionic NE uptake, resulting in a central sympathomimetic action. It also has the effect of reducing the core-to-peripheral heat distribution **[18]**.

Magnesium sulphate is a natural calcium antagonist and is a non-competitive antagonist of NMDA receptors. The medication not only has a central impact, but also acts as a modest muscle relaxant, which may help to minimise the shivering gain (incremental shivering intensity with progressing hypothermia) **[19]**.

Others:

Other agents for the treatment and prevention of PSS have been explored. The cholinergic system of physostigmine suppresses post-anaesthetic shivering (PAS), although it can also cause nausea and vomiting, as well as an increase in heart rate and blood pressure **[18]**.

Doxapram, a stimulant used to treat respiratory failure, had been shown to reduce PSS, although it had a negative effect on haemodynamics **[18]**.

In patients receiving day care knee arthroscopy under general anaesthesia, hydrocortisone (1–2 mg/kg IV) is an effective prophylactic against postoperative shivering **[9]**.

One of the most studied effective antishivering medications is nefopam, a centrally acting analgesic that inhibits synaptosomal reuptake of three neurotransmitters: dopamine, NE, and serotonin **[20]**.

Moreover, antiserotonergic Ondansetron and α_2-central agonists Dexmedetomidine are recently used in prevention of PSS with effective results and fewer side effects **[21]**.

Antiserotonergic agents

Ondansetron is a highly specific and selective serotonin 5-HT_3 receptor antagonist, with low affinity for dopamine receptors.

Molecular Formula

$C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$

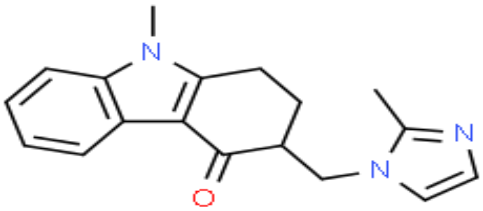

Figure 3: *Molecular formula of Ondansetron*[91]

Pharmacokinetic

Ondansetron is extensively degraded by numerous hepatic cytochrome P-450 enzymes and eliminated in the urine and faeces after oral intake or intravenous (IV) injection **[22]**.

Pharmacodynamics

Mechanism of action as anti-shivering

5-HT3 receptors are found both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the region postrema in the medulla. In response to chemotherapeutic drugs, enterochromaffin cells in the small intestine release serotonin, which may stimulate vagal afferents via 5-

HT3 receptors, triggering the vomiting reflex. Ondansetron's antiemetic effect is assumed to be mediated mostly through antagonism of vagal afferents, with a slight complement from antagonism of central receptors **[13]**.

Serotonin (5-hydroxytryptamine), a biochemical amine present in the brain and spinal cord, is involved in shivering thermoregulation and neurotransmission **[23]**. Serotonin antagonism appears to limit the human thermal set range, lowering metabolic cold defences and the unpleasantness of perioperative hypothermia **[24]**.

The hypothalamus's preoptic area releases 5-HT3 to activate heat-producing pathways and raise body temperature. By inhibiting 5-HT reuptake in the preoptic area, 5-HT3 antagonists may help to reduce postoperative shivering **[15]**.

5-HT3 receptor antagonists have recently gained popularity as a prophylaxis for postoperative shivering. According to previous studies, 5-HT3 receptor antagonists appear to be almost as effective as pethidine in preventing postoperative shivering **[11]**.

Using of weight adjusted dose of Ondansetron (0.1mg/kg) was according to volume of distribution according to relation between binding volume to albumin and free one. The more volume free of drug the more drug excretion that means according to pharmacokinetic that Ondansetron is dose dependant drug. Therefore, using of dose dependant of Ondansetron is more efficient to avoid low dosing decreasing the effectiveness or overdosing increasing the side effects of it. Also, several studies reveals the efficacy of weight adjusted Ondansetron over fixed doses in preventing of shivering comparing to fixed doses **[12, 25,26]**.

Recent studies established that treatment with Ondansetron is safe in the obstetric population and may reduce PSS **[38]**. This result corroborates the use of Ondansetron to prevent PSS, but its effectiveness and safety are still debatable **[27]**.

Also, because of the low incidence of sedation, hypotension and bradycardia. It offers a potential advantage in geriatric anaesthesia **[28]**.

Side effects

The most commonly reported side effects (occurring in more than 10% of adults) include headaches, fatigue, dry mouth, malaise, and constipation. Less common effects range from central nervous system (CNS) manifestations, such as drowsiness and sedation, to local injection site reactions and pruritus **[29,30]**.

Although typically clinically insignificant, ECG interval changes such as QTc elongation can be seen. These changes typically occur within 1 to 2 hours after administration, returning to baseline within 24 hours IV administration has a higher risk for arrhythmias; consequently, the FDA does not recommend a single dose greater than 16 mg IV **[31,32]**.

References

1. **Crowley, L.J. and D.J**. Buggy, Shivering and neuraxial anesthesia. Reg Anesth Pain Med, 2008. 33(3): p. 241-252.
2. **Bozgeyik, S., et al.,** The effects of preemptive tramadol and dexmedetomidine on shivering during arthroscopy. Saudi J Anaesth, 2014. 8(2): p. 238-243.
3. **De Witte, J. and D.I. Sessler,** Perioperative shivering: physiology and pharmacology. J Am Soci Anesthesiol, 2002. 96(2): p. 467-484.
4. **Lopez, M.B.,** Postanaesthetic shivering–from pathophysiology to prevention. Rom J Anaesth Intensive Care, 2018. 25(1): p. 73-81.
5. **Sessler, D.I.,** Perioperative thermoregulation and heat balance. Lancet, 2016. 387(10038): p. 2655-2664.
6. **Kimberger, O., E**fiects of Anaesthesia on Thermoregulation, in Personalized Anaesthesia: Targeting Physiological Systems for Optimal Effect, P.L. Gambús and J.F. Hendrickx, Editors. 2020, Cambridge University Press: Cambridge. p. 222.
7. **du Toit, L., et al.,** Core temperature monitoring in obstetric spinal anesthesia using an ingestible telemetric sensor. Anesth Analg, 2018. 126(1): p. 190-195.
8. **Cattaneo, C.G., et al.,** The accuracy and precision of body temperature monitoring methods during regional and general

anesthesia. Anesth Analg, 2000. 90(4): p. 938-945.
9. **Díaz, M. and D.E.** Becker, Thermoregulation: physiological and clinical considerations during sedation and general anesthesia. Anesth Prog, 2010. 57(1): p. 25-33.
10. **Bräuer, A. and M.** Quintel, Forced-air warming: technology, physical background and practical aspects. Curr Opin Anesthesiol, 2009. 22(6): p. 769-774.
11. **Rao, S. and M.** Rajan, Heat production and loss. Update Anaesth, 2008. 24(2): p. 182-187.
12. **John, M., J.** Ford, and M. Harper, Peri-operative warming devices: performance and clinical application. Anaesthesia, 2014. 69(6): p. 623-638.
13. **Sultan, P., A. Habib, and B.** Carvalho, Ambient operating room temperature: mother, baby or surgeon? BJA: Br J Anaesth, 2017. 119(4): p. 839-839.
14. **Park, S.M., et al.,** Efficacy spectrum of antishivering medications: meta-analysis of randomized controlled trials. Crit Care Med, 2012. 40(11): p. 3070-3082.
15. **Kurz, A.,** Physiology of thermoregulation. Best Pract Res Clin Anaesthesiol, 2008. 22(4): p. 627-644
16. **Dabir, S., et al.,** The efficacy of a single dose of pethidine, fentanyl and morphine in treating postanesthesia shivering. Pak J Pharm Sci, 2011. 24(4): p. 513-517.
17. **Lema, G.F., et al.,** Efficacy of intravenous tramadol and low-dose ketamine in the prevention of post-spinal anesthesia shivering following cesarean section: a double-blinded, randomized control trial. Int J Womens Health, 2017. 9(1): p. 681-688.
18. **Ameta, N., et al.,** Comparison of prophylactic use of ketamine, tramadol, and dexmedetomidine for prevention of shivering after spinal anesthesia. J Anaesthesiol Clin Pharmacol, 2018. 34(3): p. 352-356.
19. **Wadhwa, A., et al.,** Magnesium sulphate only slightly reduces the shivering threshold in humans. Br J Anaesth, 2005. 94(6): p. 756-762.
20. **Kim, Y.A., et al.,** Comparison of meperidine and nefopam for prevention of shivering during spinal anesthesia. Korean J Anesthesiol, 2013. 64(3): p. 229-233.

21. **Hou, X.-M., et al.** Ondansetron Reduces the Incidence of Hypotension after Spinal Anaesthesia: A Systematic Review and Meta-Analysis. Pharmaceuticals, 2022.
22. **Aho, M., et al.,** The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. J Am Soc Anesthesiol, 1991. 74(6): p. 997-1002.
23. **Huddart, R., R.B**. Altman, and T.E. Klein, PharmGKB summary: Ondansetron and tropisetron pathways, pharmacokinetics and pharmacodynamics. Pharmacogenet Genomics, 2019. 29(4): p. 91-97.
24. **Nallam, S.R., K.** Cherukuru, and G. Sateesh, Efficacy of intravenous ondansetron for prevention of postspinal shivering during lower segment cesarean section: A double-blinded randomized trial. Anesth Essays Res, 2017. 11(2): p. 508-513.
25. **Mahoori, A., et al**., Comparison of ondansetron and meperidine for treatment of postoperative shivering: a randomized controlled clinical trial. Iran Red Crescent Med J, 2014. 16(8): p. e13079.
26. **Abdelhameed, S.M**., Comparison of weight-adjusted dose versus fixed dose ondansetron in Prevention of shivering following spinal anaesthesia for caesarean deliveries. Al-Azhar International Medical Journal, 2021. 2(6): p. 41-47.
27. **Rajib, H. a**nd C. Ananya, Comparison of Weight-Adjusted Dose versus Fixed Dose Ondansetron in Preventing Shivering Following Spinal Anaesthesia for Caesarean Deliveries. Journal of Evolution of Medical and Dental Sciences, 2022. 11(12): p. 898-903.
28. **Li, M., et al.,** Meta-analysis of randomized controlled trials on the efficacy and safety of ondansetron in preventing postanesthesia shivering. Int J Surg, 2016. 35: p. 34-43.
29. **Browning, R.M., et** al., Prophylactic ondansetron does not prevent shivering or decrease shivering severity during cesarean delivery under combined spinal epidural anesthesia: a randomized trial. Reg Anesth Pain Med, 2013. 38(1): p. 39-43.
30. **Owczuk, R., et al.,** Ondansetron attenuates the decrease in blood pressure due to spinal anesthesia in the elderly: a double blind, placebo-controlled study. Minerva Anestesiol, 2015. 81(6): p. 598-607.
31. **Khan, R.B.,** Migraine-type headaches in children receiving chemotherapy and ondansetron. J Child Neurol, 2002. 17(11): p. 857-8.
32. **Fernandes, F.M., et al.,** Assessment of the risk of QT-interval prolongation associated with potential drug-drug interactions in patients admitted to Intensive Care Units. Saudi Pharm J, 2019. 27(2): p. 229-234