ORIGINAL ARTICLE

ROLE OF GRANISETRON IN MINIMISING USE OF MEPERIDINE AS A RESCUE DRUG FOR POST SPINAL SHIVERING

Maheen Wahid, Shabana Ali, Mudassar Noor, Kulsoom Farhat

Department of Pharmacology, Army Medical College, National University of Medical Sciences, Rawalpindi-Pakistan

Background: Shivering is one of the most common adverse outcomes associated with the administration of spinal anaesthesia, which, when clinically relevant, leads to numerous detrimental effects on the human body. Hence, its management becomes imperative. Meperidine, an opioid analgesic, is the drug of choice for this condition. However, the use of meperidine is controversial, as it carries the devastating adverse effect of respiratory depression. We explored the role of granisetron, a $5HT_3$ antagonist and a commonly used antiemetic premedication, in minimising the incidence of post-spinal shivering and decreasing the use of meperidine as a rescue drug. **Methods:** Overall, 160 parturient patients, between the ages 18–50, undergoing uncomplicated, elective caesarean section, were enrolled in the study, and randomized into two groups with 80 participants each: Group A received 3ml of normal saline, and Group B was administered 3 mg granisetron,15 minutes before spinal anaesthesia institution. Incidence of clinically relevant shivering (score of 3 or more) was noted, and it was recorded whether meperidine was used or not. **Results:** 67.5% of participants in Group A, and 32.5% of patients in Group B, experienced clinically relevant shivering, with 62.5% of patients in Group A and 28.75% in Group B warranting the use of meperidine. There was a statistically significant difference between the two groups in terms of incidence of clinically relevant shivering, and meperidine consumption (*p*-value <0.001). **Conclusion:** Premedication with 3 mg granisetron effectively attenuates the occurrence of post-spinal shivering and, hence, lowers the requirement of meperidine as rescue medication.

Keywords: Granisetron; Spinal; Anaesthesia; Shivering; Meperidine

Citation: Wahid M, Ali S, Noor M, Farhat K. Role of granisetron in minimising use of meperidine as a rescue drug for post spinal shivering. J Ayub Med Coll Abbottabad 2023;35(4):530-3.

DOI: 10.55519/JAMC-04-11651

INTRODUCTION

Spinal anaesthesia is the technique of choice for the performance of multiple surgical procedures, owing to the various advantages it carries when compared to general anaesthesia (lack of intubation, negligible danger of pulmonary aspiration, brief stay in hospital, and faster recovery).[1]

However, there are numerous problems associated with the use of spinal block – the most injurious of which is shivering,[2] which is defined as involuntary, asynchronous contractions of body musculature, aimed to raise the heat production of the body.[3] Even though it is a defensive mechanism aimed at elevating the body temperature, excessive or intractable shivering can jeopardize the health of the patient undergoing surgical procedures, by enhancing oxygen demand and carbon dioxide generation, precipitating lactic acidosis,[4] and escalating the metabolic rate of the body up to six times the normal.[5] Elevated oxygen consumption ultimately precipitates a rise in intraocular and intracranial pressures, and may even lead to myocardial ischemia. Unrestricted shivering can also manifest mechanical problems, such as postoperative wound disruption (increasing the risk of surgical site infections), and interfering with blood pressure, electrocardiogram (ECG), and oxygen saturation monitoring (spO_2). Additionally, shivering restricts skin to skin contact between mother and neonate after delivery.[6] It is reported that about 20–80% of patients experience clinically severe shivering after spinal block institution, with a higher incidence in parturient subjects.[7]

As shivering is a significant clinical challenge faced by anaesthetists and surgeons, and a major jeopardy to the well-being of patients, management of this adverse condition becomes vital. Meperidine, an opioid analgesic, is considered the drug of choice in this regard. It is widely used in surgical setups for the effective management of post spinal shivering. However, meperidine carries a significant risk of respiratory depression, and therefore poses peril to the patient, warranting continuous monitoring and provision of supplemental oxygen.[8] Consequently, there is a growing interest worldwide in exploring newer agents with a safer pharmacological profile that can be used for the prevention of shivering altogether, and hence lower the requirement of meperidine as a rescue medication for post spinal shivering. Granisetron, a $5HT_3$ antagonist and a very potent antiemetic,[9] is being recently employed for this purpose.

In neuraxial block, two major factors contribute to creating a mild hypothermic environment. Firstly, there is dysregulation of temperature control at the level of the central nervous system. Secondly, sympathetic blockade leads to loss of vascular tone, and hence vasodilatation in the regions that are blocked, due to which blood moves from the central compartment to the periphery, and heat is lost from the body. This mild hypothermia acts as a stimulus to activate the heat generating pathways via activation of $5HT_3$ receptors in the preoptic region of the anterior hypothalamus.[10] Therefore, the occurrence of clinically relevant shivering will be attenuated by prophylactic blockade of these receptors, which will lead to a lower consumption of meperidine as a rescue medication. In this study, we aimed to investigate the effectiveness of granisetron in the prevention of post spinal shivering, and ultimately in the attenuation of meperidine consumption, in parturient patients.

MATERIAL AND METHODS

This prospective comparative study was conducted in the Anaesthesiology Department at Combined Military Hospital, Rawalpindi, in collaboration with the Department of Pharmacology at Army Medical College, from October 2021 to September 2022. Ethical approval was taken from the Ethics Review Committee of both institutions. We conducted the study following the STROBE checklist, and by the rules of the Declaration of Helsinki, at the gynaecology operating complex in CMH. One hundred and sixty female patients undergoing uncomplicated elective caesarean section were enrolled in the study. Informed consent for enrolment in the study was taken from all participants. Non-probability convenience sampling was done and eligible participants were enrolled in the study. They were then randomised into two groups: Group A was administered 3 ml of normal saline intravenously (IV), and participants in Group B were administered 3 mg of granisetron IV as part of their pre-anaesthetic medication. Normal saline or granisetron, as allocated after randomisation, was administered 15 minutes prior to the institution of spinal anaesthesia. Patients eligible for enrolment in the study were pregnant females, 18–50 years of age, scheduled to undergo elective caesarean section, having ASA Grade II or below. Those patients with known hypersensitivity to the study drug, any contradiction to spinal anaesthesia, with a history of neuropsychiatric or thyroid disease, reaching anaesthetic level rise more than T4 (assessed by skin test), having intraoperative bleeding higher than 1 litre, those receiving blood transfusions during surgery, and those with body core temperature below 36.5 °C and above 38 °C at any time during the procedure, were all excluded from the study. Demographic details and a comprehensive medical history were taken from all participants. Age, weight and gestational age were recorded. Standard monitoring techniques (pulse oximetry and ECG) and pulse oximetry were used for all patients. The air conditioner settings were maintained between 24°C and 26°C for all cases.

After being preloaded with warm 10 ml/kg Ringer's Lactate, pre-anaesthetic medication was administered as per protocol. Using a 25-gauge spinal needle, a spinal block was then instituted, with 10–15 mg of 0.5% hyperbaric bupivacaine. All patients were covered in a single blanket. An infusion of warm Ringer's Lactate (15 ml/kg/hr) was administered throughout the procedure, and intraoperative blood loss was recorded at the end of the surgery. This procedure was uniform for all participants in the study.

Once the spinal block was achieved, patients were assessed for any incidence of shivering, every 5 minutes up to 1-hour post anaesthesia, based on the Crossley and Manjahan scoring system:[7]

- score 0 = no shivering
- score 1 = one or more of piloerection, peripheral cyanosis, or peripheral vasoconstriction, without muscular rigidity
- score 2 = visible muscular activity in one muscle group
- score 3 = visible muscular activity in more than one muscle group
- score 4 = gross muscular activity involving the whole body.

A score of 1 and 2 was considered as mild shivering. Clinically relevant shivering was defined as a score of 3 or more. If any patient developed clinically relevant shivering lasting for more than 3 minutes, meperidine was administered for its control, and the premedication was considered ineffective.

Core body temperature was recorded every 5 minutes up to 1 hour post anaesthesia, using a tympanic thermometer. This was done to ensure that the body temperature remained within the appropriate range of 36.5–38 °C. Since the core temperature was consistently monitored every 5 minutes, any increase or decrease in body temperature was countered by altering the room temperature, temperature of infusions, and number of blankets on the patient.

World Health Organisation sample size calculator was used to calculate a minimum sample size of 40 (with a confidence interval of 95%, and a *p*-value less than 0.05 as significant). However, we enrolled 160 patients to augment the power of the study.

IBM-SPSS version 28 was used for statistical analysis. Shapiro Wilks test was employed to check the normality of data. Qualitative parameters were reported as frequencies and percentages, whereas quantitative characteristics were reported as mean and standard deviation (SD), or median and interquartile range (IQR), as was appropriate. The chi-square test was used to analyse qualitative parameters. Independent t-test and Mann-Whitney U test were used to analyse quantitative parameters. A p-value <0.05 was considered as significant.

RESULTS

The participants in both groups were analysed based on their demographic and clinical characteristics: age, weight, gestational age and intraoperative blood loss. These variables were statistically comparable among both groups, as is shown in table-1.

The percentage of patients experiencing mild and clinically relevant shivering in each group is shown in table 2. There was no statistically significant difference between both groups in preventing the incidence of mild shivering (*p*-value = 0.677). However, patients in Group B experienced a significantly lesser incidence of clinically relevant shivering (*p*-value <0.001). The frequency and percentages of patients requiring meperidine in each study group are also shown in Table 2. A lower number of patients in Group B warranted the use of meperidine as compared to those in Group A, and this difference was statistically significant (*p*-value <0.001)

Table-1: Demographic, clinical and surgery-related characteristics of study participants in both groups

Variables	Group A	Group B	*p*-value
Age in years (mean±SD)	29.48±3.865	29.20±4.518	0.252
Weight in kg (mean±SD)	73.13±13.156	72.33±13.277	0.883
Blood loss in mL (median (IQR))	225 (150-300)	200 (150-300)	0.463
Gestational age in weeks (mean±SD)	38.10±1.208	38.35±1.115	0.948

Table-2: Frequency and percentage of patients experiencing mild and clinically relevant shivering in both groups

	Group A	Group B	*p*-value
Mild shivering (score 1 OR 2)	15 (18.75%)	13 (16.25%)	0.677
Clinically relevant shivering (score 3 OR 4)	54 (67.5%)	26 (32.5%)	<0.001*
Meperidine needed	50 (62.5%)	23 (28.75%)	<0.001*

*=significant

DISCUSSION

The use of spinal anaesthesia is escalating with time due to the innumerable merits it possesses in comparison to general anaesthesia. In caesarean section, the use of a spinal block becomes imperative, as there are two different individuals involved, the mother and the foetus, and the universally depressant effects of general anaesthesia can jeopardize maternal and foetal health. Despite the added advantages of spinal anaesthesia, the adverse effects it manifests can themselves bring significant harm to the patient as well as the neonate. Shivering induced by the spinal block may prove to be injurious to the patients, not only via physical disruption of the incision and site of surgery but also through metabolic derangements in the body (higher O2 consumption, lactic acidosis, myocardial ischemia, raised intraocular and intracerebral pressures).[11] Hence, spinal anaesthesia-induced shivering is a major clinical challenge for anaesthetists and surgeons, and management of this unfavourable outcome becomes crucial to prevent subsequent complications. Employment of meperidine is the mainstay of treatment for this colossal drawback of spinal anaesthesia. However, meperidine is brought to use once shivering has already occurred, and it carries a wide spectrum of untoward effects, the most devastating of which is respiratory depression.[8]

Hence, the development of newer approaches is essential to manage the drawbacks associated with spinal block and minimise the use of rescue drugs. Recently, there has been a growing interest in exploring the use of 5HT3 antagonists as premedication to prevent shivering in patients undergoing caesarean section under spinal anaesthesia. This novel study was designed to evaluate the preventive role of commonly used antiemetic, granisetron, as premedication, in Pakistani parturient subjects, so that this well-tolerated drug with a favourable safety profile may replace and minimise the use of meperidine during surgical procedures performed under spinal anaesthesia.

In our study, granisetron appreciably mitigated the incidence of clinically relevant shivering and lowered the consumption of meperidine as rescue anti-shivering medication. These findings coincide with those of a study carried out by Isngadi and his colleagues in 2019. Twenty-three parturient women, scheduled to undergo elective caesarean section, were enrolled and divided into two groups, with one receiving 10 µg/kg granisetron, and the other receiving no premedication. Isngadi *et al*. deduced that 10 µg/kg granisetron effectively prevents post spinal shivering and reduces the need for rescue anti-shivering medication.[7] Similarly, Khajuria and Farooqi conducted a study in 2020 enrolling 100 participants undergoing elective caesarean section under spinal block. One group was administered 3mg granisetron whereas the other group did not receive any drug. It was demonstrated that patients receiving granisetron had a much lower incidence of post spinal shivering, without any adverse effects.[12] These findings support the results of our study. Additionally, Abdelsalam, in 2020, compared the effects of prophylactic granisetron, meperidine and tramadol in three groups with 20 participants each, undergoing various procedures under spinal anaesthesia. He proved that all three drugs are equally effective in preventing post spinal shivering, but participants in the granisetron group did not experience any adverse effects, whereas patients in the tramadol and meperidine group experienced sedation and a fall in

respiratory rate, establishing the suitability and safety of granisetron as premedication.[13] These findings are advocated in our study as well. Similarly, Abotaleb *et al*. conducted a study comparing prophylactic use of 40 µg dexmedetomidine and 2 mg granisetron in 120 patients and found that both drugs have similar efficacy in the prevention of perioperative shivering and in lowering the requirement of rescue drugs, with granisetron having an added advantage of maintaining hemodynamic integrity as well.[14] Hence, this study supports the role of granisetron as an appropriate premedication for the prevention of post spinal shivering, a finding endorsed by the results of our study.

In the present study, a dose of 3 mg granisetron was employed. A study by Gargari and Anvari enrolled 90 participants undergoing septorhinoplasty under general anaesthesia and compared the preventive effects of two different doses of granisetron (1 mg and 3 mg) on post spinal shivering.[15] Similarly, Dehghanpisheh carried out a study on 244 parturient patients and compared the effects of 1 mg and 3 mg granisetron in preventing shivering and nausea induced by spinal anaesthesia.[16] Both these studies have established that 3 mg is significantly superior to a dose of 1 mg. Since granisetron exerts its action in a dose dependent manner, and carries no adverse effects, even at higher therapeutic doses,[17] 3 mg granisetron is established as the most optimum and ideal dose, and therefore used in the present study.

Hence, our study proved that the 5HT3 antagonist, granisetron, at a dose of 3 mg, is an ideal drug to be used as premedication before spinal anaesthesia to prevent clinically relevant shivering and attenuate the use of meperidine. Multiple references from literature support and further prove the findings of our study, and hence, provide valid and strong evidence to advocate the recommendation that granisetron should be added to a pre-anaesthetic medication protocol.

Source of funding: National University of Medical Sciences.

AUTHORS' CONTRIBUTION

MW: Conceived, designed, data collection, statistical analysis, interpretation, write-up. SA: Supervision, literature search, proofreading. KF, MN: Review, final proofreading along with ensuring accuracy of the data.

REFERENCES

1. Capdevila X, Aveline C, Delaunay L, Bouaziz H, Zetlaoui P, Choquet O, *et al*. Factors determining the choice of spinal versus general anesthesia in patients undergoing ambulatory surgery: results of a multicenter observational study. Adv Ther 2020;37(1):527–40.
2. Luggya TS, Kabuye RN, Mijumbi C, Tindimwebwa JB, Kintu A. Prevalence, associated factors and treatment of post spinal shivering in a Sub-Saharan tertiary hospital: a prospective observational study. BMC Anesthesiol 2016;16(1):100.
3. Arnold JT, Hemsley Z, Hodder SG, Havenith G, Lloyd AB. Reliability and validity of methods in the assessment of cold-induced shivering thermogenesis. Eur J Appl Physiol 2020;120(3):591–601.
4. Lopez MB. Postanaesthetic shivering–from pathophysiology to prevention. Rom J Anaesth Intensive Care 2018;25(1):73–81.
5. Buggy DJ, Crossley AW. Thermoregulation, mild perioperative hypothermia and post-anaesthetic shivering. Br J Anaesth 2000;84(5):615–28.
6. Zhang J, Zhang X, Wang H, Zhou H, Tian T, Wu A. Dexmedetomidine as a neuraxial adjuvant for prevention of perioperative shivering: Meta-analysis of randomized controlled trials. PLoS One 2017;12(8):e0183154.
7. Isngadi I, Jaya W, Fardian D. The effect of low-dose granisetron on shivering in subarachnoid block. Bali J Anesth 2019;3(3):166.
8. Boyle JM, McCall KL, Nichols SD, Piper BJ. Declines and pronounced regional disparities in meperidine use in the United States. Pharmacol Res Perspect 2021;9(4):e00809.
9. Kothari S, Porwal S, Gupta CM, Nigam AK. Comparative evaluation of Ondansetron and Granisetron in combination with Dexamethasone for the prophylaxis of chemotherapy and radiation induced emesis in cervical cancer patients: A prospective study. Int J Health Clin Res 2021;4(11):23–7.
10. Nallam SR, Cherukuru K, Sateesh G. 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):508–13.
11. Biswa D, Sharma A, Gogna RL. Comparative assessment of clonidine and tramadol on post-spinal anaesthesia shivering among patients with lower abdominal and lower limb surgeries. IJMA 2021;4(2):130–2.
12. Khajuria K, Farooqi AK. Efficacy of granisetron in the prevention of shivering during caesarean section under spinal anaesthesia. JMS SKIMS 2020;23(Suppl 1):573.
13. Abdelsalam Y. A comparative study between pethidine, granisetron and tramadol in prophylaxis against perioperative shivering after spinal anesthesia. Int J Med Arts 2020;2(1):292–300.
14. Abotaleb UI, Abdalla AM, Abdelrahman AS, Gad GS, Elsayed AM. Dexmedetomidine versus granisetron for the management of postspinal shivering. Ain-Shams J Anaesth 2016;9(4):517.
15. Gargari RM, Anvari HM. Effect of Different Doses of Granisetron on Preventing Postoperative Shivering in Patients undergoing Septorhinoplasty under General Anesthesia. Adv Biosci Clin Med 2017;5(2):21–6.
16. Dehghanpisheh L, Azemati S, Hamedi M, Fattahisaravi Z. The effect of 1-mg versus 3-mg granisetron on shivering and nausea in cesarean section: a randomized, controlled, triple-blind, clinical trial. Braz J Anesthesiol 2021;72(4):457–65.
17. Morgan GE, Mikhail MS, Murray MJ. Clinical Anesthesiology. 6th ed. New York: McGraw-Hill; 2018.

Submitted: March 14, 2023	*Revised: August 3, 2023*	*Accepted: September 9, 2023*

Address for Correspondence:
Dr. Maheen Wahid, House-3, Street-5, Sector-C, DHA Phase-1, Islamabad-Pakistan
Email: maheenwahid92@gmail.com