Comparison of Weight-Adjusted Dose versus Fixed Dose Ondansetron in Preventing Shivering Following Spinal Anaesthesia for Caesarean Deliveries

Rajib Hazarika[1], Ananya Choudhury[2]

[1, 2] Department of Anaesthesiology & Critical Care, Gauhati Medical College and Hospital, Guwahati, Assam, India.

ABSTRACT

BACKGROUND

Spinal anaesthesia is the preferred method of anaesthesia in parturients undergoing both elective and emergency lower-segment caesarean section. A common complication of spinal anaesthesia is shivering. Shivering increases perioperative heart rate and oxygen consumption by 5 times and also increases the metabolic demand by 100 times, thereby increasing chances of myocardial ischemia, hypoxia, hypoxemia and later lactic acidosis. In this study, we wanted to compare the incidence of shivering following spinal anaesthesia when a weight-adjusted dose versus a fixed dose of ondansetron is used during caesarean delivery.

METHODS

This was a hospital-based randomized double-blinded (patient and observer blinded) single hospital-based study conducted among 190 pregnant patients who underwent elective caesarean delivery under spinal anaesthesia in the Department of Anaesthesiology and Critical Care, Gauhati Medical College and Hospital, Guwahati from 1st August 2021 to 31st July 2022 after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants. The patients were divided into two groups: group 1 (patients who received a weight-adjusted dose of ondansetron at 0.1mg/kg) and group 2 (patients who received fixed-dose ondansetron).

RESULTS

Shivering occurred in 11 patients (11.6 %) in group 1 and 21 patients (22.1 %) in group 2, but there was no statistical difference between the two groups (p-value 0.053) (using the chi-square test). 10 patients (10.5 %) developed grade I shivering and 1 patient (1.1 %) developed grade II shivering in group 1. In group 2, 10 patients (10.5 %) developed grade I shivering and 11 patients (11.6 %) developed grade II shivering (P-value - 0.0163) which was statistically significant (using chi-square test). Nausea occurred in 2 patients (2.1 %) in group 2 while no incidence of nausea was seen in group 1. Incidence of headache was seen in both groups; 1 patient (1.1 %). There was no statistical difference between the adverse effects of the groups.

CONCLUSIONS

The severity of shivering was lower in the weight-adjusted dose at 0.1 mg/kg ondansetron group in patients undergoing spinal anaesthesia for caesarean delivery. The incidence of shivering was comparable in both the weight-adjusted dose and fixed-dose ondansetron groups. The incidence of nausea, vomiting, headache and pruritus did not differ significantly among the groups.

KEY WORDS

Weight Adjusted Dose, Fixed Dose Ondansetron, Shivering, Spinal Anaesthesia, Caesarean Deliveries.

Corresponding Author:

Dr. Ananya Choudhury,
Dept of Anaesthesiology and Critical Care,
Gauhati Medical College and Hospital,
Guwahati-781032, Kamrup, Assam, India.
E-mail: meetchoudhuryananya@gmail.com

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BACKGROUND

Spinal anaesthesia is the preferred method of anaesthesia in parturients undergoing both elective and emergency lower-segment caesarean section. A common complication of spinal anaesthesia is shivering and the incidence of shivering has been reported to be about 40 – 50 % after neuraxial anaesthesia.[1] Shivering is defined as spontaneous, rhythmic, oscillatory, tremor-like muscular hyperactivity that occurs in response to core hypothermia in an attempt to raise metabolic heat production.[2] Shivering increases perioperative heart rate and oxygen consumption by 5 times and also increases the metabolic demand by 100 times, thereby increasing chances of myocardial ischemia, hypoxia, hypoxemia and later lactic acidosis. It also increases intraocular pressure and intracranial tension. Besides, the movement of shivering also interferes with the monitoring of electrocardiogram (ECG), blood pressure (BP) and pulse oximetry.[3] Shivering is also very unpleasant, and physiologically stressful for the patient undergoing surgery and it has been shown to aggravate wound pain and interferes with wound healing by stretching incisions. Though the mechanism of the origin of shivering is not clear, various hypotheses have been proposed to explain its occurrence. Perioperative hypothermia being the primary cause of shivering occurs due to neuraxial anaesthesia-induced inhibition of the thermoregulatory mechanism. However, in the postoperative period, shivering may be seen even with normothermia, suggesting that mechanisms other than heat loss with a subsequent decrease in the core temperature contribute to the origin of shivering. These may be uninhibited spinal reflexes, sympathetic overactivity, post-operative pain, adrenal suppression, pyrogen release and respiratory alkalosis.[4,5] Regional anaesthesia produces vasodilatation, which facilitates core to peripheral redistribution of heat. The core temperature drops by 0.5^{o}C to 1^{o}C after induction of neuraxial anaesthesia. This increases the sweating threshold and decreases the vasoconstriction and shivering threshold.[6] Many physical and pharmacological interventions are used to decrease the incidence of post anaesthetic shivering. Non-pharmacological methods which use specialized equipment to prevent or control shivering are expensive and not practical in all clinical settings.[3] Among the pharmacological agents, pethidine,[7] clonidine,[8] tramadol,[9] magnesium sulphate,[10] ketamine[11] have been used to control shivering. However, these drugs are associated with various side effects like respiratory depression, bradycardia, hypotension etc.[1] Ondansetron, a 5HT3 antagonist, is a widely used anti-emetic during both pregnancy and surgery. Some studies have shown its anti-shivering effect following both general and neuraxial anaesthesia.[4,12,13,14,15] It has a potential advantage in obstetric anaesthesia, because of its very low incidence of sedation, hypotension, bradycardia or risk to the neonate.[16] The exact mechanism of action of ondansetron as an anti-shivering agent is not clear, it is proposed to act centrally at the level of the preoptic anterior hypothalamic region by inhibition of serotonin reuptake.[13] There is a paucity of studies conducted comparing different doses of ondansetron in the prevention of post-spinal anaesthesia shivering. Therefore, this study tends to investigate if a weight-adjusted dose of ondansetron is more effective than a fixed dose of ondansetron in preventing post-spinal anaesthesia shivering. The null hypothesis of the study states that there is no difference in the incidence of shivering following spinal anaesthesia when a fixed dose versus weight-adjusted dose of ondansetron is used during caesarean delivery.

Objectives

- To compare the incidence of shivering following spinal anaesthesia when a weight-adjusted dose versus a fixed dose of ondansetron is used during caesarean delivery.
- To compare the severity of shivering between the two groups.
- To compare the incidence of nausea and vomiting in either group.

METHODS

This was a hospital-based randomized double-blinded (patient and observer blinded) single hospital-based study conducted among a convenient sample size of 190 pregnant patients who presented for elective caesarean delivery under spinal anaesthesia to the Department of Anaesthesiology and Critical Care, Gauhati Medical College and Hospital, Guwahati, for 1 year from 1st August 2021 to 31st July 2022 after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants. The patients were divided into two groups: group 1 (patients who received a weight-adjusted dose of ondansetron at 0.1mg/kg) and group 2 (patients who received a fixed dose of ondansetron).

Inclusion Criteria

1. American Society of Anaesthesiologists physical status 2
2. Patients who had given informed and written consent
3. Patients scheduled for elective caesarean section under spinal anaesthesia

Exclusion Criteria

1. Patients unwilling to participate in the study
2. Pre-operative use of ondansetron and tramadol
3. Presence of shivering before administration of spinal anaesthesia
4. Allergy or intolerance to ondansetron
5. With an initial body temperature of more than 38^{0}C or less than 36.5^{0} C
6. Presence of foetal distress or foetal abnormalities
7. Pre-existing or pregnancy-induced hypertension, gestational diabetes mellitus, thyroid disorders
8. Patients with cardiac diseases, liver dysfunction and renal dysfunction

Study Procedure

Random numbers were generated through the computers for both groups. After recording the baseline hemodynamic parameters of the participants, the subjects were allocated into one among the two groups using envelop method. After

allocation, the test drug or control drug was administered by the junior resident not involved in the study before the administration of spinal anaesthesia in a 10 ml syringe marked 1 or 2. Spinal anaesthesia was administered by the same junior resident with the parturient in the left lateral position with the back parallel to the edge of the operating table, thighs flexed to the abdomen. With neck is flexed to allow the forehead to be as close as possible to the knees, to open up the vertebral spaces. The L4 - L5 interspace that corresponds to the highest point of the iliac crest was identified. A 25 G Quincke's spinal needle was used to administer spinal anaesthesia in L3 - L4 space by midline approach. The stylet was removed after the loss of resistance was felt and when there was visible free flow of CSF. 2.2 ml of hyperbaric bupivacaine 0.5 % was administered intrathecally if the patient's height was ≥ 150 cm or 2.0 ml was used if the patient's height was < 150 cm [17]with inj. buprenorphine 0.2 ml (60 micrograms) as per our institutional protocol at a rate of 0.2 ml/sec. Immediately after giving the drug, the needle was withdrawn. The patient was then turned supine and a wedge placed was kept under her right buttock. Intravenous co-loading was done with Ringer's lactate 15 ml/kg[17] at the time of giving the spinal injection. Supplemental oxygen was given through a facemask at a flow rate of 5L/min.[18] A standard blanket was used to cover the chest and upper limbs of the patient. The level of the spinal block was confirmed by evaluating loss of sensation to cold using an alcohol swab bilaterally in the mid-axillary line from below upwards. Motor block was evaluated using a modified Bromage score[19](0 - no motor block, 1- inability to raise the extended leg, able to move knees and feet, 2 - inability to raise the extended leg and move the ankle, able to move feet, 3 complete block of motor limb). Shivering was assessed after spinal anaesthesia for every 5 mins till 60 mins. Shivering was assessed by the validated 4- point Bedside Shivering Assessment Scale (0- no shivering, 1- mild fasiculations in face and neck, 2- shivering involving gross movements of upper limb, 3- shivering involving whole body).

Statistical Methods

The collected data were entered into MS Excel spreadsheets and analysis was done. The procedures involved were transcription, preliminary data inspection, content analysis and interpretation. The statistical analysis was done by using the statistical package for social sciences (SPSS) software version 21.0. The decoding of data was done after the analysis phase was over. Descriptive statistical measures like percentages and inferential statistical tests like chi-square/Fisher's exact test were used. Associations were interpreted as statistically significant at $P<0.05$.

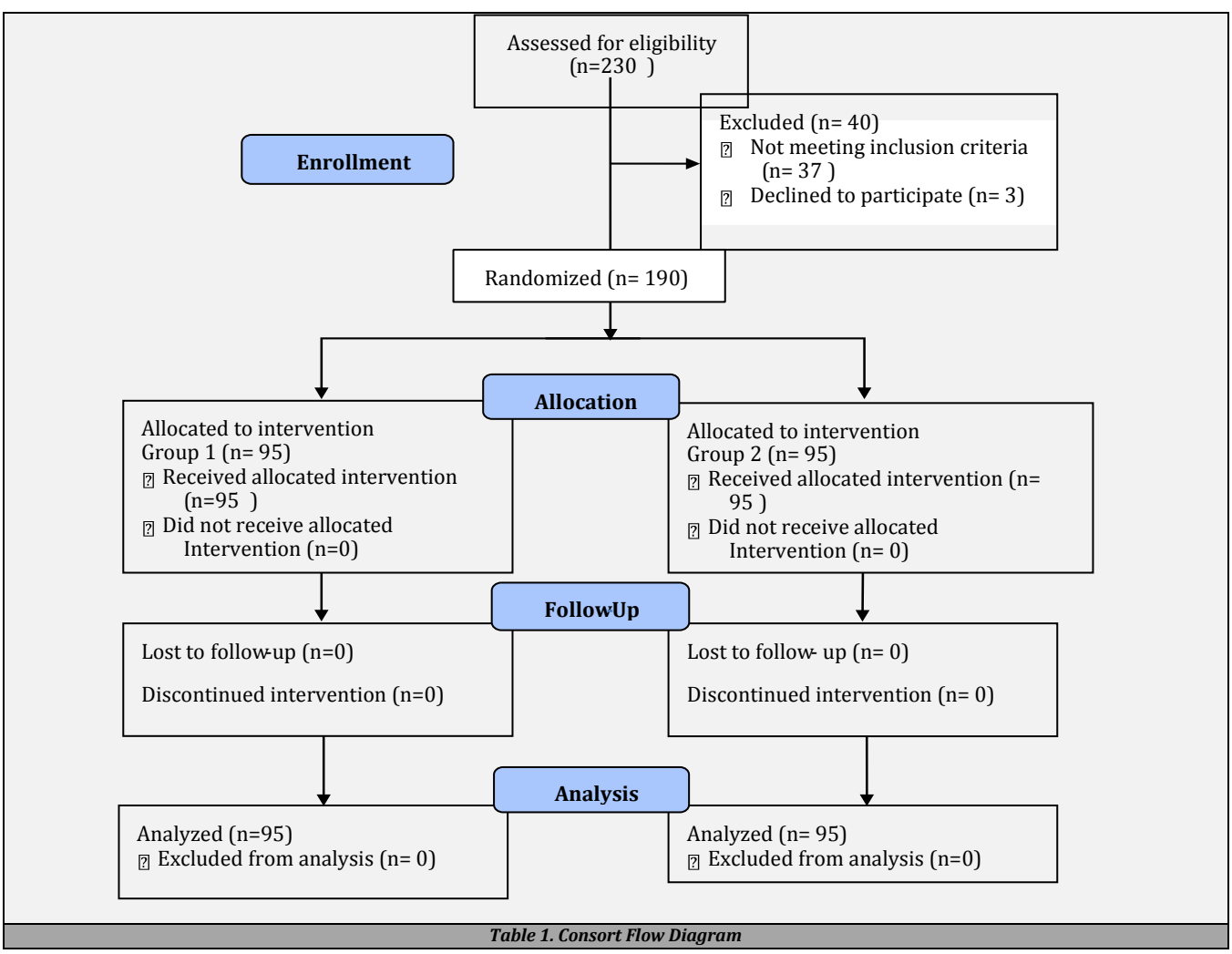

Table 1. Consort Flow Diagram

The flow of patients in our study has been depicted in the consort diagram. It can be seen that out of 190 patients enrolled in the study, 190 patients completed the study. No patients were excluded from the study and no patients developed block failure.

RESULTS

Shivering	Group			p Value
	Group 1	Group 2	Total	
Absent	84 (88.4 %)	74 (77.9 %)	158 (83.2 %)	
Present	11 (11.6 %)	21 (22.1 %)	32 (16.8 %)	0.053 (C)
Total	95 (100 %)	95 (100 %)	190 (100 %)	

Table 2. Distribution of Shivering between the Two Groups

Shivering occurred in 11 patients (11.6 %) in Group 1 and 21 patients (22.1 %) in Group 2 but there was no statistical difference between the two groups (p-value 0.053) (using Chi-square test).

Shivering Grade	Group			P-Value
	Group 1	Group 2	Total	
Grade I	10 (10.5 %)	10 (10.5 %)	20 (10.5 %)	
Grade II	1 (1.1 %)	11 (11.6 %)	12 (6.3 %)	0.0163 (C)
Total	11 (11.6 %)	21 (22.1 %)	32 (16.8 %)	

Table 3. Comparison of Shivering Grade between the Two Groups

10 patients (10.5 %) developed grade I shivering and 1 patient (1.1 %) developed grade II shivering in group 1. In group 2, 10 patients (10.5 %) developed grade I shivering and 11 patients (11.6 %) developed grade II shivering (p-value - 0.0163) which was statistically significant (using chi-square test).

Adverse event	Group 1	Group 2	Total	P-Value (C)
Nausea	0 (0 %)	2 (2.1 %)	2 (1.1 %)	0.1567
Headache	1 (1.1 %)	1 (1.1 %)	2 (1.1 %)	1.00000
Pruritus	0 (0 %)	0 (0 %)	0 (0 %)	0.00

Table 4. Incidence of Adverse Effects among the Two Groups

Nausea occurred in 2 patients (2.1 %) in group 2 while no incidence of nausea was seen in group 1. Incidence of headache was seen in both groups; 1 patient (1.1 %). No incidence of pruritus was seen in the groups (0 %). There was no statistical difference between the adverse effects of the groups.

DISCUSSION

The demographic characteristics of the patients in both study groups with respect to age, height and weight were found to be comparable and statistical tools did not show any significant difference. Similar statistically no significant demographic findings were also noted in the study done by Gicheru et al.[20] (2019), compared between fixed dose and weight-adjusted dose of ondansetron in preventing shivering following spinal anaesthesia for caesarean deliveries. Also, the study conducted by Abdel Hameed SM[21](2021) did not find any significant differences in the demographic characteristics of the patients between the fixed dose and weight-adjusted ondansetron group in his study.

The incidence of shivering in our study in Group 1 (receiving 0.1mg/kg ondansetron) was 11.6 % and in Group 2 (receiving 4 mg ondansetron) was 22.1 %, but there was no statistical difference between the two groups (p-value 0.053). The study conducted by Gicheru et al. (2019) who compared weight-adjusted (0.1 mg/kg) ondansetron and fixed dose (4 mg) ondansetron in preventing shivering following spinal anaesthesia for caesarean deliveries found no significant difference in the incidence of shivering in both the groups (p-value- 0.090) and this is in accordance with our study. In a similar study Abdelhameed SM (2021) compared if a weight-adjusted dose of ondansetron and pethidine is superior to a fixed-dose of ondansetron in preventing shivering following spinal anaesthesia for caesarean delivery. Shivering was observed in 30.2 % in the fixed dose (4 mg) ondansetron group, 25.6 % in the weight-adjusted (0.1 mg/kg) ondansetron group and 25.6 % in the 0.5 mg/kg pethidine group, but no significant difference between the groups was observed (p-value > 0.05), which is in accordance with our study. In our study, in the weight-adjusted dose of the ondansetron group 10.5 % of patients developed grade I shivering and 1.1 % of patients developed grade II shivering. In the fixed dose ondansetron group, 10.5 % of patients developed grade I shivering and 11.6 % of patients developed grade II shivering. None of the patients in either group developed shivering above grade II. So, we see that the weight-adjusted dose of ondansetron decreased the severity of shivering which is similar to the study conducted by Gicheru et al. (2019), Abdelhameed SM (2021) where the severity of shivering was statistically less in the weight-adjusted group of ondansetron compared to the fixed dose ondansetron group.

The temperature before spinal anaesthesia was comparable between both the groups in our study but statistically insignificant. There was a gradual reduction in temperature in the two groups starting from 20 minutes after spinal anaesthesia which is similar to the findings of Abdelhameed SM (2021) and Gicheru et al. (2019).

The hemodynamic parameters of the patients were compared among both the groups in our study. The heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and SpO2 were recorded at baseline and then at 0 minutes (immediately after giving spinal anaesthesia) and at 5 minutes intervals till 60 minutes. The hemodynamic parameters throughout the intra-operative period did not show any significant differences between the two groups which is similar to the study conducted by Gicheru et al., Abdelhameed SM, Marashi SM et al.[15], Attia ZM et al.[22] where hemodynamic parameters were comparable with no statistical difference.

We also compared the incidence of nausea and vomiting between both the study groups and the incidence was statistically insignificant between both the groups which are similar to the study conducted by Abdelhameed SM and Attia ZM et al. The incidence of pruritus and headache between the two groups were statistically insignificant and were consistent with the study of Gicheru et al., Abdelhameed SM, where no statistical difference occurred in the incidence of pruritus and headache between the weight-adjusted and fixed dose ondansetron groups.

Ondansetron in various doses ranging from 4 mg to 8 mg, to prevent shivering from occurring during regional and general anaesthesia was used in various studies conducted by

Powell et al.[23] , Mahoori et al.[24] Marashi SM et al.[15], Nallam et al.[25], Ahmed M et al[26], Nazemroaya et al.[27]

Weight-based dosing used in our study was based on the rationale that various physiological changes are seen during pregnancy, such as an increase in total body water and fat composition that contributes to better drug metabolic rates. Low albumin levels seen during pregnancy reduce the drug binding and increase total free drug concentration. Rapid clearance of medication occurs due to increased renal blood flow and glomerular filtration. These changes may result in an incorrect adjustment of drug dosing (under-dosing or overdosing).

CONCLUSIONS

The severity of shivering was lower in the weight-adjusted dose at 0.1mg/kg ondansetron group in patients undergoing spinal anaesthesia for caesarean delivery. The incidence of shivering was comparable in both the weight-adjusted dose and fixed dose ondansetron groups. The incidence of nausea, vomiting, headache and pruritus did not differ significantly among the groups.

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