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# The role of ramosetron in the prevention of post-spinal shivering in obstetric patients. A prospective randomized double blind study

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## Abstract

**Background and Aim:** Intra/post-operative shivering is frequently observed in parturients posted for elective cesarean delivery (C/D) under spinal anaesthesia. Several studies have advocated the anti-shivering effect of 5-$HT_3$ antagonists, although none has revealed convincing results. The study aims to evaluate the prophylactic effect of a single intravenous dose of ramosetron (0.3 mg), compared with a placebo (N – normal saline), for the prevention of post-spinal shivering (PSS) during elective C/D.

**Method:** The study comprised 80 parturients of the American Society of Anaesthesiologists (ASA) physical status I/ II, posted for elective C/D under spinal anaesthesia who were randomly divided into 2 equal groups; Group N: 0.9% normal saline (4 ml) immediately before induction of spinal anaesthesia and Group R: ramosetron (0.3 mg) intravenously diluted to 4 ml volume. Shivering at any time on a (0-4) scale and total dose of tramadol required for its treatment was recorded. The study also includes the recording of haemodynamic parameters and the incidence of early onset nausea and vomiting.

**Results:** Statistically significant data was obtained while comparing incidence of shivering and maximum shivering at any time (P = 0.001). A lower incidence of early onset nausea and decreased total dose of tramadol was also observed in the ramosetron group.

**Conclusion:** Ramosetron (0.3 mg) is advocated to be an effective drug in preventing post-spinal shivering among parturients posted for elective C/D. Moreover, its role in preventing maternal nausea together with better haemodynamic parameters further supported the advantageous role of ramosetron in our group of patients.

**Keywords:** cesarean section, post-spinal shivering, ramosetron

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## Introduction

Elective cesarean delivery (C/D) is a procedure which is most commonly carried out under neuraxial anaesthesia. Intra/post-operative shivering is frequently observed in parturients posted for C/D under spinal anaesthesia. The etiology of shivering is yet unstated; however, it is deemed to involve a blend of mechanisms, which includes impairment of thermoregulatory thresholds, a decrease in body core temperature (hypothermia), an alteration in body heat distribution, and a cooling effect of the fluids injected in the body, any/ all of which in turn lead to a reduction in the threshold for vasoconstriction and shivering [1]. Severe shivering hinders the monitoring of blood pressure, pulse oximetry, and electrocardiogram (ECG), during the period of sympathetic sensory block, when hypotension is likely to occur. It also results in maternal irritability and hampers the mother's ability to hold her baby [2].

Classically, various drugs such as tramadol, meperidine, ketamine, and clonidine are used for the preven-

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tion/treatment of intra/post-operative shivering in parturients [1]. These medications are associated with different adverse effects both on the mother and fetus, such as nausea, vomiting, hypotension, sedation and bradycardia. The above stated adverse effects restrain the use of these drugs during the surgery, so as to eliminate any unwanted effect on the mother and the fetus [3].

Serotonin (5-hydroxytryptamine [5-$HT_3$]) is a biologic amine located in the brain and spinal cord, which plays a vital role in neurotransmission. Several studies propose that serotonergic system helps in controlling pre-operative shivering [4]. The mechanism behind the anti-shivering effect of 5-$HT_3$ antagonists is that it acts by inhibiting serotonin reuptake at the pre-optic anterior hypothalamic region [5]. The anti-shivering effect of 5-$HT_3$ antagonists is advocated in various studies although none has revealed convincing results.

Ramosetron, a 5-$HT_3$ antagonist, is widely used as an antiemetic agent during both pregnancy and surgery. It possesses an indole ring, which is the nucleus of serotonin joined by a tetrahydrobenzimidazol radical. These components are linked by a carbonyl radical. It has been re-counted that out of all available 5-$HT_3$ antagonists, ramosetron shows the most sustained potent antagonistic activity towards serotonin (5-$HT_3$) receptors [6, 7]. Ramosetron (ramosetron hydrochloride), has been on the market since 1996, and is widely used as an antiemetic drug in various Asian countries in oncological patients receiving chemotherapy or anaesthesia [8-10].

An extensive Medline search revealed limited literature regarding the use of ramonsetron as an anti-shivering agent, in parturients posted for C/D under spinal anaesthesia. The study aims to evaluate the prophylactic effect of a single intravenous dose of ramosetron (0.3 mg), compared with a placebo, on the prevention of post-spinal shivering during elective C/D. Also the study aims to identify the possible preventive effect of ramosetron on other adverse effects occurring due to spinal anaesthesia, such as nausea, vomiting, and hypotension.

## Methods

After obtaining clearance from the Institutional Ethical Committee (TMMC/IEC/2017/07) and written informed consent, this prospective, randomized, double blind placebo controlled study was conducted in the Department of Anaesthesia, Teerthankar Mahaveer Medical College, Moradabad, from January to July 2017. The study enrolled 80 parturients of the American Society of Anesthesiologists (ASA) physical status I/II, 20-40 year old patients, posted for elective C/D under spinal anaesthesia.

Demographic data of all subjects was collected preoperatively which included age, weight, height, body mass index (BMI), and history of shivering during previous C/D. Exclusion criteria for the study included a complicated pregnancy, preoperative fever (> 38°C), preoperative shivering, known allergy to the test drug, preoperative use of ramosetron or tramadol, any contraindication to spinal anaesthesia, Raynaud's syndrome, Parkinson's disease (or any other extrapyramidal disease), intraoperative administration of vasodilator drugs, clonidine, or opioids, intraoperative blood transfusion, hypo or hyperthyroidism.

All patients were randomly divided into 2 equal groups; Group N: 0.9% normal saline and Group R: ramosetron (0.3 mg) intravenously using chit-pull randomization technique. All patients were administered an intravenous (i.v.) bolus of the test drug in 4 mL volume, immediately before induction of spinal anaesthesia. Group R (40 patients) were administered ramosetron (0.3 mg) intravenously diluted to 4 ml volume while Group N were administered 0.9% Normal Saline (4 ml). The doses administered above were prepared by an independent anaesthesiologist in a veiled 5 mL syringe who was not allowed to participate further in the study.

In the operation theater; noninvasive blood pressure, electrocardiogram, and pulse oximetry were measured using GE Monitor (Model: B40, SN: SJF13461779WA, Auckland, New Zealand). Core temperature of the parturient during pre- and intra-operative period was measured using a tympanic membrane thermometer using a Braun Thermoscan instant Thermometer IRT 3520. After carefully establishing a wide bore (18-20 gauge) i.v. cannula, Ringer's solution (15 mL/kg warmed up to 37°C) was infused over 30 minutes before introducing spinal anaesthesia. Infusion rate was then reduced to 2 mL/kg/h. Next, the patient was made to sit in the lateral decubitus position, and spinal anaesthesia was introduced at L3/4 or L4/5 level using a 27-gauge pencil point spinal needle and 2.5 mL of hyperbaric bupivacaine (0.5%) was administered. Without any delay, the patient was placed supine in a left tilt position; by using loss of pinprick sensation the spinal block level was assessed, and the level of block was recorded. Any pre or intraoperative opioids were not allowed to be administered apart from supplemental oxygen (3 L/min) which was given via a nasal cannula till the surgery was concluded. To maintain ideal body temperature, the entire body of the patient was covered with two layers of surgical drapes intraoperatively, and with one lightweight cotton blanket postoperatively. The room humidity was kept around 60% with room temperature maintained at 21-22°C.

Shivering was taken as a primary outcome and it was observed and graded by a blinded observer, during

the intra and post operative period, using the scale given by Crossley and Mahajan [11], and Tsai and Chu [12] (0 = no shivering, 1 = piloerection or peripheral vasoconstriction but no visible shivering, 2 = muscular activity in only one muscle group, 3 = muscular activity in more than one muscle group but not generalized shivering, 4 = shivering involving the whole body).

Shivering was considered positive if grade 3 and 4 shivering persisted for more than 3 minutes. Maximum shivering was considered if grade 4 (generalized shivering) occurred which interfered with the ECG monitoring and with the mother's ability to hold the baby. Any shivering described as disturbing by the patient was treated with tramadol (50 mg) intravenously. Haemodynamic parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), incidence of early onset nausea/vomiting (0-6 hours postoperatively), and duration of surgery were recorded as secondary outcomes. Hypotension (more than 20% drop in MAP compared to baseline reading) was treated with a repeated i.v. bolus dose of ephedrine (10 mg/bolus), as required. Bradycardia (heart rate < 50 beats/min) was treated with a repeated dose of i.v. atropine (0.5 mg), as needed. The total dose of tramadol and/or ephedrine administered was recorded.

Kelsaka et al. showed that 5-$HT_3$ antagonists can trim down the incidence of post spinal shivering to 8% compared with 36% in the control group [13]. A sample size was designed based on these results, with an α value of 0.05 and a power (1-β) of 0.80. It was calculated that each group required 36 subjects. We therefore enrolled 80 patients (40 per group) to allow for drop-outs.

Statistical analysis was performed using the SPSS (version 20.0; SPSS Inc, Chicago, IL). As per the type of data, it was either represented as mean ± standard deviation or number and percentage. All parametric data was evaluated using the Student's t-test and non-parametric data using Fischer Test. The value of $P < 0.05$ was accepted as statistically significant.

## Results

The study involved 80 parturients, out of which 3 patients were excluded as two patients from the ramosetron group and one patient from the normal saline group encountered failed spinal block and therefore surgery was conducted under general anaesthesia. Therefore, the data was compiled from 39 patients in Group N and 38 patients in Group R (Fig. 1).

On comparing demographic data between the two groups no significant difference was observed (P >

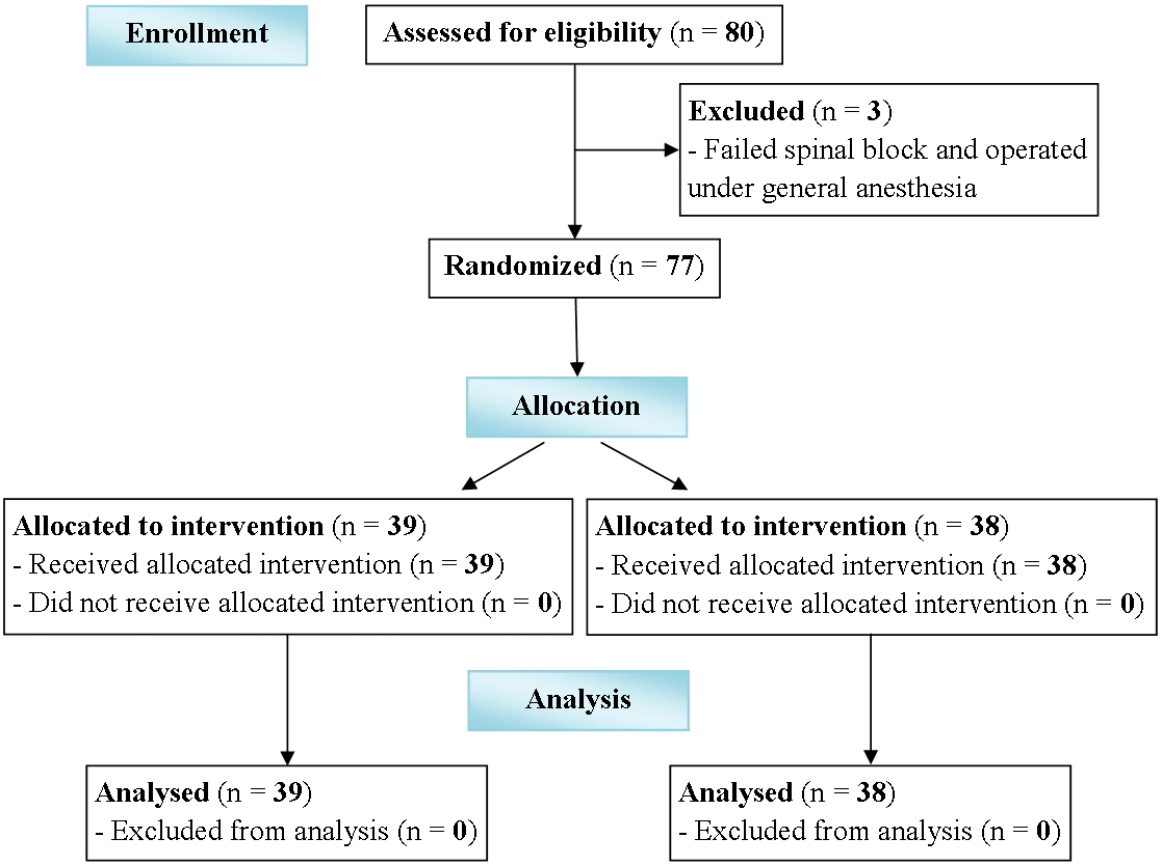


**Fig. 1.** Flow diagram of the study

0.05) (Table 1). The total dose of intravenous tramadol in Group N and Group R was 12.37 ± 11.59 and 6.31 ± 10.92 mg respectively (P = 0.02) (Table 1).

Table 2 reveals no significant change in the mean arterial pressure between the two groups. However, after 2 minutes of post-spinal positioning the patient supine (MAP2), a significant fall in mean arterial pressure was observed in Group N (P = 0.001) (Table 2).

The incidence of shivering at any time in Group N and Group R was observed in 53.8% and 21% parturients respectively (P < 0.001) (Table 3). The incidence of maximum shivering at any time in Group N and Group R was observed in 25.6% and 5.2% parturients respectively (P < 0.001) (Table 3). 15 patients in Group N and 3 patients in Group R reported early onset nausea within 0-6 hours (P < 0.001) (Table 3). No incidence of vomiting was observed in any of the patients during early onset period.

The maximum block level for Group N and Group R was T5 (T4-T6) and T5 (T3-T6) respectively (P = 0.86). The minimum block level for the normal saline and ramosetron group was T6 (T6-T8) and T6 (T6-T9) respectively (P = 0.55). The core temperature for Group N was 36.5 ± 0.18°C and that for Group R was 36.3 ± 0.22°C (P = 0.21) (Table 4).

## Discussion

In the present study, the prophylactic effect of a single intravenous dose of ramosetron (0.3 mg), in the prevention of post-spinal shivering in parturients posted for elective cesarean delivery (C/D) under spinal anaesthesia was observed. Kim et al. observed promising results of ramosetron on shivering in patients who underwent knee arthroscopy under spinal anaesthesia [14]. However, the study conducted by Song and Lee proposed no significant anti-shivering role of

**Table 1.** Demographic and operative data in the two studied Groups

| Variables | Group N (n = 39) | Group R (n = 38) | P value |
|---|---|---|---|
| Age, mean ± SD, years | 29.56 ± 5.34 | 30.12 ± 3.48 | 0.58 |
| Height, mean ± SD, cm | 155.7 ± 7.23 | 156.12 ± 5.89 | 0.78 |
| Weight, mean ± SD, kg | 69.87 ± 6.59 | 70.23 ± 7.25 | 0.82 |
| Operative duration, mean ± SD, min | 47.47 ± 12.11 | 49.49 ± 10.50 | 0.44 |
| Total ephedrine dose, mean ± SD, mg | 6.34 ± 8.8 | 6.1 ± 7.6 | 0.90 |
| Total tramadol dose, mean ± SD, mg | 12.37 ± 11.59 | 6.31 ± 10.92 | 0.02* |

Group R = Ramosetron group; Group N = Normal Saline group; SD = standard deviation
* Statistically significant difference between groups; (P < 0.05)

**Table 2.** Haemodynamic data in the two studied Groups

| Variables | Group N (n = 39) | Group R (n = 38) | P value |
|---|---|---|---|
| MAP0, mean ± SD (just before induction of spinal anaesthesia), mmHg | 93 ± 7.52 | 94 ± 9.83 | 0.61 |
| MAP1, mean ± SD (just after induction and lateral tilt position), mmHg | 89 ± 9.23 | 91 ± 8.89 | 0.33 |
| MAP2, mean ± SD (2 min after positioning), mmHg | 82 ± 7.57 | 88 ± 7.28 | 0.001* |
| MAP3, mean ± SD (5 min after positioning), mmHg | 81 ± 7.56 | 83 ± 8.67 | 0.28 |
| MAP4, mean ± SD (just after delivery of the baby), mmHg | 78 ± 8.56 | 80 ± 8.12 | 0.29 |
| MAP5, mean ± SD (at the end of the surgery), mmHg | 87 ± 8.34 | 89 ± 10.09 | 0.34 |

Group (R) = Ramosetron group; Group (N) = Normal Saline group; MAP = mean arterial blood pressure; SD = standard deviation
* Statistically significant difference between groups; (P < 0.05)

**Table 3.** Incidence of shivering and nausea/vomiting in the two studied Groups

| Variables | Group N (n = 39) | Group R (n = 38) | P value |
|---|---|---|---|
| Incidence of shivering at any time, number (percentage) | 21 (53.8%) | 8 (21%) | < 0.001* |
| Incidence of maximum shivering at any time, number (percentage) | 10 (25.6%) | 2 (5.2%) | < 0.001* |
| Median and range of shivering | 2 (0-4) | 1 (0-4) | < 0.005* |
| Incidence of early onset nausea, number (percentage) | 15 (38.4%) | 3 (7.8%) | < 0.001* |
| Incidence of vomiting, number (percentage) | 0 | 0 | - |

Group (R) = Ramosetron group; Group (N) = Normal Saline group
* Statistically significant difference between groups; (P < 0.05)

**Table 4.** Block level and core temperature during surgery after spinal anaesthesia

| Variables | Group N (n = 39) | Group R (n = 38) | P value |
|---|---|---|---|
| Block level (maximum), median (range) | T5 (T4-T6) | T5 (T3-T6) | 0.86 |
| Block level (minimum), median (range) | T6 (T6-T8) | T6 (T6-T9) | 0.55 |
| Core temperature, mean ± SD, $^{o}$C | 36.5 ± 0.18 | 36.3 ± 0.22 | 0.21 |

Group (R) = Ramosetron group; Group (N) = Normal Saline group; SD = standard deviation

ramosetron in patients undergoing thyroid surgeries [15]. Based on the above conflicting results by various researchers, the present study was planned to evaluate the anti shivering effect of ramosetron in obstetric patients under neuraxial blockade.

In our study, we observed a significant difference in the incidence of shivering at any time in Group N and Group R of parturients ($P < 0.001$), and also in the incidence of maximum shivering ($P < 0.001$). The results of Kim et al. support our study as they also observed that only 2 patients in the Ramosetron Group complained of post spinal shivering (PSS) as compared to 9 patients in the saline Group ($P = 0.038$) [14]. Badawy and Mokhtar evaluated the role of ondansetron in the prevention of post-spinal shivering in obstetric patients. They observed that there was a statistically significant difference in the incidence of PSS in the ondansetron group 10/38 (26%) as compared to the normal saline group 19/37 (51%) ($P = 0.007$) and the incidence of maximum shivering at any time was 8/37 (22%) vs. 3/38 (7.8%) ($P = 0.004$) [16]. Shakya et al. performed a study on patients posted for lower abdominal surgeries under spinal anaesthesia. They concluded that only 10% of the patients given ondansetron had post-spinal shivering as compared to 42.5% in the control group [17]. Although, the studies conducted by Shakya et al. and Badawy and Mokhtar used ondansetron in the prevention of PSS, which has a similar mechanism of action and pharmacokinetic profile as ramosetron. The latter drug is more effective with lesser adverse effects as compared to the former one [18].

Furthermore, a study conducted by Browning et al. suggested no promising role of ondansetron in the treatment of post-spinal shivering among parturients under neuraxial blockade [19]. They observed no significant difference in the incidence of shivering between the control and ondansetron groups. They administered intrathecal fentanyl during spinal anaesthesia which reduces the chances of post-spinal shivering, thereby decreasing the incidence and severity of shivering in the parturients, thus leading to conflicting results [20, 21].

In the present study, we observed a statistically significant difference in the requirement of intravenous tramadol between Group N (12.37 ± 11.59 mg) and Group R (6.31 ± 10.92 mg) ($P = 0.02$). The requirement of intravenous tramadol corresponds with the incidence of shivering in both groups. In the Badawy and Mokhtar study, the use of ondansetron was associated with the reduction of the requirement of intravenous meperidine in comparison with the control group [16]. We decided to use tramadol for the treatment of PSS in the parturients according to Kaya et al., who suggested that the use of intravenous tramadol is as effective in the treatment of shivering in intra-operative settings as meperidine [22]. Moreover, the ease of availability of tramadol in our hospital settings further supports our use of this particular drug for our study.

In the present study, the parturients in the ramosetron group experienced a better haemodynamic profile as compared to the normal saline group. This can be explained from animal studies suggesting the role of $5\text{-}HT_3$ receptor blockers in antagonising the Bezold Jarish Reflex and thereby decreasing the incidence of post-spinal hypotension. Gao et al. conducted a study evaluating the role of prophylactic ondansetron on spinal anaesthesia-induced hypotension. They concluded from the meta-analysis that prophylactic ondansetron decreases the incidence of post-spinal induced hypotension in both obstetric/non-obstetric patients [23]. Shin et al. conducted a study to evaluate the role of preoperative ramosetron and ondansetron in spinal anaesthesia induced hypotension. On comparing the haemodynamic variables between the two groups a statistically significant difference was observed between them. Hence, they concluded that the administration of ramosetron significantly attenuated the spinal anaesthesia induced hypotension when compared with ondansetron [24].

In the present study, the parturients in normal saline group experienced a higher incidence of early onset nausea (38.4%) as compared to the ramosetron group (7.8%) ($P < 0.001$). However, none of the parturients involved in the study complained of vomiting. Ansari et al. proposed ramosetron (0.3 mg) as a more effective and safe drug compared to ondansetron (4 mg) during the early and late period in laparoscopic cholecystectomy patients [25]. Chauhan and Bhavsar further supported our study as they conducted a comparative study on ramosetron (0.3 mg) and ondansetron (4 mg) on caesarean section patients under spinal anaesthesia and concluded promising effects of ramosetron in reducing early/late onset nausea and vomiting [26].

The study involved the use of a tympanic membrane thermometer for the measurement of the core body temperature during pre and intra-operative period of the parturients. No significant change in core body temperature was observed between the groups in the present study. Badawy and Mokhtar further supports our study as they also observed insignificant difference in core temperature among parturients received either ondansetron (8 mg) intravenously or normal saline (0.9%) [18]. Safavi et al. conducted a study between intravenous ondansetron (8 mg), and intrathecal meperidine (0.2 mg/kg) for the assessment of shivering and core body temperature was measured in patients planned for lower extremity orthopaedic surgery [27]. They concluded that no significant difference was observed in the incidence of shivering between the two groups.

In the present study we observed comparable results between the study groups while evaluating the maximum and minimum sensory block level (P = 0.86 and P = 0.55) respectively. Samra et al. conducted a study to assess the effect of intravenous ondansetron on sensory and motor block after spinal anaesthesia with hyperbaric bupivacaine [28]. They concluded that intravenous ondansetron does not affect the intensity or duration of sensory block after spinal anaesthesia. Badawy and Mokhtar further supports our study as they also observed insignificant difference with intravenous ondansetron in evaluating maximum and minimum sensory block level [18].

*Limitations of the study*. In our study, we observed early onset of nausea (0-6 hours post cesarean) because the primary outcome of this study was to evaluate the anti shivering effect of ramosetron. However, this drug also acts as an antiemetic, and thus efficacy of ramosetron to prevent nausea was taken as a secondary outcome. Many of the similar studies had used meperidine to treat shivering in patients under spinal anaesthesia. The use of tramadol instead of meperidine in the present study has been justified with suitable literature in the discussion section.

## Conclusions

The study concludes that ramosetron (0.3 mg) when given intravenously just before spinal anaesthesia is an effective drug in preventing post-spinal shivering among parturients posted for elective C/D. It effectively reduces the incidence and intensity of intra-operative shivering with a better haemodynamic stability. Moreover, a promising role of intravenous ramosetron in decreasing the incidence of early onset nausea is also suggested by the present study. However, intravenous ramosetron does not affect the maximum and minimum sensory block level after spinal anaesthesia with hyperbaric bupivacaine.

**Conflict of interest**

Nothing to declare

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