IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 6 Ver. XII (June. 2017), PP 03-09
www.iosrjournals.org

Effect of Ramosetron on Peroperative Shivering and Hypotension in Patients Undergoing Transurethral Resection of Prostate Surgeries under Spinal Anaesthesia. A Prospective, Double Blind, Randomized, Comparative Study.

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Abstract
Background and Aims: *Elderly patients undergoing transurethral resection of prostate (TURP) surgeries are more prone to shivering induced peroperative complications which anaesthesiologists should aim to prevent rather than treat.*
The aim of the study is to evaluate the effect of Inj ramosetron on peroperative shivering and spinal hypotension in patients undergoing transurethral resection of prostate under subarachnoid block (SAB).
Method: *In this prospective doubleblind, randomized, comparative study, a total of 60 patients belonging to American Society of Anaesthesiologist (ASA) I and II physical status between the age group of 60 to 85 years, scheduled for elective TURP surgeries under spinal anaesthesia were selected. The patients were randomly allocated into one of the two groups of thirty patients each. For patients allocated in Group S, 2 ml of normal saline and in group R, 0.3 mg ramosetron (2ml) was intravenously injected 5 min before the SAB. The primary outcome was the reduction in the incidence of shivering by pretreatment with ramosetron. The maximum change in the mean arterial pressure from the base line was the secondary outcome. Using normal approximation to binominal distribution the sample size was calculated. Data collection such as sensory block level, haemodynamic parameters, rectal temperature and grades of shivering were performed at 10 minute intervals.*
Results: *Data among the groups were compared using Analysis of Variance (ANOVA) test in Matrix Laboratory (MATLAB) environment. Incidence and intensity of shivering and hypotension were significantly less in R group than the S group ($P<0.001$) and ($P<0.001$) respectively. There was no significant difference with respect to heart rate, saturation of peripheral oxygen (SPO2), sensory block level achieved and reduction in the core temperature between the two groups.*
Conclusion: *We conclude that pretreatment with intravenous ramosetron 0.3mg given before spinal anaesthesia in geriatric patients undergoing TURP surgeries effectively reduces the incidence and intensity of shivering and hypotension associated with spinal anaesthesia.*
Keywords: *Ramosetron, serotonergic pathway, shivering, spinal anaesthesia, TURP surgery.*

I. Introduction

Though spinal anaesthesia is the most frequenly used anaesthetic technique for transurethral resection of prostate (TURP) surgeries, shivering is known to be a frequent complication seen in 40 to 70% of the patients [1]. Neuraxial anaesthesia inhibits central,peripheral and behavioural thermoregulatory control by enlarging interthreshold range by raising the sweating threshold and decreasing the vasoconstriction and shivering thresholds [2], [3] It produces peripheral vasodilation and thus promotes redistribution hypothermia. Hypotension and bradycardia occur due to reduction in vascular resistance by sympathetic nerve blockade, relative dominance of parasympathetic system , activation of Bezold Jarisch Reflex(BJR) and increased baroreceptor activity [4]. The receptors responsible for BJR are inhibitory cardiac sensory receptors located in the heart walls which are influenced by hyper and hypovolemia and the chemoreceptors sensitive to serotonin(5-HT3 receptors).

Ramosetron, a selective serotonin 5-HT3 receptor antagonist is an antiemetic with an indole ring, which is the nucleus of serotonin (5-HT) joined by a tetrahydrobenzimidazol radical. These components are linked by a carbonyl radical. There are studies which proved that ramosetron exhibits more potent and sustained antagonistic activities against 5-HT3 receptors than existing 5-HT3 receptor antagonist –type antiemetics [7].

The aim of our study is to evaluate the effect of ramosetron on peroperative shivering and spinal hypotension in patients undergoing TURP surgeries under spinal anaesthesia.

II. Methods

After obtaining institutional ethical committee approval and written informed consent from all the participants, a prospective, randomized, double-blind,placebo-controlled study was done in South Indian Tertiary Care Referral Hospital. The study population consisted of 60 patients with American Society of Anaesthesiologists (ASA I and II), between the age group 60 to 85 years posted for elective TURP surgeries under spinal anaesthesia. The study was performed from May 2016 through August 2016. Patients older than 85 years, those with contraindication to spinal anaesthesia, obese with body mass index greater than 30%, febrile patients, those with ischemic heart disease, cerebrovascular disease, thyroid dysfunction, patients taking vasodilators/vasoconstrictors which interfere with body thermoregulation, presence of coagulopathy were excluded from the study. The patients were randomized by using sealed envelope technique. All patients had preanaesthetic evaluation and airway assessment the day prior to surgery. The patients in the control group received 2 ml normal saline (group S, n=30). The intervention group received 0.3 mg ramosetron -2ml (group R n=30). All solutions were prepared by an anaesthetist who was not involved in the patient's management and data collection. On arrival in the operating room, the baseline vital parameters and rectal temperature were monitored with routine non invasive monitors. An 18 gauge intravenous catheter was placed on the dorsum of non-dominant hand and patients received intravenous normal saline 10 ml /kg at room temperature and maintained at 6 ml/kg/h after spinal anaesthesia . Group S received 2ml saline as placebo and Group R received inj. ramosetron 0.3 mg (2ml) intravenously 5 min before spinal anaesthesia. Spinal anaesthesia, with a sensory blockade up to T9-10 level was achieved using 0.5% hyperbaric bupivacaine 2.5 ml at sitting position through midline approach at the L3-4 or L4-5 interspace using 25 gauge Quincke needle. *Patients* were then placed supine. The level of the sensory block was assessed using the pin-prick test and loss of temperature sensation by alcohol swab. Once the sensory blockade upto T9-10 was achieved, the patients were placed in the lithotomy position. All operations were performed in the same operation theatre whose ambient temperature was maintained around 23^0C to 25^0C. All the patients were covered with drapes but not actively warmed and had supplemental oxygen 4 litres/ minute with face mask. IV fluids, irrigation fluids and anaesthetic drugs were administered at room temperature. Heart rate, mean arterial pressure,SPO2 and rectal temperature(by Life Scope monitor -Nihon kohden) were recorded before the commencement of anaesthesia and then at every 10 min interval till completion of surgery and transportation of the patient to the postoperative ward. Shivering was assessed after completion of SAB by observation of the pectoralis major muscles for fasciculations of more than 10 seconds duration. Grades of shivering were done according to Wrench which is as follows;

Grade 0: No shivering.
Grade 1: Piloerection or peripheral vasoconstriction but no visible shivering.
Grade 2: Visible muscle activity confined to one muscle group.
Grade 3: Visible muscle activity in more than one muscle group but no generalised shivering.
Grade 4: Gross muscle activity involving whole body shivering.

Peroperatively if shivering occurred; it was treated in the same manner in both the groups with reassurance, warming blanket or inj. tramadol. Bradycardia (heart rate <50/min) and hypotension (systolic blood pressure < 30% of the baseline) were appropriately treated with atropine and ephedrine respectively in titrated doses when required. Postoperatively, all patients were monitored, given oxygen via face mask and were covered with one layer of drapes and one cotton blanket. The post anaesthesia care unit temperature was maintained at 25^0 C and at constant humidity. All parameters were computed through statistical analysis between the two groups by ANOVA test in MATLAB environment. The data was expressed as mean±SD. A value of P <0.05 was considered as statistically significant. Shivering was observed in 67% in group S and 33% in group R (Table 5) p 0.000108 at confidence level 95%. The sample size of 21 patients is sufficient to find out the difference between the groups with the 80% power and 5% of margin error. Using normal approximation to binominal distribution the sample size was calculated. In anticipation of the case failure, we included 30 patients in each group. Data from 60 patients enrolled in this study were analyzed without droupouts.

III. Results

All 60 patients completed the study. All the spinal blocks were successful with a satisfactory level of anaesthesia and all of the data were analysed. There were no statistical differences between the groups with respect to demographic data and duration of surgery (Table 1).

Table 1: Patient's demographic data and Characteristics of the two groups

Parameter	Group S	Group R	P value
Age (Year)	74.5±4.33	73.8±4.42	0.54
Weight (Kg)	62.2±3.24	61.3±3.57	0.3
Height (cm)	166.5±2.88	166.6±2.94	0.9
Duration(min)	57.6±4.85	57.6±5.26	1

Values are expressed in Mean ± Standard Deviation; NS - Not Significant

There were no significant differences between groups with respect to ASA status and the level of sensory block achieved after spinal anaesthesia (Table 2).

Table 2: ASA status and Spinal block level for the two groups

ASA physical Status	Group S	Group R
I	12 (40%)	10 (33.3%)
II	18 (60%)	20 (66.7 %)
Spinal block level	Group S	Group R
T9	4 (13.3%)	6 (20%)
T10	26 (86.7%)	24 (80%)

ASA –American Society of Anaesthesiologist. The values signify the number and percentage of the patients

The baseline and the lowest core temperature, heart rate and mean arterial pressure after spinal anaesthesia were recorded. Mean and the standard deviation for groups S and R were calculated respectively (0.49±0.14), (0.46±0.13)-change in core temperature, (4±1.9), (4±1.6)- change in heart rate, (8.11±2.67), (3.93±1.11)- change in mean arterial pressure (Table 3).

Table 3: Characteristics of core temperature and haemoynamic variables.

Parameters	Group S	Group R	p value
Lowest core temperature (^{o} C)	36.06±0.15	36.09±0.15	0.4
Change in core temperature (^{o} C)	0.49±0.14	0.46±0.13	0.39
Lowest heart rate	73.76±7.19	73.3±5.6	0.78
Change in heart rate	4±1.91	4±1.6	1
Lowest MAP (mm hg)	83.44±5.62	88.44±5.54	0.001
Change in MAP (mm hg)	8.11±2.67	3.93±1.11	<0.0001

MAP-mean arterial pressure. Values are expressed as mean ± standard Deviation.
Group S=saline group, Group R= ramosetron group.

Intergroup comparison showed no significant variations for the change in core temperature (figure 1) and the heart rate.

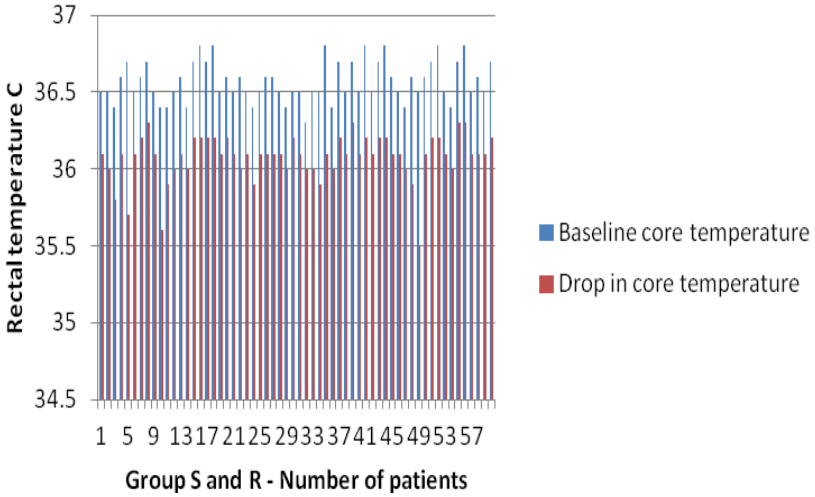

Figure 1: Drop in core temperature

But, significant p value was observed for change in mean arterial pressure(MAP) p< 0.001 (figure 2) and lowest MAP recorded p 0.001(figure 3) . No incidence of bradycardia and desaturation were noted in both the groups.

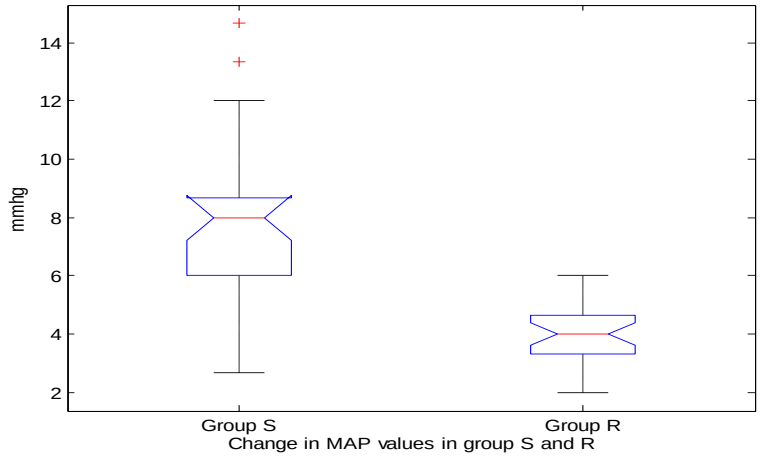

Figure 2: Change in MAP values in Group S and R

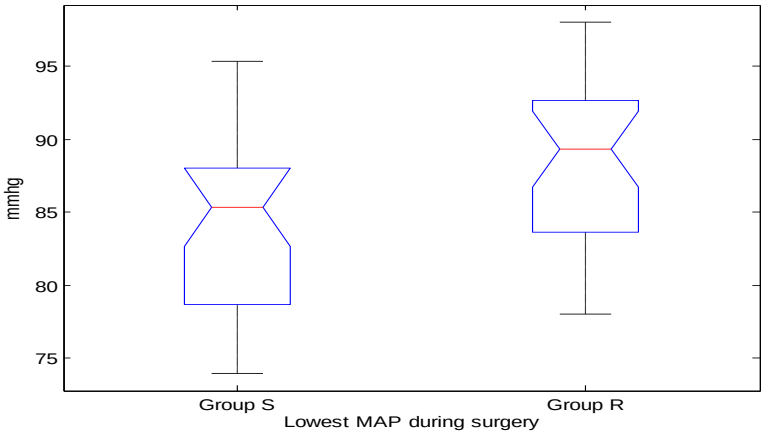

Figure 3: Lowest MAP during Surgery

The average intensity of shivering observed at 20 min and 40 min after SAB between the two groups were shown in the following figure 4.

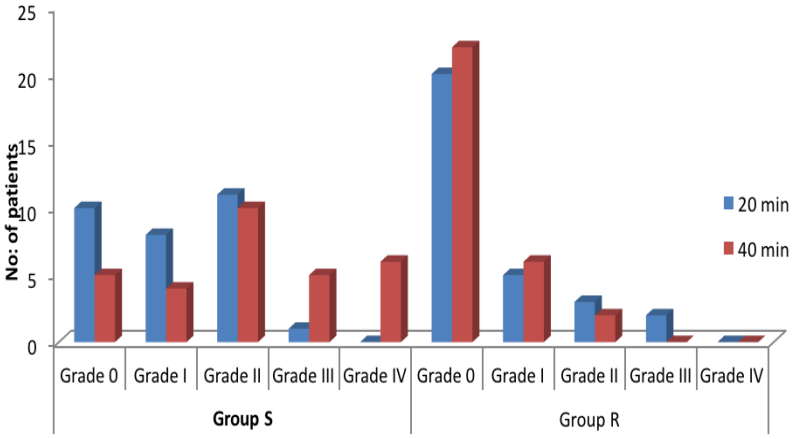

Figure 4: Diagrammatic representation of grades of shivering

The incidence of shivering is low in R group at 20 min and 40 min. At 20 min, 10 patients in group S and 20 patients in group R had no shivering. The intensity was also more in group S with grade II shivering observed in 11 patients. At 40 min, 5 patients in group S and 22 patients in group R had no shivering. The intensity was also more in group S with grade III shivering observed in 5 patients and grade IV in 6 patients. The P value is significant between the two groups at grade 0 (P 0.0001 and P 0.0005 respectively) Table 4.

Table 4: Incidence of shivering between two groups

	20 min		40 min	
	Group S	Group R	Group S	Group R
Grade 0	10 33.33%	20 66.67%	5 16.67%	22 73.33%
Grade I	8 26.67%	5 16.67%	4 13.33%	6 20%
Grade II	11 36.67%	3 10%	10 33.33%	2 6.67%
Grade III	1 3.33%	2 6.67%	5 16.67%	0 0%
Group IV	0 0%	0 0%	6 20%	0 0%

Values signify number and percentage of patients in group S-Saline group,group R-ramosetron group

The overall incidence of shivering between the groups S and R at 20 and 40 minutes is shown in the following table 5 which shows the highly significant P value (P <0.001)

Table 5: Overall incidence of shivering between S and R group

	Group S	Group R	P value
20 min	20 (66.7%)	10 (33.3%)	0.000108 P<0.001
40 min	25 (83.3%)	8 (26.7%)	0.000491 P<0.001

Values signify number and percentage of the patients in group S-saline group, group R-ramosetron group

IV. Discussion

In our study, we found that pretreatment with intravenous ramosetron in patients undergoing TURP surgeries under spinal anaesthesia effectively reduced the incidence of peroperative shivering and is considered as the primary outcome of the study. The incidence of shivering in patients who were given ramosetron was only 33.3% and 26.7% at 20 min and 40 min respectively as compared with 66.7% and 83.3% in the saline group(P < 0.001) . The patients in the ramosetron group , who shivered , experienced only Grade 1- 2 shivering , only 2 patients in R group had grade 3 shivering at 20 min while the patients in saline group experienced Grade 1 – 4 shivering. P value was significant at grade 0 level (P< 0.001). Shivering was graded using Wrench scale [24]. Similar results were found in previous studies which showed that ramosetron reduces the incidence and severity of peroperative shivering [8][9].

The drop in core temperature and the block height achieved after spinal anaesthesia were similar in both the groups S and R in our study. Bradycardia and desaturation were not observed in both the groups. The mean arterial pressure was significantly reduced in group S (control group) patients after spinal anaesthesia (P<0.001)which is the secondary outcome of our study. It was consistent with the results of previous study by Kim, H.B.: who studied about the effect of different kinds and different doses of 5-, HT3 receptor antagonists on prevention of hypotension after spinal anaesthesia in 80 healthy parturients of four groups(ramosetron0.3mg, ondanstron 8mg and 4mg and placebo respectively. He concluded that ramosetron was more effective [28]. A systemic review and meta analysis by Heesen M et al [31] had found out that 5-hydroxytryptamine-3 receptor antagonists are effective in reducing the incidence of hypotension and bradycardia in patients undergoing cesarean delivery. Also Marashi SM in his study found that intravenous ondansetron administered 5 min before spinal anaesthesia effectively reduced the spinal induced hypotension ,bradycardia and shivering compared to the control saline group [4]. It is imperative to prevent and treat shivering in geriatric patients as it produces damaging sequelae , including sympatho adrenal stimulation , increased oxygen consumption and carbon dioxide production . Also, it may interfere with monitoring of electrocardiogram [25]. However , there are a limited number of studies on prevention of peroperative shivering in geriatric patients undergoing TURP surgeries [10] [11] [12] [13] [14] Various pharmacological therapies such as ketamine, clonidine, dexmeditomidine, ketanserin, butorphanol, nefopam and magnesium sulphate have been used to prevent shivering in various surgical procedures under spinal and general anaesthesia [15] [16] [17] [18] relative

efficacy of these drugs remain unclear with their anti-shivering effects mediated via different receptors. These drugs are associated with side effects such as bradycardia ,pruritus , respiratory depression and vomiting [19] [20] Non – pharmacological methods using equipment to maintain normal temperature of the body are effective but costly and not always possible.

In a few studies, 5-HT3 antagonists such as ondansetron, dolasetron , granisetron and ramosetron , the well known drugs for postoperative nausea and vomiting , have been suggested to prevent post anaesthetic shivering [21] [22] [23] [30]. Serotonin [5-hydroxy tryptamine (5-HT)], a biological amine found in the brain and the spinal cord has a role in the neurotransmission [26]. Specific inhibition of the 5-HT3 system causes a generalised thermoregulatory inhibition at the level of hypothalamus where the bulk of thermoregulatory control occurs. It produces decrease in human thermal set-range there by reducing metabolic cold defence and discomfort associated with postoperative hypothermia. Studies have shown that serotonergic system has a role in the control of peroperative shivering [5]. A serotonin 5-HT3 receptors antagonist inhibits the uptake of serotonin in the preoptic anterior hypothalamic region thereby influencing both heat production and heat loss [6]. BJR can be decreased by 5-HT3 antagonists [27]

Ramosetron is a newly developed 5- HT3 antagonist with a higher receptor affinity and longer duration of action than older agents in its class. Myeong Jong Lee and Song YK had found out that the combination of ramosetron and dexamethasone safely reduced the incidence postoperative nausea ,vomiting, pain and shivering in patients undergoing thyroid surgeries under GA [9] [21] Kim MS et al [8] in their study in patients undergoing knee arthroscopy under spinal anaesthesia concluded that pretreatment with ramosetron reduced the incidence of shivering in ramosetron group to 7.7% which was more than four times less than the incidence in saline group 34.6%. Similar to our study, the drop in core temperature after spinal anaesthesia was similar between the two groups, but without any significant difference in the mean arterial pressure.

There are some earlier studies which showed that IV ondansetron may antagonize the effects of intrathecal local anaesthetics . This could be the mechanism behind the attenuation of haemodynamic changes following spinal anaesthesia [29]. In our study also , the mean arterial pressure in R group did not show much variation from the baseline values.

The major limitation of our study is the small sample size. A bigger sample size would be a better authentication of our results. Another limitation is that our study included short duration surgeries. The antishivering effect of ramosetron needs to be evaluated in surgeries of longer duration. Also, we did not assess the different doses of ramosetron. However, the strength of our study is the conclusion we derived.

V. Conclusion

In this study, we found that pretreatment with ramosetron 0.3mg given intravenously just before spinal anaesthesia effectively reduces the incidence and the intensity of shivering in geriatric patients undergoing TURP surgeries without affecting the haemodynamic stability. Ramosetron may find a place in future urological surgeries for preventing Post anaesthetic shivering and spinal hypotension.

Competing interests

We (authors) declare that there is no conflict of interest in terms of financial and personal relationships with other people or organization that could not appropriately manipulate our work.

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