Effect of ramosetron on shivering during spinal anesthesia

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Background: Shivering associated with spinal anesthesia is uncomfortable and may interfere with monitoring. The aim of this study is to evaluate the effect of ramosetron, a serotonin-3 receptor antagonist, on the prevention of shivering during spinal anesthesia.

Methods: We enrolled 52 patients who were ASA I or II and who had undergone knee arthroscopy under spinal anesthesia. Warmed (37°) lactated Ringer's solution was infused over 15 minutes before spinal anesthesia. Patients were randomly allocated to a control group (group S, N = 26) or study group (group R, N = 26). Spinal anesthesia was performed with a 25-G Quincke-type spinal needle between the lumbar 3–4 interspace with 2.2 ml 0.5% hyperbaric bupivacaine. For patients allocated in groups S and R, 2 ml 0.9% saline and 0.3 mg ramosetron, respectively, was intravenously injected immediately before intrathecal injection at identical times. Shivering and spinal block levels were assessed immediately after the completion of subarachnoid injection, as well as 5, 10, 15, 20, 25, 30, 60, and 120 minutes after spinal anesthesia. Systolic and diastolic blood pressures, heart rate, and peripheral oxygen saturation were also recorded. Core temperatures were measured by tympanic thermometer and recorded before and during spinal anesthesia at 30-minute intervals.

Results: Shivering was observed in 2 patients in group R and 9 patients in group S ($P = 0.038$, odds ratio = 6.14, 95% C.I. = 1.08–65.5). The difference in core temperature between the groups was not significant.

Conclusions: Compared to control, ramosetron is an effective way to prevent shivering during spinal anesthesia. (Korean J Anesthesiol 2010; 58: 256-259)

Key Words: Ramosetron, Shivering, Spinal anesthesia, Thermoregulation.

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Introduction

Shivering is a relatively common complication in regional anesthesia. Regional anesthesia significantly impairs thermoregulation and predisposes patients to hypothermia, which reduces the threshold for vasoconstriction and shivering. Various pharmacological therapies such as meperidine, ketamine and clonidine have been used to prevent shivering, because shivering may affect the cardiovascular system and induce hypertension and tachycardia, ultimately increasing oxygen consumption by 400–500% [1].

Serotonin (5-hydroxytryptamine [5-HT₃]), a biologic amine found in the brain and spinal cord, plays a part in neurotransmission; studies suggest that the serotonergic system plays a role in controlling perioperative shivering [2]. A serotonin 5-HT₃ receptor antagonist inhibits the uptake of serotonin in the preoptic anterior hypothalamic region, which influences both heat production and heat loss [3], but there has been no evidence of this during spinal or epidural anesthesia.

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. It has been reported that ramosetron exhibits more potent and sustained antagonistic activities against 5-HT₃ receptors than existing 5-HT₃ receptor antagonist-type antiemetics [4,5].

The aim of our study is to evaluate the efficacy of ramosetron on the prevention of shivering during spinal anesthesia.

Materials and Methods

After informed consent, 52 patients of the American Society of Anesthesiologists (ASA) physical status classification I or II between the ages of 18 to 62 years who had undergone knee arthroscopy under spinal anesthesia were enrolled in this study. Patients with obesity (BMI > 30), perioperative fever (temperature > 38°C), hypo- or hyperthyroidism, Parkinson's disease, a requirement for blood transfusion during surgery, and medications likely to alter thermoregulation were excluded.

All patients were randomly allocated to receive 0.9% saline (group S, N = 26) or ramosetron 0.3 mg (group R, ramosetron (Nasea[®], Astellas, Tokyo, Japan, N = 26). A sample size was calculated based on the study by Kelsaka et al., which reported the incidence of postanesthetic shivering to be 8% (ondansetron group), compared with 36% in the control group. Therefore, 26 patients were required in each group in order to have a power of 80% and $\alpha = 0.05$ [6].

On arrival in the operating room, 5 ml/kg lactated Ringer's solution warmed to 37°C was infused over 15 minutes before spinal anesthesia. The temperature of the operating room

during the perioperative period was kept at a set average temperature of $24 \pm 0.6^\circ\text{C}$ in all cases. The treatment drugs were presented as coded syringes by an anesthesiologist who was not involved in the management of the patients. For patients allocated in group S, 2 ml 0.9% saline and in group R, 0.3 mg ramosetron was intravenously injected immediately before intrathecal injection at identical times. Eleven mg of 0.5% hyperbaric bupivacaine was injected using a 25-G Quincke spinal needle. Spinal anesthesia was performed at the L3-4 interspace. Shivering was assessed after the completion of the subarachnoid injection by observation of the pectoralis major muscles for fasciculations of more than 10 seconds duration. The presence of intraoperative shivering was noted by a blinded observer. If the patient shivered continuously, intravenous meperidine 25 mg was administered as a rescue drug. The spinal block level was assessed by pinprick and alcohol swab. The degree of spinal block was assessed in the intraoperative period and also in the recovery unit. Core temperature and the presence or absence of shivering were recorded before and 5, 10, 15, 20, 25, 30, 60, and 120 minutes after spinal anesthesia. Core temperatures were measured by tympanic thermometer (Infrared Thermometer IRT 4520; accuracy range $\pm 0.2^\circ\text{C}$, Braun, USA) and recorded before, after and during spinal anesthesia. Systolic and diastolic blood pressures, heart rate, and peripheral oxygen saturation were also recorded. Decreases in systolic blood pressure more than 20% of the preoperative value were treated by crystalloid infusion. If necessary, ephedrine 5 mg was administered intravenously.

All statistics were analyzed using S-PLUS 8.0 (TIBCO Software Inc, CA, USA). Comparison of demographic data and recovery characteristics between groups was done by Student's t-test. Comparison of the incidence of shivering between groups was done by Fisher's exact test. The correlation of core temperature and anesthetic level was analyzed by Pearson's correlation test. Repeated data on the same participants (changes of block level, core temperature, blood pressure and heart rate with time) were analyzed by repeated measures ANOVA. $P < 0.05$ was considered statistically significant.

Results

Demographic data, duration of surgery, duration of anesthesia, and volume of infused crystalloid are given in Table 1, which shows no significant difference between control group S and group R. The range of sensory blockade levels (maximum to minimum) was T3-T11 in group S compared to T4-T11 in ramosetron group R (Table 2). Two patients in control group S showed a maximum block level of T3, while three patients in group R showed a maximum block level of T4. The average spinal block level in both groups was T6. The mean core

Table 1. Demographic Data

	Group S (N = 26)	Group R (N = 26)
Age	31 ± 12	45 ± 11
Gender (Female/Male)	6/20	7/19
Weight (kg)	67 ± 8	63 ± 8
Height (cm)	169 ± 8	166 ± 8
Duration of surgery (min)	55 ± 18	45 ± 20
Duration of anesthesia (min)	99 ± 20	85 ± 25
Crystalloid infused (ml)	1,121 ± 271	1,030 ± 276

Values signify the number of patients or the mean ± SD. Group S: saline group, Group R: ramosetron group.

temperature during the perioperative period is also shown in Table 2. The mean core temperature decreased after spinal anesthesia in both groups compared to preoperative values ($P = 0.01$), but there was no significant difference in temperature between groups S and R during the intraoperative phase after spinal anesthesia.

Shivering was observed in 9 patients (34.6%) in group S and 2 patients (7.7%) in group R (Table 3) (Fisher's Exact Test; $P = 0.038$, odds ratio = 6.14, 95% C.I. = 1.08-65.5). Meperidine was given as a rescue drug in 8 patients in group S and 1 patient in group R ($P = 0.02$).

There was no statistically significant correlation between block height and mean core temperature in both group S (Pearson's correlation coefficient, $r = 0.14$, $P = 0.06$) and group R (Pearson's correlation coefficient, $r = 0.07$, $P = 0.39$).

There was also no significant difference in systolic blood pressure and diastolic blood pressure between the two groups. In control group S, 3 patients required ephedrine 5 mg for hypotension perioperatively. The peripheral oxygen saturation did not fall below 97% in any of the patients during surgery.

There were no other complications during or after surgery.

Discussion

In this study, we found that pretreatment with ramosetron is an effective way to prevent shivering during spinal anesthesia. The incidence of shivering in the ramosetron group was 7.7%, which was more than four times less than the incidence of the saline group, which was 34.6%.

It has been reported that shivering develops in up to 40% of cases of regional anesthesia [7]. In our study, the incidence of shivering in the control group was 34.6%, which is similar to the previous report [7]. Shivering is an involuntary, oscillatory muscular activity that augments metabolic heat production, which is a physiological response to a decrease in core temperature. Various pharmacological therapies have been used to prevent shivering, because shivering may affect the

Table 2. Block Level and Core Temperature during Surgery after Spinal Anesthesia

	Group S	Group R
Block level (maximum)	T6 (T3–T11)	T6 (T4–T11)
Block level (minimum)	T10 (T6–T12)	T11 (T8–T12)
Core temperature (°C)	36 ± 0.24	36.5 ± 0.43

Values signify mean ± SD or block level and range of the median for that level. Group S: saline group, Group R: ramosetron group.

Table 3. Incidence of Shivering

	Group S	Group R
Shivering	9	2
No shivering	17	24

Values signify number of patients. Group S: saline group, Group R: ramosetron group.

cardiovascular system, causing hypertension and tachycardia, ultimately increasing oxygen consumption by 400–500% [1]. Clonidine affects noradrenaline through alpha-2 receptors located on presynaptic axon terminals in the hypothalamus [8]. Meperidine is a very commonly used drug that is used prophylactically for shivering. Although the mechanism of meperidine is not fully understood, evidence has shown that the anti-shivering activity of meperidine may be mediated by its kappa opioid receptor activity [1]. Evidence has also suggested that the anti-shivering effect of meperidine may be due to actions such as monoamine reuptake inhibition, N-methyl-D-aspartate antagonism or stimulation of alpha-2 adrenoreceptors [1]. Ketamine, a competitive NMDA receptor antagonist, has been shown to prevent shivering without hemodynamic alteration in patients undergoing regional anesthesia; its effects are likely due to its influence on the hypothalamus or by the beta adrenergic effect of norepinephrine. Ondansetron, dolasetron and granisetron, which are all 5-HT₃-receptor antagonists, have been used effectively to ease postoperative shivering. The mechanism for 5-HT₃-receptor antagonists is still unclear but is thought to be related to inhibition of serotonin reuptake on the preoptic anterior hypothalamic region. Powell and Buggy [9] reported the amount of shivering after general anesthesia in patients in a control group who received no drug versus patients who received ondansetron 4 mg or 8 mg. Shivering occurred in 57% of patients in the control group, while 33% and 15% of patients in the ondansetron 4 mg and 8 mg groups, respectively, experienced shivering, showing that administration of 8 mg ondansetron was more effective than 4 mg for shivering in patients. In Powell and Buggy's study [9], the effect of ondansetron was independent of intraoperative core hypothermia, suggesting that ondansetron inhibits thermoregulatory responses by a central mechanism.

In regional anesthesia like spinal anesthesia, Kelsaka et al. [6] reported the incidence of postanesthetic shivering to be 8% (ondansetron 8 mg group) compared to 36% in the control group, which was very similar to our results of 7.7% in the ramosetron group versus 34.6% in the control group.

It is well known that ramosetron, a new antagonist of the 5-hydroxytryptamine type-3 receptor, has more potent and longer acting properties for anti-emesis than other 5-HT₃-receptor antagonists such as ondansetron and granisetron. Fujii et al. [10] showed that the percentage of patients who were emesis free 0–24 hours after anesthesia was 85% with granisetron (40 µg/kg) and 90% with ramosetron (6 µg/kg) ($P = 0.37$); the corresponding rate 24–48 hours after anesthesia was 70% and 95% ($P = 0.003$), respectively. Unfortunately, there is limited information on the length of time during which ramosetron can retain its anti-shivering effect after spinal anesthesia. Because we did not directly compare the potency and duration of ramosetron to other 5-HT₃ receptor antagonists in this study, we need further studies to do so.

There are various risk factors for shivering, such as age, level of sensory block, temperature of the operating room and temperature of infusion fluid, which is a response to hypothermia in regional anesthesia. In this study, there were no significant differences in age, temperature of the operating room and infusion fluid between groups; therefore, the level of sensory block was a major risk factor for shivering. It has been shown that spinal anesthesia reduces the threshold for vasoconstriction and shivering [1]. In spinal anesthesia, reduction in the shivering threshold is proportional to the level of spinal blockade. Frank et al. [11] proved that a high level of spinal blockade is a significant predictor of core temperature during spinal anesthesia. For each increase in block level, the core temperature decreases by 0.15°C [1]. High levels of spinal blockade are known to decrease the core temperature threshold for shivering. In our study, this correlation was not observed in either group. Although it looked as if there was some correlation between the spinal block level and the decrease in core temperature in the control group ($r = 0.14$, $P = 0.059$), there was no statistical significance. Moreover, in the study group (ramosetron 0.3 mg), a negative correlation ($r = 0.07$, $P = 0.39$) was shown, which was similar to a previous report of Kelsaka et al., which showed that there was a significant correlation between the spinal block height and mean rectal temperature in the control group. However, this correlation was lost in the ondansetron and the meperidine groups [6].

It is unclear why our study did not find a correlation between core temperature and block level during spinal anesthesia. More clinical studies are needed to compare the efficacy of ramosetron to other drugs that can be used to prevent shivering in patients undergoing spinal anesthesia.

In conclusion, we found that pretreatment with ramosetron is an effective way to prevent shivering during spinal anesthesia. It is common knowledge that meperidine is used as the gold standard for the prevention and treatment of perioperative shivering. However, its use can be limited because of the risk of respiratory depression, sedation, nausea, and vomiting, especially when repeated doses are necessary [2]. Therefore, we think pretreatment with ramosetron as an alternative to meperidine can be a useful way to prevent shivering in spinal anesthesia.

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