Original Article

Comparative Study of Granisetron Versus Pethidine for the Prevention of Perioperative Shivering Under Spinal Anesthesia

Savitri D Kabade, Y Venkatesh, SL Karthik, Vikas Kumar

Department of Anesthesiology, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India

Abstract

Aims: Shivering, the "big little problem," has an incidence of 19–33% following spinal anesthesia. Recently, studies showed the involvement of serotonergic system in the control of postanesthetic shivering. Pharmacological management includes opioids (pethidine) and nonopioids like 5-HT3 receptor antagonists (ondansetron and granisetron). Pethidine which is considered as a time-tested drug for control of shivering can have adverse effects such as respiratory depression, nausea, and vomiting. This study was performed to compare the effect of prophylactic granisetron versus pethidine in prevention of perioperative shivering in patients under spinal anesthesia. **Settings and Design:** A prospective randomized, double blinded study was conducted on 60 patients of ASA I and II physical status aged between 20-50 years scheduled for elective lower abdominal surgeries under spinal anesthesia.**Subjects and Methods:** After obtaining ethical committee clearance and patient consent, sixty American Statistical Association Grade I and II patients, aged 20–50 years scheduled for elective lower abdominal surgeries under spinal anesthesia were recruited for a randomized double-blinded study divided into Group G and Group P and received intravenous (IV) granisetron 40 mcg/kg and pethidine 0.4 mg/kg, respectively. Perioperatively, vitals and core temperature were monitored and shivering was assessed using 5-item scale once in every 15 min up to 6 h. **Statistical Analysis:** The results were analysed using Statistical Package for Social Science software. **Results:** Of the sixty patients we studied, the demographic profile between the two groups was comparable. Six patients had shivering in each group. The mean temperature at which patient developed shivering was 36.31°C in Group G and 35.85°C in Group P. The mean time of onset for shivering to occur in Group G was 95 min and in Group P was 65 min. None of the patients received rescue drug. Patients in both the groups were hemodynamically stable. **Conclusions:** Prophylactic granisetron 40 μg/kg IV is as effective as pethidine 0.4 mg/kg IV in preventing perioperative shivering following spinal anesthesia and also reduces the need of antiemetics.

Key words: Granisetron, pethidine, shivering

Introduction

Shivering, the "big little problem," has an incidence of 60% following general anesthesia and up to 33% following regional anesthesia.[1] Shivering is unpleasant and causes several undesirable physiologic consequences such as increase in oxygen consumption, carbon dioxide production, increased chances of myocardial ischemia, infection, bleeding, and increase in the minute ventilation. It also induces hypoxemia, lactic acidosis, increased intraocular pressure, intracranial pressure (ICP), and interferes with patient monitoring such as electrocardiogram (ECG), noninvasive blood pressure (NIBP), and SpO_2. Spinal anesthesia is known to decrease the shivering threshold, preceded by core hypothermia and vasoconstriction above the level of block.[2]

Various methods are available for the control of shivering such as nonpharmacological or pharmacological. Nonpharmacological preventing measures such as fluid warmers, maintaining ambient operating room temperature, space blankets, surgical drapes, and active circulating water mattress have been used. Pharmacological methods include various drugs such as opioids (pethidine, pentazocine, and tramadol), α2 agonists (clonidine, ketansarin), others such as doxapram, neofam, neostigmine, and magnesium sulfate have been tried.[3]

Recently, studies on serotonin (5-hydroxytryptamine), a biological amine found in the brain and the spinal cord, which has a role in neurotransmission and thermoregulation suggest that the involvement of serotonergic system in the control

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Address for correspondence: Dr. Savitri D Kabade, Department of Anesthesiology, Karnataka Institute of Medical Sciences, Hubli - 580 022, Karnataka, India. E-mail: sdkabade20@gmail.com

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of postanesthetic shivering. Serotonin antagonism seems to lower the human thermal set-range thereby reducing metabolic cold defenses and discomfort associated with postoperative hypothermia. These 5-HT3 receptor antagonists used as antiemetics routinely are easily available and cost-effective.[4]

Pethidine which is considered as a time-tested drug for control of shivering can have adverse effects such as respiratory depression, nausea, and vomiting. This begs to investigate the efficacy of other drugs.

Thus, in search of an ideal antishivering agent, we compared the effect of prophylactic granisetron versus pethidine for the prevention of perioperative shivering in patients undergoing elective lower abdominal surgeries under spinal anesthesia.

Subjects and Methods

Following institutional ethical committee clearance and after obtaining written informed consent, a prospective, randomized, double-blind study was undertaken. The power of the study was calculated based on the number of the patients who shivered, setting a significant level of $P = 0.05$, it was calculated that a group size of 30 patients allowed detection of a difference between groups with a power of 85%. Therefore, we selected 60 patients aged 20–50 year, American Statistical Association (ASA) physical Status I and II, scheduled for lower abdominal surgery under spinal anesthesia. Patients with cardiopulmonary disease, psychological disorder, and thyroid disorders, patients who are likely to receive blood transfusion intraoperatively and with body temperature more than 38°C or <36.5°C were excluded from the study. The patients were randomly allocated to Group P ($n = 30$) receiving pethidine 0.4 mg/kg and Group G ($n = 30$) receiving granisetron 40 mcg/kg intravenous (IV) as study drug before spinal anesthesia.

Standardized monitoring was done throughout the perioperative period. Heart rate, NIBP, respiratory rate, and oxygen saturation were recorded during the surgery. Core body temperature was measured by tympanic thermometer, and skin temperature was measured using skin probe. Operation room temperature was maintained at 24°C by air-conditioning. Peripheral IV access is secured using 18 gauge cannula. All patients preloaded with warm Ringer's lactate solution of 10 ml/kg before spinal anesthesia. Patients received respective drugs intravenously before spinal anesthesia. Patients from both the groups received 0.5% hyperbaric bupivacaine 15 mg intrathecally with the help of 26 or 27 G Quincke's spinal needle at L3–L4 interspace in the lateral position. After subarachnoid block, the patients were turned to the supine position. Patients received oxygen 6 L/min by face mask throughout the procedure. Except surgical field patients were properly covered with cotton drapes. The hypotension if following spinal injection was treated by increasing the rate of IV fluid administration and by injection of Mephentermine 3–6 mg IV. An anesthesiologist blinded for the study drug observed the patients for shivering, pain, nausea, and vomiting. Heart rate, NIBP, oxygen saturation, and temperature were measured and recorded on admission and every 15 min up to 6 h. The shivering was graded using a 5-item scale [Table 1].[1] The possible side effects of the study drug (i.e., nausea, vomiting, hypotension, tachycardia, dry mouth, and dizziness) were recorded. In the recovery room also all patients were monitored, received oxygen through facemask and were covered with woolen blanket. Patient with nausea and vomiting were treated with metoclopramide 10 mg. Tramadol 1 mg/kg was kept as rescue medication to treat the shivering more than Grade II on 5-item scale. Statistical analysis of data was done using IBM corp. Released 2013. IBM SPSS statistics for windows. Version 22.0. Armonk, NY.

Results

Of the sixty patients we studied, the demographic profile [Table 2] between the two groups was comparable. The results of our study showed that, among sixty patients, shivering occurred in 12 patients (20%), six patients in each group. In Group G, four patients (13.33%) had Grade I shivering and 2 (6.66%) patients had Grade II shivering compared to Group P where two patients (6.66%) had Grade I shivering and four patients (13.33%) had Grade II shivering [Figure 1]. The mean temperature at which patient developed shivering was 36.31°C

Table 1: 5-item scale of assessing shivering

No shivering
Piloerection, peripheral vasoconstriction or peripheral cyanosis without other cause
Visible muscular activity confined to one muscle group
Visible muscular activity in more than one muscle group
Gross muscular activity involving the entire body

Table 2: Demographic profile

Variables	Group G	Group P	*P* value
Age	41.63	40.33	0.4617
Sex (M/F)	4/26	0/30	0.1212
Weight	52.63	50.87	0.1588
Height	151.53	151.60	0.9325
ASA (I/II)	25/5	26/4	0.9999

ASA: American Statistical Association, M: Male, F: Female

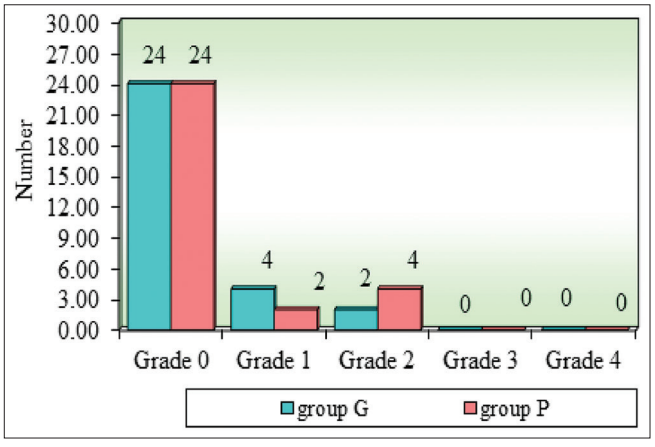

Figure 1: Shivering grades between two groups

in Group G and 35.85°C in Group P. The mean time of onset for shivering to occur in Group G was 95 min and in Group P was 65 min. None of the patients received rescue drug. Patients in both the groups were hemodynamically stable. Oxygen saturation levels were well-maintained in Group G, and there was a mild decrease in oxygen saturation levels in Group P during postoperative period which was statistically significant but clinically insignificant. The incidence of side effects such as nausea and vomiting was absent with Group G which was statistically significant.

Discussion

Shivering is a common problem encountered by an anesthesiologist during intraoperative as well as in postoperative period.[5] Shivering occurs during both general anesthesia and regional anesthesia. Incidence of shivering is up to 33% in the patients undergoing surgery under regional anesthesia and up to 56–66% under general anesthesia.

A number of factors including age, duration of surgery, temperature of the operating room, type of regional anesthesia (spinal or epidural), and infusion solution are risk factors for hypothermia and shivering.[6-9]

Shivering increases metabolic activity and oxygen consumption. It may induce hypoxemia, lactic acidosis, increased intraocular, and ICP. It may interfere with patient monitoring such as ECG, NIBP, and SpO_2. Hence, prevention of shivering is essential for better perioperative patient outcome. Various drugs have been used to treat or prevent postoperative shivering, but the ideal drug has not yet been found.[10-16]

Pethidine has been shown to be one of the most effective treatments to prevent postoperative shivering at a dose of 0.4 mg/kg. The antishivering effect of pethidine is due to stimulation of kappa receptors and drug-induced decrease in the shivering threshold. In addition, pethidine is a potent alpha two receptor agonist which contributes to antishivering effects. Butorphanol – a kappa receptor agonist – antagonist stops shivering more effectively than opioids with a predominant mu-opioid receptor agonist effect. Evidence for a role of kappa receptors in the antishivering effects of meperidine and butorphanol is the failure of naloxone to completely inhibit this drug-induced effect. A disadvantage of pethidine is that it can cause respiratory depression in the presence of previously administered opioids or anesthetics. Moreover, nausea and vomiting are also important adverse effects of pethidine.[17,18]

This begs to either prevent or treat and the need to investigate the efficacy of yet other drugs. 5-hydroxytryptamine may influence both heat production and heat loss pathways. Recently, 5-HT3 receptor antagonists such as ondansetron, dolasetron, and granisetron are well-known drugs for postoperative nausea and vomiting have been suggested to prevent postanesthetic shivering. However, in some clinical trial, a single drug granisetron used on prevention of shivering, nausea, and vomiting performed under spinal anesthesia and found effective.[19]

The study was conducted on sixty patients of ASA Class I and II undergoing elective lower abdominal surgeries under spinal anesthesia. Each group consisted of thirty patients and received either IV granisetron or pethidine. After spinal anesthesia, characteristics of motor and sensory blockade were assessed and noted. Perioperatively, monitoring of cardiopulmonary parameters was done throughout. Incidence of shivering along with the occurrence of other adverse effects was noted.

Since shivering is a response to hypothermia, body temperature should be maintained within limits of 36.5–37.5°C. However, shivering may be seen even in normothermic patients undergoing regional anesthesia. A number of factors including age, level of sensory block, temperature of the operating room, internal redistribution of body heat, heat loss to the environment, inhibition of centrally mediated thermoregulatory control, and infusion solution are risk factors for developing hypothermia in regional anesthesia.[20] For these reasons, in our study, patients between 20 and 50 years of age were included, the temperature of the operating room was maintained at 24°C, and infusions of cold crystalloid solutions were avoided.[21,22] Cutaneous warming is also the most effective means of preventing intraoperative hypothermia, so patients are covered with cotton drapes.[23]

Saito *et al*. reported that hypothermia is likely to develop faster during spinal anesthesia due to impairment of thermoregulation. A natural consequence of the rapid temperature decreases during spinal anesthesia is that the shivering threshold will be reached sooner and that more shivering will be required to prevent further hypothermia.[24]

We measured the skin temperature by skin probe of multiparameter monitor placing over the chest and core temperature by tympanic thermometer. Our study results showed that the mean skin temperature in Group G was 35.59 ± 0.40°C and in Group P was 35.62 ± 0.32°C. The mean skin temperatures were comparable among the two groups. At the baseline time, 0th min, 5th min, and 315–360th min – the difference in the mean skin temperature between the two groups was statistically significant ($P < 0.05$). P value at baseline – 0.0007, at 0 min – 0.0064, 5 min – 0.0479, 315 min – 0.0114, 330 min – 0.0033, 345 min – 0.0041, and 360 min – 0.0061. This can be compared to the study by Kelsaka *et al*. who concluded that the mean skin temperatures were higher in ondansetron group than in meperidine group, and the control groups throughout the study period reaching significance at 8, 9, and 10 min after spinal anesthesia ($P < 0.05$).[25]

Core temperature analysis

In our study, the mean core temperature in Group G was 36.87 ± 0.16°C and Group P was 37.04 ± 0.11°C. The mean core temperatures in both the groups are comparable and correlate with the results of earlier studies [Figure 2 and Table 3].

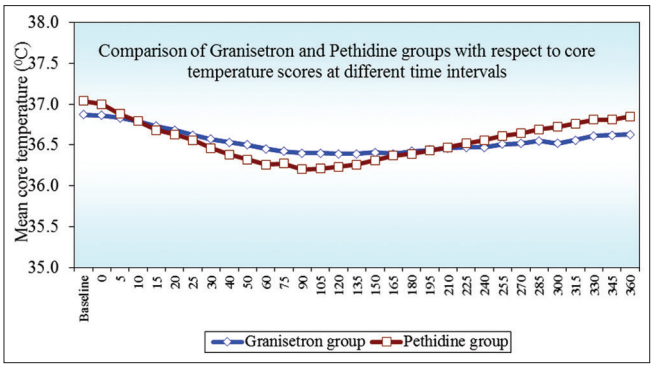

Figure 2: Comparison of Group G and P with respect to core temperature scores at different time intervals

Table 3: Comparison of core temperature between two groups and other studies

Study group	Core temperarure		*P* value
	G	P	
Our study	36.87±0.16°C	37.04±0.11°C	
Sagir A *et al*.[4]	36.4	36.5	>0.05
Sajedi *P et al*.[26]	36.2±0.5	36.1±0.5	>0.05
Iqbal A *et al*.[1]	35.59±0.27°C	35.48±0.18°C	>0.05
Sayed AM *et al*.[27]	37.021	36.98	>0.05
Mohammadi SS *et al*.[19]	36.5	36.4 (placebo)	

The results of our study showed, preoperatively the mean core temperatures in Group G was 36.87 ± 0.16°C and Group P was 37.04 ± 0.11°C. Postoperatively, at 360th min, the mean core temperature in Group G was 36.63 ± 0.23°C and Group P was 36.85 ± 0.16°C. Perioperatively at 40–135th min and 240–360th min, the difference in the mean core temperatures among both groups was statistically significant ($P < 0.05$). The difference between the mean core temperatures in the two groups at other time interval was statistically not significant ($P > 0.05$).

In our study, incidence of hypotension was more noted in Group G compared to the Group P and nausea was more in Group P compared to the Group G [Figure 3].

Mild hypotension was observed in three patients (10%) in the Group G compared to one patient (3.33%) in the Group P which is comparable with a study done by Sagir *et al*.; on control of shivering comparing ketamine with granisetron reporting hypotension in 8 (20%), 3, 5, and 7 patients in Groups G, K, GK, and P, respectively. In our cases, hypotension was managed with 6 mg of IV mephentramine.

Nausea was observed in one patient (3.33%) in the granisetron group compared to three patients (10%) in the pethidine group. Kranke *et al*.,[28] in their review found that three trials reported on nausea or vomiting with meperidine 25 mg, 50 mg, or 0.4 mg/kg. In those, six of 82 patients (7.3%) had nausea or vomited with meperidine compared with two of

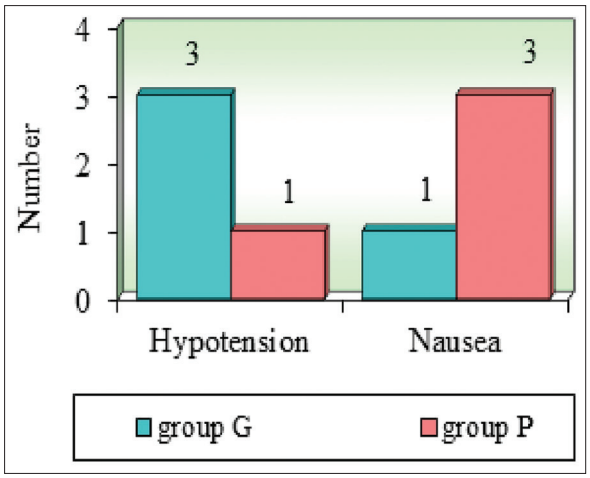

Figure 3: Comparison of side effects between two groups

76 (2.6%) with placebo, a difference that was not statistically significant (risk ratio, 2.84; 95% confidence interval, 0.60–13.5). Sajedi *et al*. reported a higher incidence of nausea (27.3%), vomiting (3%), and respiratory depression (12.1%) in meperidine group. The study also showed nausea in 3% patients in granisetron group.[26] Mohammadi *et al*. study concluded granisetron prevents shivering, and it also reduced nausea and vomiting.

The incidence of side effects such as nausea and vomiting was absent with granisetron but was seen with pethidine, and the results of our study are in consistent with the above-mentioned other studies. Nausea in pethidine group was treated with IV metoclopramide 10 mg.

Conclusions

Prophylactic granisetron 40 mcg/kg IV is equally effective as pethidine 0.4 mg/kg in the prevention of perioperative shivering following spinal anesthesia, maintains core temperature and oxygen saturation levels above that of pethidine. Prophylactic granisetron also reduces the need of antiemetics.

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Conflicts of interest

There are no conflicts of interest.

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