RESEARCH ARTICLE

High Dose but not Low Dose Granisetron Decreases Incidence and Severity of Post Anesthesia Shivering (PAS) and Postoperative Nausea and Vomiting (PONV) following Lower Abdominal Surgeries under Spinal Anesthesia

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Background: Post Anesthesia Shivering (PAS) is one of the common complications throughout recovery from general and regional anesthesia. The incidence of this complication is reported to be 40-70% among patients. PAS occurrence depends on various factors such as age, gender and drugs used in anesthesia and surgery time. Granisetron is a serotonin 5HT3 receptor antagonist. Beneficial effects of such drugs have been shown in a limited number of studies. In this study, preventive effects of granisetron in prevention of shivering, nausea and vomiting following spinal anesthesia were evaluated in patients undergoing lower abdominal surgery.

Methods: One hundred and five patients aged 18-60 years and with ASA class I or II who were scheduled to undergo elective lower abdominal surgery under spinal anesthesia were studied in 3 groups of 35 patients. After spinal anesthesia, group L received low dose granisetron with a dose of 10µg/kg, group H received high dose granisetron with a dose of 40 µg/kg and group C received normal saline as placebo. After leaving the operating room, patients were monitored in terms of shivering occurrence, time and severity of it and incidence of nausea and vomiting.

Results: Incidence of shivering, nausea and vomiting was significantly lower in group H than C. (P=0.009 and 0.008, respectively). However, there was no significant difference between L and C or L and H groups in terms of shivering, or nausea and vomiting occurrence. No side effects of granisetron were observed in the study.

Conclusion: High dose granisetron with dose of 40µg/kg significantly reduced the prevalence and severity of PAS and PONV in comparison to placebo.

Keywords: granisetron; post anesthesia shivering; pas; postoperative nausea and vomiting; PONV

Post Anesthesia Shivering (PAS) is one of the common complications throughout recovery from general and regional anesthesia. The incidence of this complication is reported to be 40-70% in patients [1-3]. PAS occurrence depends on various factors such as age, gender and drugs used in anesthesia and surgery time [4]. PAS is characterized by peripheral vasoconstriction and visible involuntary muscular activity. Considered as a physiologic response to increase body metabolic heat production, PAS mostly occurs as either a response to hypothermia during surgery or extrapyramidal complications of the used drugs [5]. Throughout neuroaxial anesthesia, shivering and hypothermia occur as result of central neuroaxial blockage which in turn leads to the lack of sensory input from the lower extremities under anesthesia. Perioperative hypothermia is considered the most common cause of PAS [6].

Spinal anesthesia (SA) impairs body thermoregulation and it subsequently increases the shivering to 56.7% [1]. Shivering has some potentially harmful effects such as increased CO2 production, heart activity, oxygen consumption and pulmonary ventilation and decreased mixed venous oxygen saturation [1]. Furthermore, shivering increases the metabolic rate by up to 500 percent of the base. Based on monoamine thermoregulation theory mentioned by Felberg and Meyers, 5HT3 serotonin receptors located in pre-optic part of anterior hypothalamus have a significant role in thermoregulation and shivering [1].

While PAS is described by patients as an extremely unpleasant incident, it might also be accompanied by numerous physiologic disturbances [7]. Increased oxygen consumption and arteriolar hypoxemia with linear increase in CO2 production can lead to lactic acidosis which cannot be tolerated in critical patients [7]. Increased intraocular pressure (IOP) and intracranial pressure (ICP) are the two most dreaded probable complications. Furthermore, PAS

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causes artefacts in the monitoring systems making it challenging to monitor parameters such as pulse rate (PR), blood pressure (BP), pulse oximetry (SpO2) and ECG [8].

Deterioration of surgical wound pain, impaired wound healing and delay in discharge from the PACU are also considered as the complications of PAS [1]. Due to these malicious and unwanted effects of PAS, it seems necessary to prevent and treat PAS timely.

Numerous pharmacologic and non-pharmacologic interventions are routinely used to treat PAS [9]. Warming the skin surface with various methods can increase the tolerance to the reduction in core temperature in hypothermic patients [4,6]. Unfortunately, current available methods and equipment of heat engineering can only assist trivially in increasing body core temperature. Consequently, these methods are effective only in very few while most patients need more effective pharmacologic treatment methods [4]. Relative efficacy of different drugs in controlling and treatment of PAS has been evaluated in many studies [10].

Pethidine, butorphanol and ketamine are the drugs whose prophylactic anti-shivering properties have been well-studied [11]. Although the relative prophylactic effects of these drugs have been determined in studies, their administration for prevention of shivering has not been satisfactory due to some complications such as increased incidence of postoperative nausea and vomiting (PONV) and hemodynamic changes [6,12-13]. Granisetron is a serotonin 5HT3 receptor antagonist which is used as an antiemetic drug for treatment of chemotherapy induced nausea and vomiting [14]. It mainly acts through reducing the activity of the vagus nerve; the vomiting center in the medulla oblongata is activated through the vagus nerve stimulation. Granisetron is tolerated well by the patients thanks to its low adverse effects. The most commonly reported adverse effects of granisetron are but not limited to headache, dizziness and constipation. No significant drug interactions have been reported with the use of this drug [14].

Granisetron has been shown to be more effective than ondansetron in preventing nausea and vomiting after spinal anesthesia for laparoscopic surgeries [16]. Ondansetron is more effective than meperidine in shivering prevention after OPCABG [8].Occurrence of PONV and itching is lower in patients having received granisetron in comparison to metoclopramide [20].

This study aimed at evaluating the effects of two different granisetron doses (10μg/kg vs. 40μg/kg) in the prevention of PAS and PONV following spinal anesthesia in patients undergoing lower abdominal surgery.

Methods

This study is a randomized clinical trial performed on patients 18-60 years undergoing lower abdominal surgery under spinal anesthesia with ASA class of I or II from both genders in 2014-2015. The study has been registered by the IRCT number: 201411203915N14. Considering the frequency of shivering as the primary outcome of the study, and a prevalence of 40% shivering in patients, power of 80% and alpha of 0.05, sample size for of 32 each group was defined which was increased to 35 to empower the study. Our study was a double blind study in which neither the physician nor the patients were aware of the intervention used. Sampling method was based on using sealed envelopes and a computerized numbering. Inclusion criteria are all patients from both genders between 18-60 years and ASA class of I or II undergoing elective lower abdominal surgery under spinal anesthesia. Exclusion criteria were patients refusing spinal anesthesia or those having contraindications for regional anesthesia including but not limited to lack of patient satisfaction, history of coagulopathies such as thrombocytopenia or administration of anticoagulant drugs, infection at the site of lumbar puncture, anatomic lesions of the spinal cord, brain space occupying lesions and any probable reduction in the volume of body fluids for example in surgeries with severe bleeding. Sensitivity to drug was the only contraindication for granisetron (Shanghai, China, Shucan Industrial Company) administration in this study. After obtaining approval from the ethics committee of Tabriz University of Medical Sciences and written informed consent from the participants, 105 patients who met the inclusion criteria were allocated into three groups of 35: Groups L (low dose granisetron with a dose of 10 μg/kg), H (high dose of granisetron with a dose of 40 g/kg) and C (control group receiving normal saline as placebo). Injections containing five milliliters of granisetron with dosage of 10 g/kg or 40 g/kg or normal saline were administered intravenously in patients in study and placebo groups. Method of spinal anesthesia was the same in all groups. Spinal anesthesia was performed through L2-L3 or L3-L4 spaces using 10-15 mg of bupivacaine 0.5%. Instantly after spinal injection was performed and patients were positioned, medications were administered. Noninvasive BP monitoring, EKG monitoring, pulse oximetry and axillary thermometry were performed for all patients. Temperature of the operating room and post-anesthesia care unit (PACU) was maintained at the range of 24 C °. Shivering occurrence and severity, hemodynamic parameters and complications including post-operative nausea and vomiting (PONV)until discharge from PACU were controlled and recorded. Vital signs and hemodynamic parameters are recorded every five minutes until discharge of the patient from recovery. Severity of shivering was measured based on Wrench five-point rating score3 (0, no shivering; 1, peripheral vasoconstriction without visible muscular activity; 2, visible muscular activity confined to one muscle group; 3, visible muscular activity in more than one muscle group; 4, gross muscular activity involving the entire body) by a recovery nurse who was blinded to the medications used in all groups. For shivering with the severity of ≥3, heating was used. If shivering continued, intravenous pethidine (25mg) and in the patients with nausea and vomiting intravenous metoclopramide (10mg) was administered. Response to treatment was monitored at five-minute intervals. Statistical analysis for comparison of the three groups in terms of shivering, PONV and complications was performed using paired T-test, ANOVA, Chi square, Mann Whitney tests with SPSS 18 software. P value less than 0.05 was considered statistically significant.

Results

This study was conducted on 105 patients undergoing spinal anesthesia. Demographic characteristics of the studied patients are presented in (Table 1). There was no statistically significant difference between 3 groups in terms of demographic characteristics. Comparison of the duration of anesthesia, the amounts of received intravenous fluid during

surgery, duration of surgery and ASA class between 3 groups is shown in (Table 1). There was no significant difference between 3 groups in terms of duration of anesthesia, the amounts of received intravenous fluid during surgery, duration of surgery and ASA class. (Table 2) shows the incidence and severity of shivering in 3 groups.

Five, three and 15 people experienced shivering of grade 3 or higher in groups L, H and C, respectively. In terms of shivering incidence, there was no significant difference between groups L and C, and L and H. However, there was a significant difference between groups H and C (P=0.009). In terms of need to treatment which indicated shivering of grade 3 or higher, there was no significant difference between groups L and H; however, there was significant difference between groups H and C (P=0.003), and L and C (P=0.023).

None of the patients needing treatment responded to the treatment with warmer. Thus, in these patients, we had to use pethidine. Since all patients responded to a single dose of pethidine, these two treatment methods were not considered for statistical analysis.

Time of shivering occurrence is shown in (Table 3). There was no significant difference in this parameter between the three groups. In terms of PONV occurrence, there was no significant difference between groups L and C, and L and H. However, there was a significant difference between groups H and C (P=0.008).

Table 1- Demographic characteristics of the patients in 3 groups

	Group L	Group H	Group C
Average age (year)	43.74±2.500	42.83±2.107	41.91±2.208
Average weight (kg)	70.17±1.768	69.43±1.376	71.57±1.936
Average height (cm)	168.74±1.119	169.26±1.036	166.34±0.970
Average of surgery duration (hour)	1.10±0.100	1.23±0.126	1.364±0.118
Average of received intravenous fluid during surgery (L)	1.258±0.097	1.314±0.108	1.285±0.089
Average of duration of anesthesia (hour)	2.257±0.136	2.328±0.143	2.357±0.150

Table 2- The incidence and severity of shivering in 3 groups

	Group L (person)	Group H (person)	Group C (person)
No shivering	21	25	13
Piloerection	6	4	4
One muscle	3	3	3
More than one muscle	5	3	10
Whole body	0	0	5

Table 3- Time of shivering occurrence

	10 min	20 min	30 min	40 min	50 min	60 min
Group L	2	2	1	1	2	4
Group H	4	2	1	0	0	3
Group C	2	7	2	2	1	3

Discussion

Shivering is a substantial concern in patients after surgery. In this study, incidence of shivering of degree 3 or higher in control group was 57% which is similar to the incidence of shivering reported in Shakya [15], Igbal [7] and Abdollahi atudies [8].

In our study, high dose granisetron (40 g/kg) had a significant effect on PAS. In a study comparing the effect of ondansetrone and low dose ketamine (0.25mg/kg) on shivering after spinal anesthesia in lower abdominal surgeries on 256 patients, shivering occurred significantly more often in patients treated with ketamine, ondansetrone was used as a rescue therapy in those not responding to ketamine in this study [18]. Similar to our study, PAS following laparoscopic surgery under general anesthesia has been reported to be significantly lower in patients having received granisetron (40 g/kg) [7].

Ondansetron has been reported to be of significant effect on prevention of shivering after off-pump CABG; shivering occurred in 31.18% in ondansetron group and 60.83% in control group [8]. In a study performed on 4 groups of 40 patients undergoing urologic surgeries, in the group receiving granisetron, shivering occurred in only 6 patients [10].

In a study on children undergoing lower extremity surgery, in control group of 40, 6 patients had shivering. Shivering was not observed in any patient among 40 patients who received granisetron (10 g/kg) [17]. Shakya et al. study demonstrated that ondansetron had a significant effect on shivering control after abdominal surgery [19]. Likewise, shivering occurrence was significantly lower in granisetron (40 g/kg) receiving group in comparison to control group in a study on 132 patient following elective orthopedic surgery [20].

In another study on 160 patients, 15% of patients in granisetron (3mg) and 55% of patients in control group experienced significantly higher incidence of PAS following elective surgery [21]. Ramosetron with dose of 0.3 mg was shown to have a significant effect in reduction of postoperative shivering in a study performed on 52 patients undergoing knee arthroscopy [22].

A significant decrease in PAS occurrence was also reported in patients who received ondansetron (4mg) in comparison to control group in a study conducted on 105 orthopedic surgery patients who underwent general anesthesia [23].

Forty percent of patients in control group and 6% in granisetron group had shivering in a study performed on 45 urologic, orthopedic and general surgery patients [24].

In our study, high dose but not low dose granisetron reduced the insidence of shivering significantly. Likewise, high dose but not low dose granisetron reduced the insidence of PONV significantly.

In our study, granisetron with doses of 1 and 3 mg did not have any significant effect on time of shivering occurrence. Time of shivering occurrence was not evaluated in any of the similar studies which might be considered the strength of our study. Furthermore, in this study, it was shown that granisetron can be effective in prevention of PONV. Granisetron in dose of (40 g/kg) had a significant effect on PONV after surgery but it did not have significant effect on PONV in dose of (10 g/kg).

In a study on patients undergoing laparoscopic cholecystectomy, incidence of PONV was 75% in patients who received placebo; whereas, it was 35% with ondansetron, 30% with granisetron and 25% with dexamethasone [17].

In a study evaluating the effect of granisetron and ondansetron in prevention of PONV on 90 laparoscopic surgery patients under spinal anesthesia, nausea occurrence of 10%, 30% and 40% was reported in granisetron, ondansetron and normal saline groups, respectively. Based on findings of this study, it was shown that granisetron was more effective than ondansetrone in prevention of PAS after spinal anesthesia for laparoscopic surgeries [25].

Conclusion

High dose granisetron (40 g/kg), without having any undesirable complications, decreases incidence and severity of post anesthesia shivering (PAS) and postoperative nausea and vomiting (PONV) following lower abdominal surgeries under spinal anesthesia.

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