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Research Article

Different drugs for prevention of post subarachnoid block shivering. Randomized, controlled, double blind study

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KEYWORDS

Granisetron;
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Tramadol;
Shivering

Abstract *Background:* Shivering is one of the most stressful complications for both the surgeon and the anesthesiologist during neuraxial anesthesia. The aim of this prospective randomized double blinded study was to evaluate the effectiveness of preoperative administration of granisetron, dexmedetomidine, and tramadol in prevention of shivering in patients undergoing elective operations with subarachnoid anesthesia.

Methods: 320 patients ASA I or II aged between 18 and 65 years scheduled for elective operations under subarachnoid block were included in the study. They were divided randomly into four equal groups, and 10 min before performance of subarachnoid block, patients in group G (n = 80) received 40 μg/kg intravenous infusion of granisetron in 100 ml of normal saline, patients in group D (n = 80) received 0.5 μg/kg intravenous infusion of dexmedetomidine in 100 ml of normal saline, patients in group T (n = 80) received 1 mg/kg intravenous infusion of tramadol in 100 ml of normal saline, and patients in group C (n = 80) received 100 ml of normal saline as control.

The following parameters were assessed: heart rate, mean arterial blood pressure, SPo2 and core temperature at the following times: 0 time, 5 min,10 min, 15 min, then every 15 min till end of the surgery. The incidence and intensity of shivering during the operation were recorded.

Results: Study found statistically significant decrease in the incidence of shivering in group G, group D, and group T in comparison with group C without statistical significant difference between group G, group D, and group T. There was no statistical significant difference in the core temperature between the four groups.

Conclusion: Preoperative administration of granisetron, dexmedetomidine, and tramadol was effective in decreasing the incidence and intensity of post subarachnoid shivering without increasing the incidence of the side effects.

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1. Introduction

Shivering is a fasciculation or tremors of the face, jaw, head, trunk, or extremities lasting longer than 15 s [1]. Multiple sequelae caused by shivering were increase in oxygen consumption, carbon dioxide production, metabolic rate up to 400%, and lactic acidosis [2]. Shivering usually associates anesthesia either general or subarachnoid anesthesia [3]. Multiple mechanisms are suggested to explain occurrence of shivering such as inhibition of central thermoregulation [4] or inhibition of the autonomic vasoconstrictive tone in the lower half of the body after subarachnoid anesthesia leading to redistribution of core temperature to the peripheral tissues and then to the environment leading to hypothermia [5]. Researches continue to find the best anti-shivering drug but still the optimum one is not discovered yet [6].

Granisetron is serotonin (5-hydroxytyptamine 3,5-HT) antagonist which is used mainly as anti-emetic but recently it has been reported that it can prevent post anesthetic shivering as serotonin (5-hydroxytyptamine 3,5-HT3) is involved in the regulation of body temperature as it is responsible for adjustment of thermoregulatory set range in the anterior hypothalamus [7] so administration of 5-HT3 antagonists would decrease the set range and prevent post anesthetic shivering [8].

Dexmedetomidine is an α 2-agonist that decreases vasoconstriction and shivering thresholds and when administered with meperidine additively can reduce the shivering threshold in healthy volunteers. Intraoperative dexmedetomidine reduces postanesthetic shivering as the meperidine does after surgery [9].

Tramadol, which is a weak opioid, has a role in prevention of post subarachnoid shivering as it inhibits reuptake of nor epinephrine, dopamine, and serotonin [10].

Hypothesis of this study was that each of granisetron, tramadol, and dexmedetomidine when administered intravenously before the subarachnoid block could decrease the incidence and severity of post subarachnoid shivering.

This prospective randomized controlled double blinded study aimed to evaluate the effectiveness of granisetron, dexmedetomidine, and tramadol in decreasing the incidence and severity of the post subarachnoid block shivering and their effect on the core temperature of the patients during anesthesia.

2. Methods

This study was done in El Minia University Hospital in the period from January to December 2013, after approval of the local ethical committee from the faculty of medicine in El-Minia University and obtaining written informed consents from the patients. 320 patients, ASA I or II aged 18–65 years prepared for elective operations under subarachnoid anesthesia, were included in this study. Patients with coagulopathy, impaired renal or hepatic function, thyroid disease, alcohol intake, use of vasodilators, and patients with fever more than 37.5 °C, and those who are allergic to any of the used drugs are excluded from the study.

This was a prospective randomized study, and patients eligible for the study (320 patients) were randomly allocated into the four study groups as 80 patients per group using random allocation software (windows software, version 1.0, may 2004). The allocation ratio is 1:1, and the group identification paper was put in a sealed and opaque envelops to hide allocation and it was opened just before the patients entered the study.

This was a double blind study in which the drugs of the study were administered preoperatively in 100 ml of normal saline by an anesthesiologist not involved in the study, and the bottles are labeled as G, D, T, and C and given to the blinded patients via intravenous route 5 min before performance of subarachnoid anesthesia. All the members of anesthetic team, surgeons, and patients were blinded with the type of the test drug. At the end of the study these labels were known as follows:

Group (G) received 40 μg/kg granisetron.
Group (D) received 0.5 μg/kg dexmedetomidine.
Group (T) received 1 mg/kg tramadol.
Group (C) received only 100 ml normal saline.

Temperature of the operating room was maintained at 22–24 °C and measured by wall thermometer. Intravenous fluids were used at room temperature and no other warming devices were used. No premedications were given to the patients. Monitor was used to record heart rate, noninvasive blood pressure, and SPo2 of the patients. Core temperature probe was introduced in the ear until touching tympanic membrane and covered with cotton swap. Advisor monitors (Smith Medical PM, Inc., Wakkesha, WL 53186) were used in this study. These parameters were measured immediately after the subarachnoid block considered 0 time, and then at 5, 10, 15 min and then every 15 min till the end of the surgery. Under complete aseptic conditions subarachnoid anesthesia was performed at L4–5 through midline approach with 25 gauge spinal needle while the patients were in the sitting position using 15 mg of hyperbaric bupivacaine hydrochloride after keeping at room temperature for 15 min. Patients were repositioned supine with oxygen 4 l/min was applied via nasal cannula. Patients were covered with one surgical drape. Motor block was assessed with modified Bromage scale after 5 min of subarachnoid anesthesia (0 = no block 1 = hip block 2 = hip and knee block 3 = hip, knee, and ankle block). Sensory block was evaluated by pin prick sensation. Shivering was assessed by 5 point scale (0 = no shivering, 1 = piloerection, peripheral vasoconstriction, peripheral cyanosis or combination with no other cause, without visible muscular activity, 2 = visible muscular activity confined to one muscle group, 3 = muscular activity in more than one muscle group, 4 = gross muscular activity involving the entire body) [11]. Intravenous meperidine (10–25 mg) was given if patients had shivering (grade 3 or 4) not controlled by the test drugs and the total dose was recorded for each group. Atropine 0.5 mg intravenous was given if there was bradycardia less than 50 beat per minute. Ephedrine 10 mg intravenous was given if the blood pressure decreased less than 20% of the baseline measurement. Side effects of the drugs such as nausea, vomiting, hypotension, excessive sedation, respiratory depression (SPo2 less than 90%) are recorded. At the end of the operation the patients are transferred to the Post Anesthesia Care Unit (PACU) covered with one cotton blanket.

The primary outcome was the incidence and severity of post subarachnoid block shivering, while the 2nd outcome was the core temperature of the patients.

2.1. Statistical analysis

Sample size was calculated by PASS 2000 (Power Analysis Software; NCSS, Kaysville, UT, USA) and it was determined on the base that the incidence of shivering was 55% and could be reduced to 30% with effective treatment, with alpha error of 0.05, power of 80%. It was calculated to be 72 patients and it was increased to 80 patients for dropout and more accuracy.

SPSS software, version 17 (SPSS Inc., Chicago, IL, USA) was used to analyze the statistical data. Results are expressed as mean ± SD or numbers. Categorical data including incidence of shivering were analyzed using Chi square test. Numerical data as core temperature were analyzed using Student's *T*-test between two groups, while independent *T*-test was used to compare data within the same group, and between the 4 groups was done by one-way ANOVA test. *P* value < 0.05 was considered significant.

3. Results

This study included 320 patients who were divided into four groups of 80 patients for each flowchart Fig. 1. There was no significant difference between the 4 groups as regards age, weight, height, gender, type of operations, and duration of surgery.

There was no significant difference between the 4 groups as regards vital signs (SPo2, HR, B.P) when compared to each other.

There was a statistically significant decrease in the core temperature after the subarachnoid anesthesia in the 4 groups when compared to the baseline values before subarachnoid anesthesia but there was no statistical significant difference between the 4 groups when compared to each other at different points Fig. 2.

The incidence of shivering (Fig. 3) was in 44 (55%) patients in the control group ($n = 80$) who developed shivering: only 2 patients developed grade 4 shivering, 7 patients developed grade 3 shivering, 20 patients developed grade 2, and 15 patients developed grade 1 while 36 didn't develop shivering at all. In granisetron group 11 (13.75%) patients developed different grades of shivering, no patient developed grade 4 or 3 shivering, 6 patients developed grade 2 shivering, 5 patients developed grade 1 shivering, while 69 patients developed no shivering. In dexmedetomidine group 9 (11.25%) patients developed different grades of shivering as follows, no patients developed grade 3 or 4, 4 patients developed grade 2 shivering, 5 patients developed grade 1 shivering while 71 patients developed no shivering. In tramadol group 10 (12.5%) developed different grades of shivering as follows, no patients developed grade 3 or 4 shivering, 5 patients developed grade 2 shivering, 5 patients developed grade 1 shivering while 70 patients developed no shivering.

As regards side effects only 1 patient in control group and tramadol group developed nausea and vomiting. 7 patients in each group of granisetron group, dexmedetomidine group, and control group while 8 patients in tramadol group developed hypotension which was treated with ephedrine intravenously.

As regards total dose of meperidine was given to each group for treating shivering which was not controlled by the study drugs and there was a significant increase in its dose in the control group 450 mg more than the 4 other groups (see Tables 1–3).

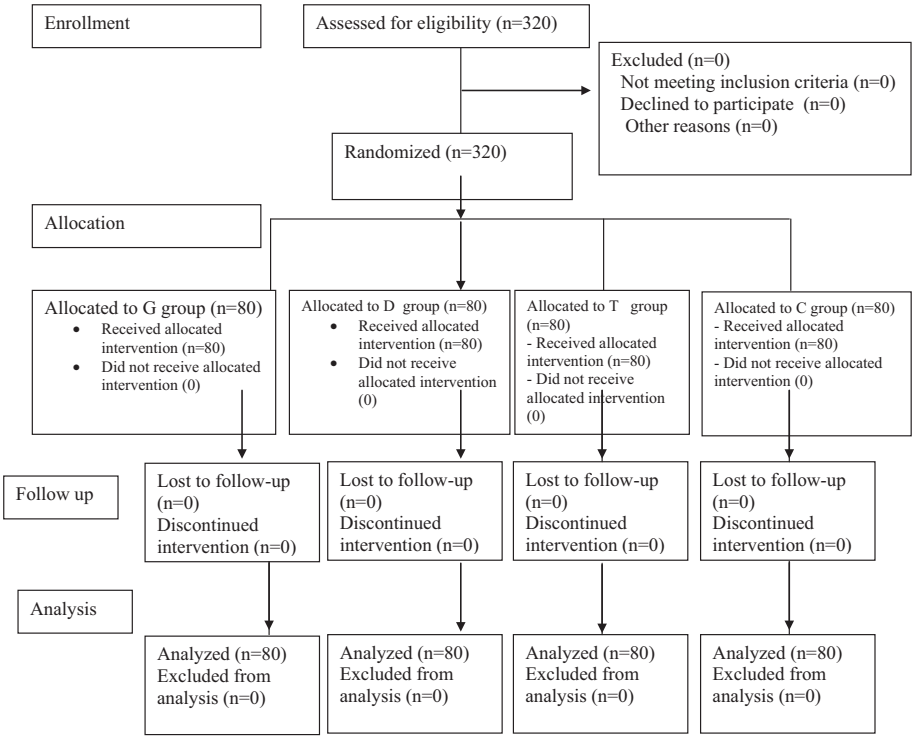

Figure 1 Flowchart in the study.

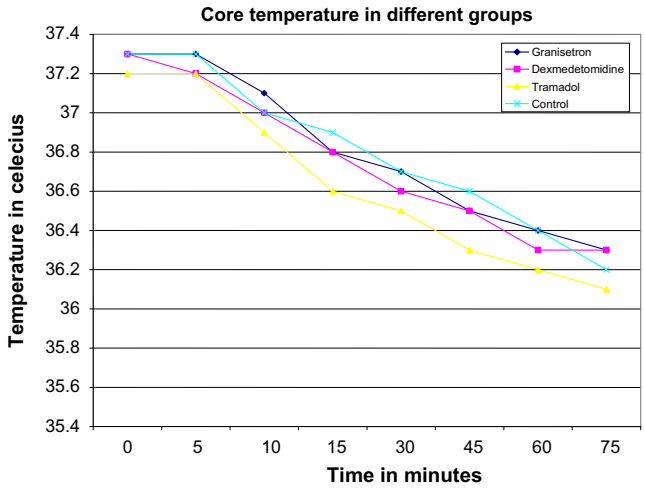

Figure 2 Core temperature in different groups. Significant decrease in core temperature in the 4 groups after subarachnoid block compared to the baseline measurement. No significant difference between the 4 groups.

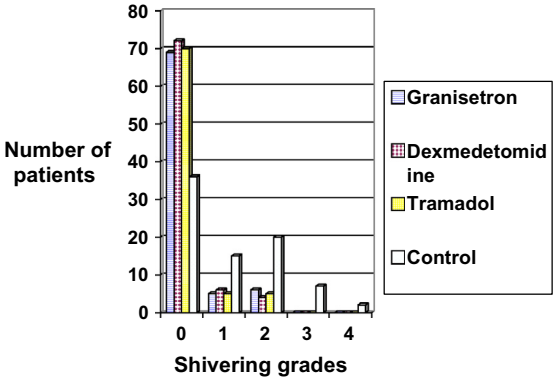

Figure 3 Shivering grades in different study groups. $^{*}p < 0.05$ compare control group with the other 3 groups.

4. Discussion

Shivering represents a body response to the decreased body temperature which should be maintained within the range of 36.5–37.5 °C [12]. Multiple risk factors such as age, high level of the sensory block, and temperature of the operation room and fluids are contributing to shivering in neuraxial anesthesia [13].

Different drugs have been used in prevention and treatment of shivering such as meperidine, clonidine, and ketamine but these drugs still have many drawbacks limiting their use as hypotension with clonidine, tachycardia and hypertension with ketamine [14]. The best drug for prevention of shivering is the one which can reduce the temperature threshold for shivering near the patient's body temperature with fewer side effects [15]. Although the room temperature was maintained in this study within 22–24 °C and the fluids given to the patients were at room temperature keeping body temperature of the patients within its normal range was not applicable and also shivering could be observed in patients with normal temperature under neuraxial anesthesia [16].

The current study showed that each of granisetron 40 μg/kg, dexmedetomidine 0.5 μg/kg and tramadol 1 mg/kg, decreased the incidence and intensity of shivering in patients exposed to elective operations under subarachnoid anesthesia when compared to placebo, but these drugs couldn't prevent the significant decrease in the core temperature after the subarachnoid block. This anti-shivering effect was not associated with increase in the side effects.

Kose et al. [17] examined effectiveness of prophylactic intravenous administration of 0.25/kg mg and 0.5 mg/kg of ketamine in cesarean section under spinal anesthesia and they found that the incidence of shivering in control group was 40% which is lower than what was noticed in the control group of this study (55%). This difference may be caused by additional warming measures such as warming of the fluids and forced-warm air that maintained body temperature of the patients.

Incidence of shivering in the control group in the prospective randomized study by Powell and Buggy [18] to evaluate the efficacy of ondansetron and dolasetron which are serotonin

Table 1 Demographic data, type, and duration of surgery.

Item	Granisetron (n = 80)	Dexmedetomidine (n = 80)	Tramadol (n = 80)	Control (n = 80)	P value
Age (years)	44 ± 13 years	42 ± 14 years	42 ± 14 years	45 ± 12 years	0.985
Weight (kg)	84 ± 12	85 ± 10 kg	87 ± 8 kg	83 ± 12 kg	0.945
Height (cm)	172 ± 8 cm	173 ± 9 cm	172 ± 7 cm	172 ± 8 cm	0.707
Sex (male/female)	49/31	40/40	46/34	48/32	0.835
Duration of surgery (min)	80 ± 17 min	75 ± 20 min	89 ± 11 min	85 ± 14 min	0.573
Type of surgery					
General	12	16	13	15	
Vascular	13	15	12	14	
Plastic	7	6	8	7	
Andrology	13	10	14	10	
Orthopedics	7	9	15	10	
Urological	14	13	10	11	
Gynecology	14	11	8	13	

$^{*}p$ value < 0.05 considered significant.
One-way ANOVA test used to compare between numerical data.
Chi-square test used for categorical data.

Table 2 Side effects in each study group.

Item	Granisetron ($n = 80$)	Dexmedetomidine ($n = 80$)	Tramadol ($n = 80$)	Control ($n = 80$)	P value
Nausea, vomiting	0	0	1	1	0.52
Respiratory depression	0	0	0	0	1
Hypotension	7	7	8	7	0.74
Bradycardia	0	0	0	1	0.54
Excessive sedation	0	0	0	0	1

One-way ANOVA test was used to analyze number of side effects occurred.
No significant difference between the 4 groups.

Table 3 Total dose of drugs administered to all patients (80 patients) in each study group.

Item	Granisetron ($n = 80$)	Dexmedetomidine ($n = 80$)	Tramadol ($n = 80$)	Control ($n = 80$)	P value
Atropine	0	0	0	1 mg	0.65
Ephedrine	100 mg	105 mg	110 mg	110 mg	0.86
Metoclopramide	0	0	15 mg	10 mg	0.52
Meperidine	80 mg	60 mg	80 mg	450 mg*	0.03

One-way AOVA test used for analysis of data between the 4 groups.
* p value < 0.05 considered significant.

antagonist in prevention of shivering in patients under spinal anesthesia was 55% which was in agreement with the present study, and they found that serotonin antagonist (ondansetron and dolasetron) decreases this incidence to 33%. Granisetron is more potent than ondansetron.

These findings was in agreement with the prospective randomized double blinded study by Sajedi et al. [19] to evaluate the efficacy of prophylactic administration of 40 μg/kg of granisetron in comparison with tramadol 0.1 mg/kg and meperidine 0.4 mg/kg in elective orthopedic surgeries under general anesthesia and they found that granisetron, and tramadol were effective as meperidine in prevention of shivering without prolonging the emergence time from anesthesia.

Usta et al. [20] in their study on 60 patients scheduled for minor elective surgeries under spinal anesthesia to evaluate the effectiveness of 1 μg/kg dexmedetomidine infusion as a loading dose followed by 0.4 μg/kg/hr during surgery in prevention of shivering when compared to placebo group and they found that dexmedetomidine decreases the incidence of shivering from 57% in the control group to 10% but this effect was associated with increased sedation which was caused with the high dose used.

This study found that there was a statistically significant decrease in the core temperature in the four groups after the subarachnoid block when compared to the baseline value but without significant difference in between the four groups.

This is in agreement with Bozgeyik et al. [21], who compared between dexmedetomidine 0.5 μg/kg and tramadol 1 mg/kg in 100 ml of normal saline against placebo after spinal anesthesia in prevention of shivering in patients that underwent knee arthroscopy and they found that in spite of the efficiency of dexmedetomidine and tramadol in decreasing the incidence of shivering they cannot prevent occurrence of hypothermia. Talke et al. [22] suggested that dexmedetomidine action in prevention of shivering is related to its ability to increase the range of temperature that did not stimulate the thermoregulatory defense mechanism and can decrease shivering threshold temperature.

Elvan et al. [23] who found that dexmedetomidine 1 μg/kg followed by 0.4 μg/kg infusion could reduce the incidence of shivering in 90 female patients did hysterectomy and they found that the core temperature decreased in the patients after anesthesia.

Bicer et al. [24] compared dexmedetomidine 1 μg/kg with 0.5 mg/kg meperidine in 120 patients under general anesthesia exposed for major abdominal or orthopedic surgeries for 1–3 h and they found that dexmedetomidine could reduce the incidence of shivering but it was associated with delayed orientation time which may be related to the dose 1 μg/kg they used which is double the dose that I have been used 0.5 μg/kg.

The incidence of excessive sedation, respiratory depression, nausea and vomiting in this study was low in spite of using dexmedetomidine and tramadol may be related to the low dose used 0.5 μg/kg dexmedetomidine and 1 mg/kg of tramadol and slow infusion rate.

There are some limitations to this study, first is the wide variation of surgeries included in the study with different size of the area exposed for surgery, different volume of irrigating and washing fluids in urological operations. Second limitation is not using nasopharyngeal probe (more accurate) for core temperature measurement but it was not suitable for awake not sedated patients. Third limitation is the duration of included surgeries which was around 95 min; lengthy operations should be investigated to know the later effects of these drugs.

5. Conclusion

Preoperative administration of granisetron, dexmedetomidine, and tramadol in small dose and slow infusion rates was effective in decreasing the incidence and intensity of shivering in

patients that underwent surgeries under subarachnoid anesthesia without increase in the incidence of the side effects.

Conflict of interest

The author declares no conflict of interest in this study.

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