ORIGINAL ARTICLE

Comparison of intravenous butorphanol, ondansetron and tramadol for control of shivering during regional anesthesia: A prospective, randomized double-blind study

Joshi Smita Suresh, MD, DA*, Adit Arora, MBBS**, Arun George, MBBS**, Shidhaye Ramchandra Vinayak, MD, DA***

*Professor; **Resident
Department of Anesthesiology and Critical Care, Dr. D.Y. Patil Medical College Pimpri, Pune 411018 (India)

***Professor of Anesthesiology and Critical Care
Pravara Institute of Medical Sciences, Loni 413736 (India)

Correspondence: Dr.R.V.Shidhaye, Shraddha Clinic, Babhaleshwar Tal. Rahata, Dist. Ahmednagar-413737 (India); Phone: 02422 253459; Cell: +91 9822034601; E mail: rvshidhaye@yahoo.com

ABSTRACT

Aim: We conducted this study to compare the efficacy and safety of butorphanol, ondansetron and tramadol for control of shivering in patients undergoing surgical procedures under spinal anesthesia.

Methodology: In this prospective double-blind, randomized, controlled study, 150 patients of both genders, 18-60 years old, ASA I or II, booked for elective surgery under spinal anesthesia were randomly distributed into three groups of 50 each. Each patient, who developed shivering, was given either 0.03 mg/kg of inj. butorphanol 1% (Group-B), 0.06 mg/kg of inj. ondansetron (Group-O) or 1.0 mg/kg of inj. tramadol 1% (Group-T) IV. Demographic characteristics, incidence of shivering, response rate after 1, 3, 5, 10 and 20 min, recurrence rate, hemodynamic parameters and complications were observed.

Results: All patients were relieved of shivering after butorphanol; 66.6% of them were relieved within 1 min, 93.33% within 3 min and 100% within 5 min. Ondansetron could relieve shivering in only 29.4% of the patients; 5.88% within 1, 11.76 % within 3, 23.52% within 10 and 29.4 % within 20 min. Tramadol relieved shivering in 92.30%; 46.15% within 1, 84.61% within 3 and 92.30% within 5 min respectively ($p < 0.05$). Recurrence of shivering was observed in 26.67% of butorphanol group and 15.38% of tramadol group ($p > 0.05$).

Conclusion: Ondansetron was not found to be much effective for the control of shivering during regional anesthesia. Butorphanol and tramadol were equally effective in controlling shivering under regional anesthesia, the only difference being in their onset of action. Butorphanol was quicker in onset which is essential for control of shivering and should be preferred.

Keywords: Perioperative shivering; Spinal anesthesia; Regional anesthesia; Tramadol; Ondansetron; Butorphanol; Thermoregulatory center

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INTRODUCTION

Shivering is one of the most common complications of a central neuraxial blockade, due to impairment of the thermoregulatory control.[1] It has been reported in 40 to 70% of patients undergoing surgery under regional anesthesia.[2,3] Shivering, an involuntary, oscillatory muscular activity, is a physiological response to core hypothermia in an attempt to raise the metabolic heat production.[2] Prolonged impairment of thermoregulatory autonomic control under anesthesia along with the cold environment of operating rooms and cold infusion fluids, contributes to a fall in core body temperature, and hence shivering.[2,4] Other known causes of shivering include transfusion reactions, drug reactions, pre-existing high grade fever or bacteremia,

or infusion of contaminated intravenous fluids (fungal growth in dextrose containing fluids). Perioperative hypothermia is the most common cause of shivering, though the exact incidence of each is difficult to evaluate.

It causes arterial hypoxemia due to 200–500% increase in oxygen consumption, a liner increase in carbon dioxide production,[5] lactic acidosis, increased intraocular pressure (IOP) and increased intracranial pressure (ICP); and interferes with pulse rate, blood pressure (BP) and electrocardiographic (ECG) monitoring.[6-8] Thus in a patient with limited myocardial oxygen reserve or known coronary disease, shivering may further compromise myocardial function.[9] It may contribute to increased wound pain, delayed wound healing, and delayed discharge from post anesthetic care.[4] It is very unpleasant, physiologically stressful for the patient undergoing surgery, and some patients find the accompanying cold sensation to be worse than the surgical pain. All these deleterious effects warrant primary prevention and prompt control on occurrence of shivering.

A number of pharmacological interventions have been studied for the treatment and prophylaxis of shivering, including clonidine, ketamine, butorphanol, doxapram, tramadol, pethidine and other opioids, ondansetron and other $5HT_3$ receptor antagonists.[4,10-14] Ondansetron is $5HT_3$ receptor antagonist, primarily used to prevent emesis. It has also been tried successfully for prevention of shivering in dose of 8mg IV without any side effects.[15] We could not find studies that directly compare ondansetron to other two opioids, butorphanol and tramadol regarding its efficacy.

In this study we compared these three drugs regarding their efficacy and safety as an antishivering agent, aiming to find more effective, faster and safer agent to control shivering after regional anesthesia. Primary outcome measure was response rate within one minute after injecting the study drug. Secondary outcome measures were incidence of shivering, response rate after 3, 5, 10 and 20 min, total response rate, recurrence rate, hemodynamic parameters in patients having shivering and complication rate.

METHODOLOGY

A prospective double-blind, randomized study, designed with three parallel groups was conducted at Pad. Dr. D. Y. Patil Medical College Hospital Pimpri, Pune (India) during the period from June 2007 to May 2008. After obtaining approval from the institutional ethical committee, 150 patients of both genders, of age group between 18-60 years, and of American Society of Anesthesiologists physical status (ASA) I or II, booked for elective surgery under spinal anesthesia were enrolled in the study. Informed consent was obtained from all the patients. Exclusion criteria were severe systemic disorders like diabetes mellitus, hypertension, obesity (body mass index of ≥ 40 kg/m^2), compromised cardiovascular and respiratory conditions, renal insufficiency, peptic ulcer disease, thyroid disease, abnormal psychological profile, acute infections e.g. upper respiratory tract infection or urinary tract infection etc., and fever due to any other cause, allergy to any of the study drugs and all known contraindications to spinal anaesthesia. Patients unwilling to get enrolled in the study, unwilling for spinal anesthesia and those on long term phenothiazines and MAO inhibitors were also excluded from the study. Patients were randomly distributed into three groups of 50 patients each and randomization was concealed.

Group-B (Butorphanol group): In this group, each patient, who developed shivering, was given 0.03 mg/kg of inj. butorphanol 1% intravenously (IV.) It was considered as control group.

Group-O (Ondansetron group): In this group, each patient, who developed shivering, was given 0.06 mg/kg of inj. ondansetron IV. It was considered as study group.

Group-T (Tramadol group): In this group, each patient, who developed shivering, was given 1.0 mg/kg of inj. tramadol 1% IV. It was also considered as study group.

Method of Randomization: A 2-operator technique was employed to maintain blinding. The cases were randomly allocated (sealed envelope technique using computer generated random numbers) to one of three groups by an investigator selected to prepare the study drug solutions. Further interventions and monitoring were done by an investigator blinded to the group allocation.

Sample size and power calculations: Sample size was based on previous study of Maheshwari BS et al,[13] where shivering was controlled within 2 min in 92% of patients who received tramadol as compared to 28% of patients who received butorphanol. To detect a 64% difference in the response rate among the groups with 90% power and 5% alpha error (2-tailed), sample size of 13 cases per group was required. Previous studies found an incidence of shivering of the order of 40–70%.[2,3] Considering this we decided to take the sample size of 50 patients per group. Post-hoc power analysis was carried out for response rate within 1 minute. This study had 95% power to detect effect size of 60.78 between Group-B and Group-O and power of 60%

to detect effect size of 40.27 between Group-T and Group-O.

All patients were administered 0.5% bupivacaine 3-4 ml intrathecally, at L2-L3 or L3-L4 interspinous spaces, with 26G Quinke's spinal needle after preloading with 6-8 ml/kg of lukewarm crystalloid infusion and after recording the baseline vital parameters, e.g. pulse rate, blood pressure (BP), ECG, oxygen saturation (SpO_2), and axillary temperature. Sedatives and hypnotics inclusive of opioids were avoided in pre-medication as well as intra-operatively. Ambient temperature of the operating room and recovery room was maintained at 22–28°C.

After induction of spinal anesthesia, patients were observed for the occurrence of shivering, its disappearance, hemodynamic status and complications (if any) until the postoperative period. The intensity of shivering was graded on a scale 0–3 as: 0 = no shivering; 1 = shivering observed in face and head (mild), 2 = visible tremors involving more than one group of muscles (moderate), 3 = gross muscular activity involving the entire body / bed shaking (most severe degree). Only cases that developed shivering of grade 2 or 3 during the perioperative phase were given treatment on an intention to treat basis. At the onset of shivering (grade 2 or 3), all patients were given oxygen via face mask at 6 L/min and 1 ml of studied drug as per group allocation. Shivering control was defined as complete when the shivering score declined to 0, incomplete when the scores decreased but did not abolish the shivering completely, and failed if no change in scores was observed. The time taken for cessation of rigors and hemodynamic changes were observed at intervals of 1 min till 5 min and thereafter at 10, 20, 30, 45 and 60 min. Pulse rate, BP, ECG, SpO_2, respiratory rate and axillary temperature were noted immediately after regional anesthesia and during shivering and after drug administration at regular intervals. We did not use the nasal, esophageal or rectal probes for electronic temperature monitoring. Recurring (any rise in shivering scores post treatment), and side effects of the study drugs were noted in each group.

After completion of the study a statistical analysis was done, using the ANOVA test, paired t-test and chi square test. Statistical analysis was done using SPSS software, version 10.

RESULTS

Patients from all groups were comparable regarding age, gender, height, weight and ASA status (Table 1). Overall incidence of shivering was found to be 30% as shown in Table 2. The incidence of shivering in the butorphanol group was 30%, in the ondansetron group 34% and in the tramadol group it was 26% ($p > 0.05$). So 15 subjects received butorphanol, 17 subjects received ondansetron and 13 received tramadol. Butorphanol was found to be most effective among all study drugs in relieving shivering as it produced complete relief within one minute in more patients (66.66%) as compared to with tramadol and ondansetron (46.15% and 5.88% respectively). All patients were relieved of shivering after butorphanol; 66.6% within 1 minute, 93.33% within 3 min and 100% within 5 min, whereas ondansetron relieved shivering in only 29.4% patients; 5.88% within 1 minute, 11.76 % within 3 min and 23.52 within 10 min and 29.4% within 20 min . 70.6% of the patients who received ondansetron had no relief at all. In tramadol group 92.3% patients were relieved of shivering; 46.15% within 1 min, 84.61 % within 3 min, 92.3% within 5 min and no relief in 7.7% of patients. The difference in the relief of shivering was highly significant at 1 min ($p < 0.01$). Comparing the ondansetron group with the tramadol group, tramadol was found to be more effective in controlling shivering while both tramadol and butorphanol were found to be equally effective after 5 min (Table 3).

Table 1: Demographic characteristics

Characteristics		Butorphanol Group (n = 50)	Ondansetron Group (n = 50)	Tramadol Group (n = 50)
Age in years		36.5 ± 14.89	36.5 ± 13.06*	38.22 ± 16.75*
Height in cm.		164.86 ± 0.95	164.54 ± 11.09*	164.06 ± 11.43*
Weight in kg		64.1 ± 11.42	62.44 ± 12.66*	62.34 ± 10.79*
Gender	Male	28(56)	31(62)*	27(54)*
	Female	22(44)	19(38)*	23(46)*
ASA Grade	I	42(84)	31(62)	36(72)
	II	8(16)	19(38)	14(28)

Data given as Mean ± SD or N(%)

*p-value > 0.05 **p-value significant at 0.05; ***p-value significant at 0.01

Table 2: Incidence of shivering in three groups

Shivering	Butorphanol Group *(n = 50)*	Ondansetron Group *(n = 50)*	Tramadol Group *(n = 50)*	Total
Present	15 (30%)	17 (34%) *	13 (26%) *	45 (30%)
Absent	35 (70%)	33 (36%) *	37 (74%) *	105 (70%)
Total	50 (100%)	50 (100%)	50 (100%)	150 (100%)

*p-value > 0.05 **p-value significant at 0.05; *** p-value significant at 0.01

Table 3: Relief of shivering after giving study drug

Relief after injecting the drug	Butorphanol Group (n = 15)	Ondansetron Group (n = 17)	Tramadol Group (n = 13)
Within 1 minute	10 (66.66)	1 (5.88)	6 (46.15)***
Between 1 to 3 min	4 (26.67)	1 (5.88)	5 (38.46)**
Between 3 to 5 min	1 (6.67)	0 (0)	1 (7.69)*
Between 5 to 10 min	0 (0)	2 (11.76)	0 (0)*
Between 10 to 20 min	0 (0)	1 (5.88)	0 (0)*
No relief at all	0	12 (70.60)	1 (7.70)**
Recurrence of shivering	4 (26.67)	0 (0)	2 (15.38)*

*p-value > 0.05 **p-value significant at 0.05; ***p-value significant at 0.01

Table 4: Hemodynamic parameters in patients having shivering

Parameter		Butorphanol Group (n = 15)	Ondansetron Group (n = 17)	Tramadol Group (n = 13)
Heart rate (per min)	Pre shivering	78.53 ± 16.23	77.82 ± 12.35	77 ± 10.17*
	Intra shivering	81.53 ± 14.80	79.12 ± 11.12	79.57 ± 10.74*
	Post shivering	78.67 ± 13.57	76.89 ± 7.88	78.86 ±20.69*
Systolic Blood Pressure (mmHg)	Pre shivering	118.73 ± 11.92	120.18 ± 13.29	115.43 ±10.05*
	Intra shivering	116.13 ± 11.43	118.71 ± 14.81	113 ± 11.79*
	Post shivering	118.2 ± 10.13	123.22 ± 7.89	112.86 ±9.86*
DiastolicBlood Pressure (mmHg)	Pre shivering	74.4 ± 10.36	73.18 ± 12.72	71.14 ±9.06*
	Intra shivering	65.87 ± 13	67.76 ± 9.11	64.71 ± 9.07*
	Post shivering	70.13 ± 9.54	72.22 ± 9.15	68.57 ± 8.48*
Axillary temperature (°C)	Average	36.8 ± 0	36.74 ± 0.40	36.66 ± 0.41*

* p-value > 0.05 **p-value significant at 0.05; *** p-value significant at 0.01

Table 5: Incidence of Complications

Complications	Butorphanol Group *(n = 15)*	Ondansetron Group *(n = 17)*	Tramadol Group *(n = 13)*
Sedation	7(46.67)	0	0***
Itching	1(6.67)	0	0*
Nausea	0	0	4(30.77)***
Vomiting	0	0	1(7.69)*

* p-value > 0.05 **p-value significant at 0.05; *** p-value significant at 0.01

The recurrence of shivering was noted in 26.67% of patients in butorphanol group and in 15.38% of patients in tramadol group ($p > 0.05$) (Table 3). Table 4 shows hemodynamic status of the patients. There was no significant difference between three groups systolic and diastolic blood pressure and heart rate. There was also no significant differences in pre-, intra- and postshivering heart rate, systolic and diastolic blood pressures in any of the three groups. Axillary temperature, too, showed no differences in the groups. Table 5 shows the incidence of complications in study groups. In the butorphanol group 46.66% of the patients were sedated compared to none in the other group. One patient in the butorphanol group but none in the other two complained of itching. Four patients in the tramadol group complained of nausea and one had vomiting. This complication was noted in none of the other two groups.

DISCUSSION

Regional anesthesia, either central neuraxial block or peripheral nerve block is a safe and very popular technique used for various surgeries. However, 40-70% of patients undergoing regional anesthesia develop shivering, though it is also found to occur after general anesthesia.[2,3] The mechanism which leads to shivering after regional anesthesia is not very clear, but the probable mechanisms could be decrease in core body temperature secondary to sympathetic block; peripheral vasodilatation; increased cutaneous blood flow, which leads to increased heat loss through skin; cold temperature of operation theatre; rapid infusion of cold IV fluids; and effect of cold anesthetic drugs upon the thermosensitive receptors in the spinal cord.[16,17] There are many pharmacological and non-pharmacological methods used to prevent heat loss and decrease shivering. Non-pharmacological methods include radiant heat warmers, warming the operation theatre, blankets, warm IV fluids and using anesthetic drugs at body temperature.[18,19] It has been mentioned that hypothermia may cause postanesthetic shivering by alteration of thermoregulatory mechanism.[20] However, no relationship has been shown between axillary temperature and occurrence of shivering.[20] Rigors occur commonly, as a protective response to core hypothermia, though it may occur in the presence of normothermia.[10] In our study, there was no significant difference in axillary temperature among the groups. We had to resort to continuous measurement of axillary temperature by electronic monitors as we felt that a nasal, esophageal or rectal probe would be uncomfortable for the patients. A number of factors including age, duration of surgery, temperature of the operating room, and infusion solution, are risk factors for hypothermia and shivering.[21] So in our study, patients over the age of 60 years were excluded. The temperature of operating room was maintained at 22° to 28° C and infusions of crystalloid solution were warmed. This was probably the reason for lower overall incidence of shivering (30%) in our study as compared to other studies. We also excluded the patients having history of acute infections, sepsis and fever to reduce their confounding effect.

Pharmacological intervention does not raise body temperature, but resets the shivering threshold to a lower level, thereby decreasing rigors and its episodes. Various pharmacological therapies have been tried to prevent or treat shivering, including opioids (e.g. pethidine, nalbuphine, butorphanol or tramadol), ketanserin, propofol, ondansetron, granisetron, doxapram, physostigmine, clonidine, and nefopam etc., but debate for an 'ideal anti-shivering drug' still continues.[4,22] Tramadol hydrochloride, a μ-opioid receptor agonistic drug, has a modulatory effect on central mono-aminergic pathways, and thus inhibits the neuronal uptake of noradrenaline/serotonin and encourages hydroxytryptamine secretion which resets the body temperature regulation center. It has gained a reputation in many clinical trials for the control of shivering.[6,8,23] Butorphanol, an easily available opioid, acts through k and μ receptor agonistic modulation, though only a few studies have denoted its antishivering properties.[10,13] 5-hydroxytryptamine ($5\text{-}HT_3$) may influence both heat production and heat loss pathways.[21] Ondansetron and dolasetron, both $5\text{-}HT_3$ antagonists, have been effectively used in the treatment of postoperative shivering.[24,25]

In the present study, we compared the efficacy of butorphanol, ondansetron and tramadol for treatment of shivering after spinal anesthesia in patients undergoing various elective surgeries. All groups were comparable with regard to demographic characteristics. We found that butorphanol was as effective as tramadol in treating post-spinal anesthesia shivering, but the time to control of shivering was significantly less with butorphanol. The response rate was also higher in the butorphanol group than in the tramadol group, but the difference was not statistically significant ($p > 0.05$). Shivering is so distressing to the patient that quick response to antishivering agent is appreciated. Keeping this in mind we compared these drugs in respect of 'response within one minute' rate. We found butorphanol more effective than the other two drugs and ondansetron far less effective than the other two drugs regarding this. Regarding total response rate too,

ondansetron was found to be far inferior to the other two drugs. In contradiction to our findings, Ebru K et al[26] found ondansetron as effective as meperidine in controlling shivering. However, they used ondansetron in a dose of 8 mg as against 4 mg used by us. There was no significant difference between butorphanol and tramadol regarding total response rate after 5 min (100% as against 92.3%). Bansal et al[10] also found similar difference in butorphanol (83%) and tramadol (73%) in respect of total response rate (complete cessation of shivering after treatment) which was not significant ($p > 0.05$). Tramadol and butorphanol both had comparable results in complete suppression of shivering which accords with observations made by earlier investigators.[6,27,28] A higher incidence of recurrence of rigors was observed in tramadol treated patients in a study of Bansal et al,[10] which is in contrast to observations made by Maheshwari et al,[13] who observed a lower rate of recurrence with tramadol compared with butorphanol (8% vs. 25% respectively). We could not find statistically significant difference among the groups regarding recurrence. Sedation was noted in more in patients in butorphanol group and nausea more in tramadol group. Contrary to our results, Maheshwari et al[13] found a higher incidence of vomiting with butorphanol compared with tramadol. Bansal et al[10] found no difference in butorphanol and tramadol. All the three drugs were comparable regarding hemodynamic safety. There were no significant alterations during, pre- and post shivering period, after administration of all the three drugs similar to the results of Maheshwari et al[13] and Mathews et al.[29]

Limitations: The limitations of our study include a relatively small sample size in proportion to the burden of this perioperative problem. The results of our study may not coincide with studies done on other ethnic populations owing to variations in body surface area and their heat or cold tolerability. Another limitation of this study is that we could not measure the core body temperature. For measurement of core body temperature, the probe needs to be put in the esophagus or near the tympanic membrane. Both these are uncomfortable and unacceptable who has been given spinal anesthesia. Rectal temperature monitoring was a possibility but was not tried. One more limitation of our study is that we did not document the sepsis markers as PCT, CRP, etc. though we excluded the patients from study having fever and sepsis to reduce their confounding effect.

CONCLUSION

The incidence of shivering in our study was about 30%. Ondansetron was not found to be much effective for the control of shivering during regional anesthesia. Butorphanol and tramadol were equally effective in controlling shivering under regional anesthesia, the only difference being in their onset of action; butorphanol was quicker in onset which is essential for control of shivering and so should be preferred.

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