Original Article

Efficacy of tramadol in preventing postoperative shivering using thiopentone or propofol as induction agent: A randomized controlled trial

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Abstract

Background: Postoperative shivering (POS) is a common and distressing experience occurring in up to 60% patients postoperatively. This study was designed to compare the efficacy of tramadol in preventing POS when used with two different induction agent, propofol or thiopentone.

Materials and Methods: One hundred and twenty-four ASA I and II adult patients, aged between 18-60 years, undergoing general anesthesia of intermediate duration (60-240 min) for orthopedic, gynecological, and general surgical procedures were randomly divided to receive either thiopentone or propofol as induction agent. Each group was further subdivided (31 patients in each group) to receive either tramadol or saline 15 min before wound closure. Presence of POS after extubation till discharge from post anesthesia care unit (PACU) was recorded at six different time intervals.

Results: The highest incidence of POS was observed in thiopentone-saline (TS) group 77.4%, while the lowest (12.9%) was in propofol-tramadol (PT) group ($P < 0.001$). Total number of shivering episodes was 122 out of which, 35 (28.7%) were of grade 2 and 3 (significant shivering) requiring treatment. The incidence of significant shivering was similar to the episodes of POS, highest in TS group and lowest being in PT group ($P < 0.05$).

Conclusion: The prophylactic use of tramadol in a dose of 1 mg/kg with propofol as an induction agent significantly reduces the incidence of POS in patients recovering from general anesthesia of intermediate duration.

Key words: General anesthesia, postoperative shivering, propofol, thiopentone, tramadol

Introduction

Postoperative shivering (POS) is a common and distressing experience occurring in up to 60% of patients recovering from general anesthesia[1,2] and in up to 30% of patients receiving epidural anesthesia.[2] It depends upon various factors including age, gender, type of anesthesia, amount and temperature of intravenous (IV) fluids, duration of surgery, and temperature of operating room (OR).[2,3] POS is either of normal thermoregulatory type of shivering which occurs in response to core hypothermia and release of cytokines by the surgical trauma or non-thermoregulatory type that occurs in normothermic patients in response of anesthetics.[1]

Intraoperative hypothermia is common problem and POS is one of the undesirable response to hypothermia.[4-7] POS is not only distressing to patients, but it may also lead to potentially serious complication by increasing tissue oxygen (O_2) consumption, carbondioxide (CO_2) production, minute ventilation, cardiac output, circulating catecholamines, intracranial pressure, and intraocular pressure; and causing a significant decrease in mixed venous O_2 saturation.[1,2,4,5,6] All these factors, if severe enough, may lead to hypoxia and lactic acidosis and can significantly complicate recovery which may be potentially lethal in patients with cardiopulmonary dysfunction. POS also interferes with monitoring and aggravates postoperative pain by stretching of surgical incision site.[5,8,9]

Various pharmacological agents have been used for prevention of POS, including pethidine, tramadol, clonidine, ketamine, urapidil, nefopam, doxapram, and physostigmine; but none

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of them have shown promise.[10-12] Tramadol, a weak opioid has emerged as a potent prophylactic antishivering agent[1,5,13] and when compared to pethidine, tramadol has an upper edge, mainly due to its fewer adverse effect.[2]

Studies have also demonstrated that incidence of POS is also influenced by the IV anesthetic agents with reduced incidence seen with propofol when compared to thiopentone.[14,15] We, however, could not find any study evaluating the anti-shivering effect of tramadol when combined with these anesthetic induction agents. The objective of our study was to compare the efficacy of tramadol when used with either propofol or thiopentone in preventing POS.

Materials and Methods

After approval from Ethics Review Committee and obtaining informed consent, this randomized, double blind study was performed in operating rooms (OR) and post anesthesia care unit (PACU) of a tertiary care hospital over a period of 1 year. A total of 124 ASA I and II adult patients of either sex, aged between 18 and 60 years receiving general anesthesia with endotracheal intubation for orthopedics, gynecological, and general surgical procedures of intermediate duration (60-240 minutes) were included in the study. The number of patients required in each group was determined using power analysis based on previous study.[13] Incidence of postanesthetic shivering was estimated to be around 60%. The sample size required detecting 40% reduction at 5% level of significance and 80% power was 31 patients in each group. Patients with obesity (body mass index (BMI) > 35), history of convulsions, neuromuscular disease, allergies, and those requiring administration of blood or blood products or procedures requiring large volume of irrigating fluids (>2 L) were excluded from study. Patients whose first temperature reading on placing temperature probe intraoperatively, was found to be less than 36°C or greater than 38°C were also excluded. Patients were randomly divided into groups by using sealed, opaque envelopes. The groups were thiopentone and tramadol (TT), thiopentone and saline (TS), propofol and tramadol (PT), and propofol and saline (PS). Blinding was achieved by labeling tramadol or saline as "study drug" which was prepared by an anesthetist not involved in study. All the patients received same anesthetic technique and drugs in same doses except propofol 2 mg/kg or thiopentone 5 mg/kg for induction of anesthesia. Fentanyl 2 μg/kg was used for analgesia at induction and 1 μg/kg in incremental doses (last dose was given at least 30 min before "study drug") and atracurium 0.5 mg/kg as muscle relaxant to facilitate tracheal intubation followed by 10 mg boluses as required. Anesthesia was maintained with isoflurane and 60% nitrous oxide in oxygen to achieve and maintain a minimum alveolar concentration (MAC) of 1 at all times. All IV fluids were warmed to 37°C before transfusion by inline fluid warmer. Apart from routine intraoperative monitoring (electrocardiogram (ECG), noninvasive blood pressure (NIBP), oxygen saturation (SpO_2), end-tidal carbon dioxide ($EtCO_2$), continuous temperature monitoring was done via nasopharyngeal temperature probe. All patients were covered by standard sterile drapes and OR temperature was maintained at 22 ± 1°C. Additional measures (warming mattress and woolen and warm air blankets) were taken if patients' temperature dropped below 35°C. "Study drug" (tramadol 1 mg/kg or saline in equal volume) was given 15 min before wound closure and IV metoclopramide 10 mg was given just before skin closure as prophylaxis to postoperative nausea and vomiting (PONV). After skin closure, isoflurane and nitrous oxide were switched off and residual neuromuscular block was reversed with a mixture of glycopyrrolate 0.5 mg and neostigmine 2.5 mg and trachea were extubated. Patients were covered with blanket and transferred to PACU (ambient temperature of 24 ± 2°C) where they received supplemental oxygen 4 L/min and monitored for SpO_2 and hemodynamic variables (ECG, NIBP). In addition, patients were observed for occurrence and severity [Table 1] of POS, PONV, and pain at six different time intervals (on leaving or on arrival in PACU, at 15, 30, and 45 min of arrival in PACU and on discharge from PACU). Observations were recorded on the predesigned data collection form. Additional boluses of IV tramadol 0.5 mg/kg, 15 min apart (maximum 3 mg/kg) were given to patients with shivering grade ≥2. All those patients who suffered from pain ≥3 VAS (on a scale of 0-10) were treated with boluses of IV fentanyl 25-50 μg. Patients were discharged according to PACU discharge protocol.

Statistical analysis was done using Statistical Package for Social Sciences (SPSS), version 16. Mean and standard deviation (SD) were used to compute for quantitative variables like age, BMI, duration of anesthesia, duration of patient staying in OR and change in temperature. Frequency and percentage were used to assess overall incidence of POS as well as at different time intervals, number of POS episodes and episodes of severe POS requiring treatment. Repeated measures ANOVA were used to assess PONV, use of rescue

Table 1: Grades of shivering

Grade	Clinical signs
0	No shivering
1	Mild fasciculations of face or neck and ECG disturbances in the absence of voluntary activity of the arms
2	Visible tremor involving more than one muscle group
3	Gross muscular activity involving the entire body

ECG=Electrocardiogram

analgesia and hemodynamic parameters (SBP, DBP, MAP, and HR) at different time intervals among the study groups. A $P < 0.05$ was considered significant.

Results

All of the 124 patients completed the study. All the study groups were comparable with respect to age, BMI and ASA status; however, there was female predominance in all the groups. All other intraoperative variables (duration of patient stay in OR, duration of anesthesia, and temperature at start and end of procedure) including hemodynamic parameters were comparable and statistically insignificant [Table 2].

Shivering

The incidence of POS was highest in TS group (77.4%) and lowest in PT group (12.9%), whereas it was similar (54.8%) in both TT and PS groups. We observed POS at six different time intervals as shown in Table 3. The overall incidence of POS was 25.8% at extubation (T1) which increased to the highest level (37.1%) on arrival in PACU (T2). The incidence gradually declined thereafter with none of the patient having POS at planned discharge time [Table 3]. When incidence of POS was compared among the groups, it was highest in TS group at T1 (41.9%), T2 (67.7%), and 15 min after arrival in PACU (T3). The incidence in group TS was similar (12.9%) to TT 30 min after arrival in PACU (T4) and TS being the only group to have two patients with POS (6.5%) 45 min after arrival in PACU (T5). Following that none of the patient in any group experienced POS.

Table 4 shows the grades of shivering in various groups which have been divided into insignificant (grade 0 and 1) and significant (grade 2 and 3) requiring treatment with tramadol [Table 5]. Observation for POS was recorded at 744 times during the study period in all groups. POS was present on 122 occasions out of which 35 episodes were of significant POS requiring treatment. The episodes of significant shivering requiring treatment were significantly higher in TS group when compared with PT and TT groups ($P < 0.05$), whereas it was statistically insignificant ($P > 0.05$) when compared with PS group. Other three groups, that is, TT, PT, and PS were statistically comparable to each other ($P > 0.05$). Clinically none of the patients in PT group required antishivering treatment, whereas four episodes of shivering in TT group and eight episodes in PS group needed additional tramadol boluses to treat their shivering episodes.

Analgesic requirement

Requirement of rescue analgesia based on VAS ≥ 3 was significantly higher in saline treated groups (TS and PS) when compared to Tramadol treated groups (TT and PT) for obvious reason ($P < 0.05$). The incidence of PONV was similar in all groups ($P > 0.05$).

Table 3: Comparison of postoperative shivering among study groups at different time intervals

Time intervals	Groups (n=31) (%)			
	TT	TS	PT	PS
Extubation (T1)	11 (35.5)	13 (41.9)	1 (3.2)	7 (22.6)
PACU (T2)	10 (32.2)	21 (67.7)	2 (6.5)	13 (41.9)
15 min (T3)	6 (19.3)	13 (41.9)	1 (3.2)	10 (32.2)
30 min (T4)	4 (12.9)	4 (12.9)	2 (6.5)	2 (6.5)
45 min (T5)	0	2 (6.5)	0	0
Discharge (T6)	0	0	0	0

n=Number of patients, TT=Thiopentone and tramadol, TS=Thiopentone and saline, PT=Propofol and tramadol, PS=Propofol and saline, PACU=Post anesthesia care unit

Table 4: Comparison of severity (grades) and number of episodes of postoperative shivering among study groups

Grades of POS	Study groups (n=186)(%)			
	TT	TS	PT	PS
0	155 (83.33)	133 (71.5)	180 (96.7)	154 (82.8)
1	27 (14.5)	30 (16.1)	6 (3.3)	24 (12.9)
2	4 (2.1)	19 (10.2)	Nil	8 (4.3)
3	Nil	4 (2.1)	Nil	Nil

n=Number of shivering episodes, TT=Thiopentone and tramadol, TS=Thiopentone and saline, PT=Propofol and tramadol, PS=Propofol and saline, POS=Postoperative shivering

Table 2: Demographic data and intraoperative variables

Variables	Groups (n=31)				*P* value
	TT	TS	PT	PS	
Age (years)*	41.5±12.0	41.0±10.6	38.4±11.4	39.6±12.1	NS
Sex (M:F)	12:19	7:24	14:17	10:21	NS
ASA (I:II)	10:21	10:21	13:8	12:19	NS
BMI (kg/m^2)*	27.3±4.8	26.9±3.1	26.8±3.8	26.6±4.8	NS
Duration of patient stay in OR (mins)*	126.4±34.1	128.5±39.7	122.2±36.0	123.5±37.6	NS
Duration of anesthesia (min)*	112.2±32.7	114.3±37.7	111.4±35.1	110.7±36.0	NS
Temperature (°C) at start of procedure*	36.2±0.38	36.2±0.51	36.3±0.40	36.2±0.40	NS
Temperature (°C) at end of procedure*	35.9±0.45	35.9±0.60	36.0±0.49	36.0±0.49	NS

*TT=Thiopentone and tramadol, TS=Thiopentone and saline, PT=Propofol and tramadol, PS=Propofol and saline, NS=Not significant, BMI=Body mass index, OR=Operating room. *Mean±standard deviation*

Table 5: Comparison of presence of significant postoperative shivering (requiring treatment) among study group

Episodes of POS	Study groups (%)				(%)
	TT (*n*=31)	TS (*n*=53)	PT (*n*=6)	PS (*n*=32)	
Episodes of POS not requiring treatment	27 (87.09)	30 (56.6)	6 (100.0)	24 (75.0)	87 (71.3)
Episodes of POS requiring treatment	4*(12.9)	23 (43.4)	Nil*	8 (25.0)	35 (28.7)

*n=Episodes of POS, POS=Postoperative Shivering, *=TS vs other group: P<0.05, TT=Thiopentone and tramadol, TS=Thiopentone and saline, PT=Propofol and tramadol, PS=Propofol and saline*

Discussion

To avoid the deleterious effects of postoperative hypothermia and shivering, it is important to institute proper steps for its prevention and treatment. Several techniques have been used to diminish postoperative hypothermia: Warming blankets; warmed intravenous solutions; heated, humidified inspired gases; and increasing ambient air temperature. Baker *et al.*, demonstrated that complete intraoperative rewarming after mild hypothermia is difficult, and despite aggressive manipulation of convective heating devices and water blankets, the average rate attainable is 0.7°C/h making prevention even more important in the intraoperative period.[16] In our study, we took adequate precaution to prevent hypothermia by covering all patients with standard sterile drapes. Additional measures (warming mattress and woolen and warm air blankets) were taken if patients' temperature dropped below 35°C. All patients were normothermic upon arrival in PACU (approximately 36.0 ± 0.5°C). Among the pharmacological modalities used for prevention and treatment of POS, tramadol has been used effectively in different doses to prevent postoperative shivering,[1,17] however literature comparing the effect of induction agent on the efficacy tramadol is lacking.

In this study we found that there is statistically significant decrease ($P < 0.05$) in the incidence of grade 2 and 3 POS episodes in group receiving tramadol, four (12.9%) in tramadol groups (TT) and 23 (43.4%) in saline groups (TS). These results are comparable to the study done by Mohta *et al.*,[13] (used thiopentone as induction agent), where patient receiving tramadol in different doses had less episodes of POS when compared to normal saline as antishivering agent.

Comparison of induction agent shows that the incidence of POS in patients receiving propofol (PS Group) versus thiopentone (TS group) was 17 (54.8%) and 24 (77.4%), respectively; which was higher as compared to findings of Cheong *et al.*, and Singh *et al.*, showing lower incidence in the thiopentone group as compared to propofol group, 25 and 50% and 10 and 22%, respectively; but this could be explained by the fact that both these studies included only those patients who underwent minor surgical procedures which were associated with minimum perioperative heat loss. Average duration in our study was approximately 110 ± 10 min more than the duration mentioned in these studies.[14,18]

Although propofol or tramadol alone as antishivering agents equally reduces the incidence of POS (54.8% in both PS and TT groups); in TS group it was the highest 24 (77.4%). Combining these both antishivering agents (propofol + tramadol) results in absence of POS requiring treatment in PT group.

Timing of giving antishivering agent is also important. According to Zahedi, the incidence of shivering is highest in the first 30 min of recovery.[2] This was consistent with the findings of our study which showed that the maximum number of patients suffered from shivering on arrival in the PACU and in vast majority of patients, the POS had disappeared within 30 min of arrival in the PACU. Regarding the peak antishivering effect of Tramadol, Zahedi showed it to be 5 min after intravenous injection.[2] In our study, tramadol was given at the start of skin closure and by the time patient reached the PACU, at least 20 min would have passed to the administration of tramadol. The highest incidence of shivering was on arrival in the PACU. Question arises that what should be the ideal time to use prophylactic tramadol. Results of our study shows that the peak antishivering effect of tramadol occurs after about 30 min of its administration, and therefore it should be administered even earlier. However, further studies are required to find the optimum timing of prophylactic use of tramadol to prevent POS in the PACU.

As deleterious effects of POS are related to its severity, active treatment is indicated in more severe forms to minimize these effects. We recorded the severity of POS with grade I POS being the one not requiring treatment while grade 2 and 3 being significant POS requiring treatment. The episodes of significant shivering requiring treatment was greatest in the TS as compared to all other groups ($P < 0.05$), whereas none of the patients in PT group required antishivering treatment. These results were comparable with the study done previously by Mohta *et al.*,[13] where the incidence of shivering requiring treatment (grade 2 and 3) was 42.4% in thiopentone only group and 6% in equivalent dose tramadol group.

The occurrence of PONV was unremarkable among the study groups, which could be due to the prophylactic

use of metoclopramide in every patient. There were no significant alterations in the hemodynamic parameters during the study period among the groups. Tramadol, a synthetic opioid, can be effectively used for the prevention and treatment of moderate to severe pain. Therefore, we observed significantly lower requirement of rescue analgesia in tramadol groups.

The limitation of our study was that we included only ASA I and II relatively stable patients and were without known coronary artery disease, and therefore we did not found any cardiovascular complications.

Conclusion

The prophylactic use of tramadol in a dose 1 mg/kg administered at the time of skin closure when propofol is used as an induction agent significantly reduces the episodes of POS requiring treatment. Another advantage of tramadol is the reduced requirement of postoperative analgesia in these patients in the recovery room.

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