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Ondansetron versus Tramadol in Prevention of Post-anaesthesia Shivering following Caesarean Section Under Spinal Anaesthesia

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ABSTRACT

Background:Postanaesthesia shivering is a frequent and undesirable complication of spinal anaesthesia. Because of the increased physiological stress it places on the patient, different drugs have been used for its management. This study compared the efficacy of ondansetron versus tramadol in the prevention of postanaesthesia shivering following elective Caesarean section under spinal anaesthesia.

Patients and Methods: In this prospective, double-blind controlled trial, 90 American Society of Anesthesiologist (ASA) I or II patients, with singleton pregnancies, undergoing elective Caesarean section under subarachnoid block, were randomized to receive 4mg ondansetron, 0.5mg/kg tramadol or normal saline intravenously after spinal anaesthesia. The primary outcome was the incidence of shivering.

Results: The incidence of shivering was 20.0% in the ondansetron group, 16.7% in the tramadol group and 53.3% in the saline group (p = 0.003). Severe shivering occurred in eight patients in the saline group compared to one in the ondansetron group and none in the tramadol group (p = 0.007). Seven patients in the tramadol group, 1 patient in the ondansetron group and 2 patients in the saline group had nausea and vomiting (p = 0.031). Haemodynamic variables, neonatal outcome and perioperative complications were comparable between the 3 groups.

Conclusion:Ondansetron 4mg was comparable to tramadol 0.5mg/kg but superior to placebo in protecting Caesarean section patients undergoing spinal anaesthesia against shivering. Ondansetron further protects against nausea and vomiting while having no significant side effects. Ondansetron at a dose of 4mg may be considered for prophylaxis against shivering in this group of patients.

KEYWORDS : Ondansetron, Tramadol, Prophylaxis, Postanaesthesia shivering, spinal anaesthesia, Caesarean section

INTRODUCTION

Postanaesthesia shivering (PAS) was first described over fifty years ago with a worldwide incidence of 20-60%.1 While patients find shivering very uncomfortable, it causes artifacts in monitors and increases postoperative pain, heart rate, cardiac output, oxygen consumption by fivefold and metabolic rate by 600%.2-4 This may lead to myocardial ischaemia, hypoxaemia, hypercarbia and lactic acidosis that could complicate recovery from anaesthesia. Preventing postanaesthesia shivering may reduce morbidity and improve patient's satisfaction. Though pethidine is the gold standard used for its management, its use has become limited due to unavailability as a restricted drug in many sub-urban hospitals in india.5

In addition, opioids have major side effects such as sedation, itching, respiratory depression, nausea and vomiting. Other effective drugs such as clonidine cause sedation and hypotension while ketamine is known to cause hallucinations, delirium and sedation.

Talakoub *et al*,6 compared tramadol 0.5mg/kg and pethidine 0.5mg/kg, while Oranuch and coworkers,7 compared nalbuphine, tramadol, ondansetron and placebo for the treatment of shivering after Caesarean delivery.These studies were aimed at treating shivering rather than preventing it. Kelsaka *et al*,8 compared the anti-shivering effects of intravenous ondansetron 8mg and pethidine 0.4 mg/kg, however, the study was not done in parturients. Moreover, our study seeks to use low dose ondansetron.

There appears to be a paucity of studies on the prophylactic treatment of shivering in the india.

This study, therefore, seeks to compare the efficacy of i.v ondansetron 4mg versus i.v tramadol 0.5mg/kg in the prevention of postanaesthesia shivering following Caesarean section under spinal anaesthesia.

PATIENTS AND METHODS

This was a prospective, randomized, double-blind,placebo controlled study conducted at the svs medical college india. Following approval from the Ethics and Research Committee, American Society of Anesthesiologists (ASA) class I or II parturients, aged 18 to 45 years, scheduled for Caesarean delivery under spinal anaesthesia, who gave consent to participate in the study were recruited. Patients with known allergy to tramadol, ondansetron or bupivacaine, any disease associated with shivering or pyrexia,or any contraindication to regional anaesthesia were excluded from the study. All eligible patients were randomly assigned into one of three groups using computer generated codes.

Patients were routinely fasted and premedicated with ranitidine 150 mg and metoclopramide 10 mg orally. After preloading with 15 ml/kg 0.9% saline kept at room temperature, subarachnoid block was established in the sitting position using a 25G pencil point (Whitacre) spinal needle at the L3-4 interspace with 12.5 mg of 0.5% hyperbaric bupivacaine. Two minutes after the spinal block and prior to surgical incision, a second anaesthetist who was not involved in the study prepared and administered the study drugs. The researcher, who was blinded, monitored the patients for shivering and other side effects. Group O patients received 4 mg ondansetron **(Neomit)**, group T received 0.5 mg/kg tramadol (Tramadol), while group S received normal saline. All study drugs were diluted to 5 mls and given intravenously. Patients were routinely monitored for pulse rate, blood pressure (NIBP), oxygen saturation (SpO2), and electrocardiogram (ECG). Core temperature was measured with ear thermoscan, and skin temperature with thermistor strapped to the forehead. Ambient theatre temperature was kept at 25 oC using Air conditioner.

Supplemental oxygen was administered via nasal prongs at 2 L/min. Maintenance fluids (10 mls/kg in the first one hour and 5 mls/kg in the subsequent hours) were given at room temperature. Oxytocin was given following delivery of the foetus and neonatal outcome was assessed using Apgar score at 1 and 5 minutes.

Shivering was graded using a scale similar to that validated by Tsai and Chu,9

Grade 0: no shivering,
Grade 1: piloerection or peripheral vasoconstriction but no visible shivering,
Grade 2: muscular activity in only one muscle group,
Grade 3: muscular activity in more than one muscle group but not generalized and

Grade 4: shivering involving the whole body
Grade 1 was considered as mild, grade 2 as moderate with grade 3 and 4 as severe shivering.

Sedation was assessed using the Ramsay sedation score,10 while postoperative nausea and vomiting (PONV) was assessed using the numeric scoring system for PONV (0=no nausea or vomiting; 1= nausea but no vomiting; 2=vomiting once; 3 = two or more episodes of vomiting). The degree of patient's satisfaction with prophylaxis of post-anaesthesia shivering was assessed using the following scale; poor, satisfied, or very satisfied.

Hypotension (defined as blood pressure drop of > 20% of baseline) was treated using intravenous fluid alone or combined with ephedrine. Shivering of grade 3 or more was managed with i.v pethidine 25mg, nausea or vomiting was treated using i.v metoclopramide 10mg while i.v pentazocine 30mg was used as rescue analgesia when pain score was >4. Postoperative complications in the first 24 hrs such as post-dural puncture headaches (PDPH), backache, and difficulty in voiding were noted and managed accordingly.

With the incidence of shivering assumed to be 50%,11 type I error of 0.05, type II error of 0.1 and attrition rate of 10%, a total sample size of 90 was sufficient to detect a difference of 30% in incidence between ondansetron or tramadol and placebo. The primary outcome was the proportion of patients in each group who developed shivering following spinal block. Data entry and outcome variables were analyzed using the Statistical Package for Social Sciences (SPSS 16.0). Numerical variables were analyzed using ANOVA test and post hoc comparison done with Bonferroni correction. Categorical data were analyzed using the Chi-square test with Pearson's correction or Fisher's exact test. All statistical tests were two-tailed. P value <0.05 was considered statistically significant and formed the basis of accepting or rejecting the null hypothesis.

RESULTS

Ninety patients participated in the study. Sociodemographic data and baseline vital signs did not differ significantly between the 3 groups (Table I and II). TableIII shows intraoperative clinical characteristics. The block height, total intravenous fluid, duration of surgery and Apgar scores were comparable between the 3 groups. The time to shivering between ondansetron group and tramadol group was comparable (p = 1.000), but the time to shivering between ondansetron vs. saline (p = 0.025) and tramadol vs. saline (p = 0.015) differed significantly.

The incidence and severity of shivering is shown in Table IV. Shivering was observed in 6 (20.0%) patients in the ondansetron group, 5 (16.7%) patients in the tramadol group and 16 (53.3%) patients in the saline group; p = 0.003. Eight (26.7%) patients in the saline group, 1 (3.3%) patient in the ondansetron group and none (0.0%) in the tramadol group experienced grade 3 shivering; p = 0.007. Severity of shivering was comparable between ondansetron and tramadol, but differed significantly between ondansetron vs. saline (p = 0.003) and tramadol vs. saline; p = 0.001. The time to shivering for ondansetron (2.10 ± 4.58min), tramadol (1.85 ± 4.78min) and saline (5.97 ± 6.97min) differed significantly between the 3 groups; p = 0.007.

The trend of core and skin temperature is shown in Figure1. The 3 groups of patients experienced gradual reduction in core and skin temperatures intraoperatively, but no statistical difference was observed. Figure 2 shows perioperative complications in the first 24 hrs. The incidence of hypotension, bradycardia, pain and sedation were not significantly different between the 3 groups. Seven patients in the tramadol group, 2 patients in the saline group and 1 patient in the ondansetron group had PONV (p = 0.031).

The degree of patient's satisfaction with shivering prophylaxis (Figure 3) showed that 23 (76.7%) patients in the ondansetron group and 21 (70.0%) patients in the tramadol group were very satisfied compared to 8 (26.7%) patients in the saline group (p = 0.001). A strong inverse relationship existed between shivering and patients' degree of satisfaction as revealed by the Correlation coefficient (Pearson's r) of -0.7030 (95% CI: -0.7945 to -0.5804, p < 0.0001).

Table I: Patients' socio-demographic data

Parameter	Ondansetron	Tramadol	Saline	P value
Age (yrs)	31.33 ± 4.54	33.03 ± 5.34	31.33 ± 4.38	0.286
Weight (kg)	76.30 ± 13.41	77.60 ±12.45	79.40 ± 15.21	0.681
Height (cm)	161.23 ± 4.90	161.72 ± 5.19	162.27 ± 5.63	0.745
Gestational Age (wks)	38.03 ± 1.61	38.50 ±1.53	38.00 ± 1.23	0.339
ASA 1/2	20/10	22/8	20/10	0.821

Table II: Preoperative baseline vital signs

Parameter	Ondansetron	Tramadol	Saline	P value
Pulse Rate (bpm)	94.67 ± 13.06	95.03 ± 14.22	97.1 ± 18.95	0.810
MAP (mmHg)	87.67 ± 14.20	86.83 ± 15.22	87.67 ± 14.06	0.968
Respiratory Rate (cpm)	21.50 ± 3.69	22.45 ± 3.69	21.13 ± 2.11	0.156
Core Temperature (°C)	37.16 ± 0.39	37.31 ± 0.33	37.15 ± 0.30	0.122
Skin Temperature (°C)	36.31 ± 0.32	36.43 ± 0.31	36.37 ± 0.21	0.296
SpO_2 (%)	97.87 ± 1.14	98.20 ± 0.85	98.03± 0.81	0.395

Table III: Intraoperative clinical characteristics

Parameter	Ondansetron	Tramadol	Saline	P value
Duration of surgery (min)	66.07 ± 21.42	66.73 ± 22.81	60.33 ± 18.29	0.423
Time to extraction (min)	11.99 ± 2.65	12.24 ± 2.95	11.77 ± 3.88	0.845
Time to shivering (min)	2.10 ± 4.58	1.85 ± 4.78	5.97 ± 6.97	0.007
Total intravenous fluid (ml)	3526.67 ± 725.37	3513.33 ± 516.44	3610.00 ± 623.31	0.812
Estimated blood loss (ml)	645.00 ± 199.29	648.33 ± 164.26	616.00 ± 187.43	0.757

Table IV: Incidence and severity of shivering

	Parameter	Ondansetron	Tramadol	Saline	P value
Shivering	No	24 (80.0%)	25 (83.3%)	14 (46.7%)	0.003
	Yes	6 (20.0%)	5 (16.7%)	16 (53.3%)	
Severity	mild	2 (6.7%)	1 (3.3%)	3 (10.0%)	
					0.007
	moderate	3 (10.0%)	4 (13.3%)	5 (16.7%)	
	severe	1 (3.3%)	0 (0.0)	8 (26.7%)	

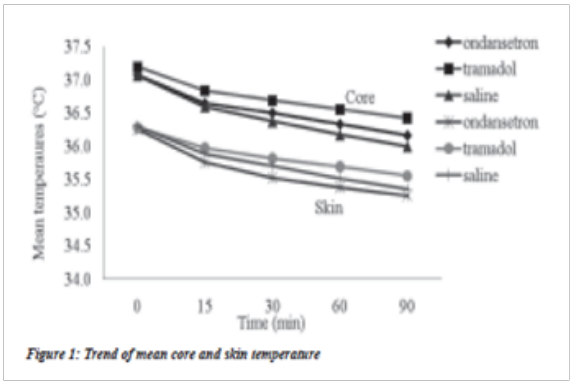

Figure 1: Trend of mean core and skin temperature

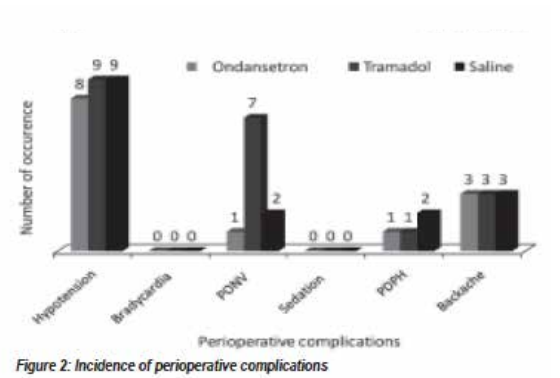

Figure 2: Incidence of perioperative complications

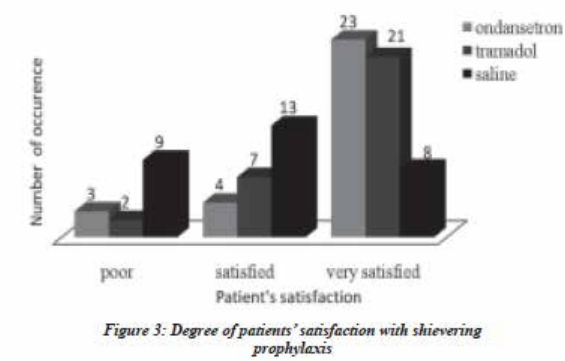

Figure 3: Degree of patients' satisfaction with shievering prophylaxis

DISCUSSION

This study shows that ondansetron and tramadol significantly reduced the incidence and severity of shivering compared to placebo. In comparison, ondansetron was superior to tramadol in prevention of postoperative nausea and vomiting. The benefits of ondansetron were observed with acceptable side effects profile and high satisfaction rate. The overall incidence of shivering in this study is 30%. This agrees with previous reports by Edomwonyi et al,1 (29.8%) and Atashkhoyi et al,12 (33.3%). In contrast, a higher incidence of 47.8% was reported by Javaherforoosh et al.13 The use of higher ambient temperature (25oC vs. 21-23oC) coupled with infusion of relatively warmer intravenous fluids in our study may have

accounted for the lower incidence of shivering we observed. Kolawole et al,14 and Sule et al,15 reported a lower incidence of 18% and 15% respectively in their studies. This low incidence may have resulted from the fact that shivering was not their primary outcome of interest.

In this study, more than half of the patients (53.3%) who did not receive prophylaxis developed shivering. Several authors have also demonstrated similar shivering rate in the absence of prophylaxis.16-19 Conversely, some authors have reported lower incidences of shivering in placebotreated obstetric patients in contrast to the findings in our study.7 For instance, Oranuch and co-workers7 reported an incidence of 45.0%. While we achieved spinal block with hyperbaric bupivacaine only, these authors combined intrathecal morphine which is a known antishivering agent. This may explain why a higher incidence of shivering among placebo-treated patients was recorded in our study. The incidence of shivering in the ondansetron group in our study was 20.0%. There is a plethora of evidence in the literature suggesting a lower incidence of PAS with ondansetron than that observed in this study.8,16,17

In particular, Kelsaka et al,8 used 8 mg of ondansetron and reported an incidence of 8%. Although the effect of ondansetron is known to be dose dependent, to assume that the difference in our observation is due to dosage alone may be too simplistic. Moreover, Shakya et al,20 and Entezariasl et al,16 used doses similar to ours but got lower results (10-13.3%). However, the low incidence in Entezariasl et al,16 may also be explained by the difference in technique as general anaesthesia was the preferred technique in their study. It has been shown that subarachnoid block reduces the threshold for vasoconstriction and shivering by only 0.5°C compared to about 1oC by general anaesthesia.21 This means that patients shiver at a higher core temperature under subarachnoid block compared to general anaesthesia (35.5oC vs. 34.5oC).22 Moreover, there is less heat production with shivering during subarachnoid block compared to general anaesthesia.22 Therefore, shivering has to be more intense for maximum gain to be achieved thereby increasing the incidence of shivering.

On the other hand, Shakya et al,20 carried out their study in non-parturients who received diazepam premedication, a known anti-shivering agent. It is against the protocol in our institution to use diazepam premedication for patients undergoing Caesarean section as it may cause global hypotonia, heart rate variability and respiratory depression in the neonate. In addition, Shakya and co-workers20 achieved a median block height of T6 whereas our study achieved a modal block height of T4 deemed necessary to avoid peritoneal irritation due to exteriorization of the uterus at delivery. It is known that the incidence of shivering is directly related to the number of spinal segment blocked. Therefore, the higher level of block achieved in our study may also account for the higher incidence of shivering observed.

The findings in this study show that the reduction in shivering rate was comparable between ondansetron (33%) and tramadol (37%), indicating a 2.65 to 3.12 fold risk of developing PAS in the absence of ondansetron or tramadol prophylaxis. Moreover, the number needed to treat (NNT) was comparable between the ondansetron group (2.9) and tramadol group (2.7). In addition, ondansetron and tramadol prophylaxis achieved similar significant reduction in the severity

of shivering. The result from this study, therefore, supports the well established efficacy of tramadol as an anti-shivering agent.12,13 That ondansetron has comparable efficacy to tramadol in the prophylaxis of shivering as shown in this study is remarkable. Furthermore, our study also reveals that ondansetron offers some protection against PONV. The risk of patients developing PONV was 7.7 times higher with tramadol and 2.3 times higher with placebo compared with ondansetron. This advantage with ondansetron is rare with other commonly used chemo-prophylactic agents against PAS like nalbuphine, pethidine, ketamine and tramadol. In addition, the lower side effects exhibited by ondansetron makes it more attractive over tramadol for the prophylaxis of PAS in patients undergoing Caesarean section under spinal anaesthesia.

There are variable results concerning the efficacy of ondansetron in the management of shivering.7,11,16 This has been attributed to the dose of ondansetron used. Specifically, Powell and Buggy11 reported that 4mg ondansetron was not significantly different from saline in preventing shivering. The findings in our study indicate otherwise as ondansetron was effective in reducing the incidence of shivering to about 1 in 5 patients (20.0%) compared to less than 1 in 2 patients (53.3%) achieved in the control group. In addition, there was significant reduction in the severity of shivering in the population with ondansetron prophylaxis. The primary objective of Powell and Buggy11 was to investigate the mechanism of PAS by evaluating the importance of 5-HT pathways using general anaesthesia in non-parturients. This may have impacted on their methodology and sample size thus resulting in failure to detect any significant difference where it could have existed. On the other hand, our study has the primary objective of evaluating the incidence of PAS in parturients undergoing Caesarean section under SAB. These differences in primary objectives and methodology may account for the conflicting results observed.

The time to shivering was significantly shorter in the ondansetron and tramadol groups than in the saline group in this study. It is possible that ondansetron and tramadol prevented further shivering after their onset of action unlike the placebo which has no pharmacological action. It is suggested that for prophylactic measures to be effective, it should be instituted within 15 minutes of SAB.

Our study supports other literature that ondansetron is haemodynamically stable.7,11 Other perioperative complication rates observed in this study were rather low.

We observed in our study that patients who received ondansetron had higher rate of satisfaction compared to those pretreated with tramadol or placebo. In addition, among the parturients who were poorly satisfied with shivering prophylaxis, almost 50% of them received placebo, suggesting that anti-shivering prophylaxis with ondansetron is desirable.

CONCLUSION:

The prophylactic administration of 4mg ondansetron is comparable to tramadol (0.5mg/kg) in producing significant anti-shivering effect in patients undergoing Caesarean section under spinal anaesthesia. Ondansetron may be preferred to tramadol because of its anti-emetic property, haemodynamic stability, lack of significant side effects and better patient satisfaction. Therefore, ondansetron at a dose of 4mg may be considered for prophylaxis of postanaesthesia shivering particularly in patients undergoing Caesarean section under subarachnoid block.

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