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ORIGINAL RESEARCH

Prophylactic Granisetron vs Ondansetron for perioperative shivering in patients undergoing elective LSCS under subarachnoid block: A prospective, double blind, randomized clinical study.

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INTRODUCTION

The advent of efficient, safer, economical anaesthetic drugs and techniques has seen a rise in the incidence of lower segment caesarean sections (LSCS) worldwide. In the Indian subcontinent, subarachnoid block is the most popular anaesthetic technique practiced for lower segment caesarean sections. However, it is associated with some unwanted effects like hypotension, nausea, vomiting and perioperative shivering.

As stated by various studies, 20-55% of patients undergoing subarachnoid block (SAB) experience perioperative shivering[1]. This causes discomfort, especially as the patient is conscious after subarachnoid block during caesarean section. Shivering is an involuntary muscle activity[1] leading to an increase in oxygen consumption and consequently hypoxemia, lactic acidosis, catecholamine release and potential hemodynamic instability[1, 2]. Shivering interferes with monitoring devices[2], raises intracranial and intraocular pressures, raises the basal metabolic rate by 100 – 300%[2]. In the postoperative period, it exacerbates postoperative pain, discomfort and causes stretching of sutures and thereby adversely affects wound healing[3]. In caesarean sections, it can hamper breastfeeding and thereby impede mother child bonding[1,2].

Many pharmacological and non-pharmacological methods are used to prevent and control perioperative shivering. The pharmacological options include meperidine[4], buspirone[5], nefopam[5], clonidine[5], alfentanil[5], dexmedetomidine[5], tramadol[6] and non-pharmacological measures[1, 17] include warmers, blankets and warm intravenous fluids. The mechanism of shivering under subarachnoid block remains unclear[7], but a definitive role of 5-hydroxytryptamine (5HT) and its pathways has been identified[8]. This led to the belief that $5HT_3$ antagonists like ondansetron and granisetron[7, 10] prevent perioperative shivering. This study aims to determine the efficacy of prophylactic granisetron versus ondansetron, both 5HT3 antagonists in preventing perioperative shivering in parturients undergoing elective LSCS under SAB.

MATERIALS AND METHODS

After the approval of Institutional ethics committee, this study was planned as an unicentric, prospective, double blind, randomized clinical trial in a tertiary teaching hospital in Southern India over a period of 6 months.

In this study, using computer software, 70 patients (n = 35 each group) were enrolled and randomly assigned to two study groups (Group A received intravenous ondansetron, group B received intravenous granisetron). Parturients in the age group of 19 – 40 years, with singleton pregnancy, undergoing elective LSCS under subarachnoid block of ASA PS II, weighing 50 – 80 kgs were included in the study. Parturients with known allergy to the study drugs, who have received the study drugs 24 hours before the surgery, who are on opioids / vasodilators / sedatives, required intraoperative blood transfusion, with preoperative initial axillary temperature $\geq 38°C$ or $\leq 36.6°C$, having Parkinson's disease or movement disorders, tremors, failed SAB requiring conversion to General anaesthesia or supplementation with other anaesthetic drugs were excluded from the study.

After a thorough Pre-anaesthetic evaluation, parturients fulfilling the inclusion criteria were explained in detail about the anaesthetic procedure, surgery and study protocol. A written informed consent was obtained from the parturients willing to participate in the study and were kept nil per orally 8 hours before the procedure.

Before shifting to the operating theatre, all participants were given intravenous Pantoprazole 40 mg and Intravenous Metoclopramide 10 mg slowly over 10 minutes and wore a cotton gown covered with a single cotton bedsheet. In the preoperative area, the participants were administered either Inj. Ondansetron (0.1 mg/kg) or Inj. Granisetron (0.01 mg/kg) intravenously over a period of 5 minutes, 30 minutes before subarachnoid block. The study drug was prepared by an anaesthesiologist not involved in the study who loaded the study drug in a 5 ml syringe, appropriately diluting the drug to a volume of 5 ml. Both the participant and investigator were unaware of the drug preparation. Participants were then coloaded with i.v. fluids Ringers lactate at room temperature at 7 to 10 ml/kg.

In the OT, the ambient temperature was set between 22 to 24°C. The participants were connected to standard monitors, hemodynamic variables noted and left axillary temperature was measured. In sitting position, SAB was then performed using 25G Quinke spinal needle and 2.2 ml of 0.5% Heavy Bupivacaine administered intrathecally. After ensuring block adequacy, the parturient was handed over to the obstetrics team and covered by surgical drapes. Active measures of warming were not used. Intraoperative events and vital parameters were recorded. Any shivering was noted and graded using a 5-point scale by Crossley and Mahajan[9] at regular 5 minutes for the first 30 minutes and every 30 minutes till return of Bromage scale of 6 postoperatively. The duration of surgery was noted in minutes.

Table 1: 5-point scale by Crossley and Mahajan

SCORE	SHIVERING INVOLVEMENT
0	No shivering
1	Piloerection or peripheral vasoconstriction but no visible shivering
2	Muscular activity in only one muscle group
3	Muscular activity in more than one muscle group but not generalized shivering
4	Shivering involving the whole body

Shivering score ≥ 3 after administration of SAB and extraction of fetus was treated with Inj. Meperidine / Pethidine 25 mg intravenously. Any side effects and complications was noted and treated appropriately. Patient satisfaction was assessed for 24 hours postoperatively using a 11 point verbal numeric rating scoring system, where 0 = not satisfied and 10 = fully satisfied.

RESULTS

The present study had 70 participants with 35 parturients in each study group. The demographic parameters are described in table 2 and both groups were comparable with respect to age, weight, height and BMI. The left axillary temperature, ambient OT temperature before the procedure and duration of surgery are depicted in table 3 and there is no statistical difference between the two groups.

The two groups were comparable with respect to mean shivering scores (Table 4) and both groups had mild shivering – grade I and II.

Table 5 depicts percentage incidence of shivering in both groups and there is no statistical significance in both groups. However, the percentage incidence of shivering is low with Granisetron than Ondansetron. 9 patients in the Ondansetron group and 10 patients in the Granisetron group were given the rescue agent (Inj. Pethidine 25 mg i.v.). However, the mean time taken to the rescue agent was longer with Granisetron (36 minutes) as compared to Ondansetron (30 minutes) and the grade of shivering was milder with Granisetron, though not significant.

Hence, both Ondansetron and Granisetron are equally effective in perioperative shivering in patients coming for elective lower segment caesarean sections under subarachnoid block.

Table 2: Depicting Demographic characteristics of both groups

PARAMETER	GROUP A	GROUP B	P value
Age (years)	26.429 ± 2.758	26.343 ± 2.733	0.886
Weight (kgs)	73.429 ± 6.26	74.086 ± 6.639	0.696
Height (cm)	163.571 ± 6.358	164.657 ± 6.593	0.408
BMI (kg/m2)	27.471 ± 2.159	27.373 ± 2.495	0.851

Table 3: Depicting Parturient left axillary temperature, Ambient OT temperature and duration of surgery

PARAMETER	GROUP A	GROUP B	P value
Parturient left axillary temperature (Celsius)	36.986 ± 0.112	36.949 ± 0.115	0.209
Ambient OT temperature (Celsius)	23.657 ± 0.873	23.629 ± 0.808	0.860

Table 4: Depicting mean shivering scores

Time	Group A	Group B	P value
	Mean ± SD	Mean ±SD	
Baseline	0	0	0
After study drug	0	0	0
After SAB	0	0	0
10 min	0.743 ± 1.010)	1.010 ± 0.571	0.461
15 min	0.857 ± 1.141)	1.141 ± 0.514	0.183
20 min	0.829 ± 0.954)	0.954 ± 0.514	0.148
25 min	0.800 ± 0.994)	0.994 ± 0.686	0.653
30 min	0.657 ± 1.056)	1.056 ± 0.886	0.373
1 hour	0.600 ± 0.946)	0.946 ± 0.771	0.481
1.5 hour	0.429 ± 0.739)	0.739 ± 0.486	0.763
2 hours	0.400 ± O.651)	0.651 ± 0.200	0.213
2.5 hours	0.286 ± 0.572)	0.572 ± 0.200	0.499
3 hours	0.286 ± 0.622)	0.622 ± 0.143	0.230

Table 5: depicting incidence of shivering in both groups

TIME POINTS	INCIDENCE (percent)		P Value
	GROUP A	GROUP B	
Baseline	0	0	0
After Study Drug	0	0	0
After SAB	0	5.71	0
After 10 minutes	42.86	28.57	0.212
After 15 minutes	45.71	25.71	0.081
After 20 minutes	48.57	31.43	0.143
After 25 minutes	48.57	34.29	0.225
After 30 minutes	37.14	38.57	0.762
After 1 hour	34.29	35	0.65
After 1.5 hours	28.57	28.57	1
After 2 hours	31.43	14.29	0.088
After 2.5 hours	22.86	20	0.771
After 3 hours	20	14.29	0.526

Table 6: depicting use and mean time of rescue agent

Use of Rescue agent Study Group	Number of times rescue agent used	Percentage	Mean time to rescue agent	P value
Group A	09	25.71	29.44 min	0.788
Group B	10	28.57	36 min	

DISCUSSION

During anaesthesia, there is a lowering of core body temperature and as part of the thermoregulatory physiological response, the patient starts to shiver[10].

Under general anaesthesia, the patient complains of shivering occur due to impaired central thermoregulation[11]. Under general anaesthesia, maximum reduction of core temperature occurs at 3 – 4 hours, whereas under subarachnoid block there is no such time interval. When the temperature reaches the vasoconstriction threshold under general anaesthesia,

vasoconstriction happens. However, this phenomenon does not happen under subarachnoid block. Under subarachnoid block, the patient complains of shivering due to impaired peripheral and central thermoregulation by increasing the interthreshold range, increasing the sweating threshold and reducing the shivering and vasoconstriction threshold.

During shivering, the preoptic area of the hypothalamus releases $5HT_3$ and activates heat production pathways and thus increases body temperature[10]. By inhibiting reuptake of 5HT in the preoptic area, the $5HT_3$ antagonists may prevent shivering[10].

Zhou et al. in their meta-analysis conducted in 2016 which analyzed 14 studies, stated that $5HT_3$ receptor antagonists appeared to prevent postoperative shivering with an efficacy comparable to meperidine (pethidine) [10]. These findings were further supported by a meta-analysis done by Shen Q H et al[7] analyzing 13 randomized control trials wherein different doses of $5HT_3$ antagonists were used.

Browning et al.[13] in 2013 published a study where they stated that $5HT_3$ antagonists were not effective in mitigating perioperative shivering in parturients undergoing LSCS under SAB. Here, they compared $5HT_3$ antagonists with a control (Saline). However, they used Intrathecal fentanyl in both groups which itself is associated with decreased incidence and severity of shivering[14]. This is in direct contrast to our study, where we found $5HT_3$ antagonists reduced the incidence and severity of perioperative shivering in parturients undergoing elective LSCS under SAB.

Sharma M K et al.[15] in 2021 compared Ondansetron vs. Palanosetron for perioperative shivering in elective LSCS under SAB wherein incidence of shivering with Ondansetron was 25% and Palanosetron was 10%. However, in their study only severe perioperative shivering ($\geq$ grade 3) was considered and scores of ≤ 3 were excluded from the study.

Isngadi I et al.[16] studied the effect of low dose granisetron (10 mcg/kg) on shivering in SAB and used saline as control. The incidence of shivering with low dose granisetron was 9.4% as against 71.9% in saline group and the severity was grade I, II with former as against grade I, II, III, IV with the latter.

Kumar H et al.[17] compared 8 mg of ondansetron and 4 mg of ondansetron for perioperative shivering. They found that incidence of perioperative shivering was 20% with 8 mg of ondansetron and 10% with 4 mg of ondansetron. Therefore, the incidence of perioperative shivering is lesser in low dose of ondansetron, though not statistically significant.

No complications were noted in our study at all time intervals during the duration of our study period.

CONCLUSION

Prophylactic Ondansetron (0.1 mg/kg) is comparable to Granisetron (0.01 mg/kg) in prevention of perioperative shivering when given in parturients undergoing elective lower segment caesarean section under subarachnoid block. However, the grade of shivering was milder and time to rescue agent longer with Granisetron, though not statistically significant. No complications were noted in both the study groups at all time periods, hence it is safe to use $5HT_3$ antagonists preemptively for prevention of perioperative shivering in parturients undergoing elective lower segment caesarean section under subarachnoid block.

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