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A randomized controlled double blind study to compare efficacy,potency and safety of clonidine and tramadol for post-spinalanaesthesia shivering in cesarean section

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ABSTRACT :

The aim of this study was to evaluate the efficacy, potency and side effects of clonidine as compared to tramadol in post–spinal anaesthesia shivering. In this prospective double-blind randomized controlled clinical trial, 90 American Society of Anaesthesiologists grade-l (ASAI) parturients aged between 18 and 35 years scheduled for lower segment cesarean section under spinal anaesthesia,who developed shivering were selected.The patients were divided into two groups. Group C (*n*=45) comprised of patients who received clonidine 0.5µg/kg intravenously (IV) and group T(n=45) patients who received tramadol 0.5 mg/kg IV. Grade of shivering, disappearance of shivering, haemodynamics and side effects were observed at scheduled intervals. Disappearance of shivering was significantly earlier in group C (3.02±0.56) than in group T (6.1±1.0) (*P*=.000001). Response rate to treatment in group C was higher (97.7%) than in group T (93.7%), but the difference was not significant. Nausea, vomiting and dizziness were found to be higher in group T s while the patients in group C were comparatively more sedated (sedation level, 2; group C, 33.3%). We conclude that clonidine gives better thermodynamics than tramadol, with fewer side effects.

Key words : Clonidine, post-spinal anaesthesia shivering, tramadol.

INTRODUCTION

Regional anaesthesia (spinal anaesthesia) is widelyused as a safe anaesthetic technique for both elective and emergency operations. Shivering is known to be a frequent complication, reported in 40 to 70% of patients undergoing surgery under regional anaesthesia[1,2] Shivering is a potentially serious complication, resulting in increased metabolic rate; increased oxygenconsumption (up to 100-600%) along with raised carbon dioxide (CO2) production; ventilation and cardiac output; adverse postoperative outcomes, such as wound infection; increased surgical bleeding; and morbid cardiac events. It causes arterial hypoxemia, lactic acidosis, increased intraocular pressure (IOP), increased intracranial pressure (ICP); and interferes with pulse rate, blood pressure (BP) And electrocardiographic monitoring.[3,4] Though the mechanism of origin of shivering is not clear, various hypotheses have been proposed to explain its occurrence.

Perioperative hypothermia is the primary cause, which occurs due to neuraxial anaesthesia–induced inhibition of thermoregulatory mechanism. Shivering occurs as a thermoregulatory response to hypothermia or muscle activity with tonic or clonic patterns, and various frequencies have been noticed.[5] However, in the postoperative period, muscle activity may be increased even with normothermia, suggesting that mechanisms other than heat loss with subsequent decrease in the core temperature contribute to the origin of shivering. These may be uninhibited spinal reflexes, sympathetic over-activity, postoperative pain, adrenal suppression, pyrogen release and respiratory

alkalosis.[5] Due to shivering and thermal discomfort, the quality of patient recovery suffers.

There are various methods available to control shivering during anaesthesia, which include nonpharmacological methods and pharmacological methods using drugs which have anti-shivering properties. Non-pharmacological methods using equipment to maintain normal temperature of the body are effective but expensive and lack practicality, while the
pharmacological methods using drugs like pethedine, tramadol, clonidine, doxapram, katenserin, nefopam, etc are simple, costeffective and easy to implement.

AIM : The aim of this prospective double-blind randomized clinically controlled study was to clinically compare the efficacy, potency, haemodynamic effects, complications and side effects of clonidine with those of tramadol for control of shivering.

MATERIAL AND METHODS: After obtaining permission from the Institutional Ethics Committee and written informed consent from all parturients, 90 ASA grade I and II parturients, between the ages of 18 and 35 years, who subsequently developed shivering intraoperatively during elective or emergency caesarean section, under spinal anaesthesia, were enrolled by random allocation in this study and divided into two groups of 45 each. Parturients with known hypersensitivity to tramadol and clonidine, cardiopulmonary, liver, or renal disease, psychological disorders, hypo- or hyperthyroidism, a need for blood transfusion during surgery, an initial body temperature > 38°C or < 36°C, a known history of alcohol or drug abuse, those receiving vasodilators, those who received drugs for labor analgesia, or other medications likely to alter thermoregulation, were excluded from the study.

The parturients did not receive any premedication. On arrival into the operating room, an 18G venous cannula was inserted and preloading done with Ringer's Lactate solution at 10 ml kg^{-1} h^{-1} before insertion of spinal anaesthesia and reduced to 6 ml kg^{-1} h^{-1} after spinal anaesthesia. Volume of preloading intravenous fluids, use of mephenteramine for hypotension and the dose of local anaesthetic were determined by the attending anaesthesiologist and were not affected by enrollment in the study. All preloading fluids and drugs were stored and administered at room temperature.

Subarachnoid anaesthesia was instituted at the L_3 - L_4 spinal interspaces, with 0.5%, hyperbaric bupivacaine 10 mg (2 ml) using a 25G Quincke spinal needle. The parturients were randomly (envelope randomization) allocated to receive Clonidine 50 µg (Group-C, n = 45) or Tramadol 50 mg (Group-T, n = 45). Parturients who developed grade 3 or 4 shivering for at least three minutes after spinal anaesthesia were included in the study; both the drugs were given as slow i.v. bolus injections. The treatment drugs were diluted to a volume of 10 ml in a 10 ml syringe and presented as coded syringes by an anaesthesiologist who was blinded to the group allocation.

Supplemental oxygen (5 liters min^{-1}) was delivered via a facemask during the operation. All parturients were covered with one layer of surgical drapes over the chest, thighs and calves during the operation and one cotton blanket over the entire body after operation. The presence of shivering was observed by an observer anaesthesiologist blinded to the administered study drug. Shivering was graded using a scale similar to that validated by Tsai and Chu [6] 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. The anti-shivering effect of the study drug was assessed by both the parturient and observing anaesthesiologist. The parturients were asked to evaluate the effect of treatment, two minutes after injection as, no response, slight response, or marked response. This was then recorded as per the statement of the parturients. The attending anaesthesiologist independently
assessed and recorded the time of cessation of shivering after treatment. Fifteen minutes after the administration of the study drug, if the shivering grade continued to be the same, the treatment was regarded as ineffective and i.v pethidine 25 mg was administered to control the shivering. Heart rate, respiratory rate and peripheral oxygen saturation were monitored continuously, arterial blood pressure was recorded every two minutes, for first 30 minutes and every five minutes for additional 60 minutes using the standard non-invasive monitors, before and after intrathecal injections, till the development of shivering, as well as after administration of study drug. During the perioperative period, body temperatures (tympanic and axillary temperature)

were recorded with an ear and an axillary thermometer. The ambient temperature was measured by a wall mounted thermometer. The ambient temperature was maintained at 24°C - 26 ° C, with constant humidity.

Side-effects such as nausea, vomiting, hypotension, bradycardia, dry mouth, sedation, skin rash and headache, if present, were recorded. Hypotension was defined as a decrease in arterial pressure of more than 20%, in relation to a baseline pressure or systolic pressure of less than 100 mmHg. If patients developed nausea and vomiting, i.v. metoclopramide 10 mg was administered.

	Group C (n =45)	Group T (n= 45)	P value
Age	26.8 ±5.8	27.4 ± 6.6	0.66
Gestational age	39.3 ±1.1	39.3 ±1.0	0.98
BMI	29.3±4.7	29.2 ±4.1	0.93
Duration of LSCS	74.1±17.0	69.0±18.8	0.22

The attending anaesthesiologist also assessed the degree of sedation on a five-point scale:

1: Fully awake and oriented; 2: Drowsy; 3: Eyes closed, but rousable to command; 4: Eyes closed, but rousable to mild physical stimulation; and 5: Eyes closed but unarousable to mild physical stimulation.[7] All data were analyzed using the Chi squire test and Z-test

Statistical analysis

Previous studies have found an incidence of shivering of the order of 40 - 65%. We anticipated an incidence of 50%. Hence, we assumed that < 35 parturients were required in each group for a type I error of 0.05 and the power of the study was > 90%, a sample size of 45 was calculated. Statistical comparisons of patient characteristics and time taken to control shivering, between the groups, were performed using the Z-test. Nominal or categorical data, including the overall incidence of shivering, response rate and side effects between the groups were analyzed and compared using the chi square test. The value of P < 0.05 was considered as statistically

Result

Ninety parturients experienced shivering of grades 3 and 4 after spinal anaesthesia, during the caesarean section. Parturients characteristics in respect of age, weight, body temperature and duration of surgery were similar between the groups [Table 1]. Response rate (shivering ceased after treatment within 15 minutes) was found to be 97.7% in the clonidine group and 93.7% in the tramadol group and the time required to cease shivering was shorter in the clonidine group than in the tramadol group [Table 2]. Nausea, vomiting, sedation and headache were more common in the tramadol group [Table 3]. No patient in any group developed hypotension or skin rash before or after treatment. In addition the heart rate, respiratory rate and oxygen saturation were not significantly different after sp inal anaesthesia, before treatment and 15 minutes after treatment.

TABLE 1 (Patient characteristic)

TABLE 2 Postspinal anaesthesia shivering and responses

	Group C (n =45)	Group T (n= 45)	P value
Onset of shivering(min)	7.6 ± 3.2	7.1 ± 3.5	0.48
Severity of shivering (grade)	3.2 ± 0.8	3.0 ± 0.9	0.30
Time interval from treatment to cessation of shivering(min)	3.02 ± 0.56	6.1 ± 1.0	0.00001
Response rate (%)	44 (97.7)	42 (93.7)	

TABLE 3 COMPLICATIONS

	Group C (n =45)	**Group T (n= 45)**
Nausea	0	34 (75.5 %)
Vomiting	0	10 (28.6 %)
Bradycardia	3 (6.6%)	1 (2.2 %)
Hypotension	3 (6.6 %)	0
Dizziness	0	20 (44.4%)
Sedation score		
1	30 (66.6%)	40 (88..8 %)
2	15 (33.3 %)	10 (22.2%)
Dry Mouth	1 (2.2 %)	0

Discussion

The results of this study indicate that the response rate is less and the time taken to control shivering is longer, and side effects are more in the tramadol group. The response rate is better and time taken to control shivering shorter in the clonidine group, with less side effects. Shivering occurs as a thermoregulatory response to hypothermia or muscle hyperactivity with clonic or tonic patterns and different frequencies have been reported. However, in the post spinal period shivering has been reported in patients with normothermia, suggesting that other mechanisms, other than heat loss and subsequent decrease in core body temperature may contribute to the development of shivering.[8]These mechanisms include inhibited spinal reflexes, apprehension, decreased sympathetic activity, pyrogen release, adrenal gland suppression and respiratory alkalosis.Hypothermia during central neuraxial blockade is common,[9] and can be nearly as severe as that observed during general anaesthesia.[10] There are three principal reasons for hypothermia under spinal anaesthesia. First, spinal anaesthesia leads to an internal redistribution of heat from the core to the peripheral compartment,[11] secondary to sympathetic block and peripheral vasodilatation. Second, loss of thermoregulatory vasoconstriction below the level of the spinal block, leads to increased heat loss from the body surfaces. Last, there is altered thermoregulation under the central neuraxial block, characterized by a decrease in shivering thresholds. In addition rapid administration of cold intravenous fluids contributes to the development of shivering.

Treatment modalities include covering the patient with blankets, application of radiant heat and warming the operating room. The use of warm local anaesthetic solution or warm intravenous fluids has met with various degrees of success. Various pharmacological treatments like i.v. opioids, alfentanil, pethidine; nalbuphine and meperidine, non-opioid analgesic tramado 5-HT3 antagonists; ondansetron, dolasetron; and cholinomimetic agent physostigmine have been used; [12-18] however, side effects like hypotension, hypertension, sedation, respiratory depression, nausea and vomiting, limit their use. Our study was designed to compare a small dose (50 μg) of clonidine, an α_2 adrenoceptor agonist, with that of tramadol a non-opioid analgesic for control of shivering during spinal anaesthesia.

Clonidine is an α_2 adrenoceptor agonist, with antihypertensive, sedative, analgesic and anti-shivering properties. The anti-shivering effects of alpha (α) adrenoceptor agonists are mediated by binding to α_2 receptors mainly the α_{2b} receptors that mediate vasoconstriction and the anti-shivering effect. [19] In addition clonidine has hypothalamic thermoregulatory effects.[20]

Tramadol has been used as an analgesic for postoperative pain and labor analgesia without any adverse effects on the mother or baby.[21] It has been shown to be effective in controlling post spinal shivering.[22] Tramadol has got agonist properties on opioid receptors, with the main opioid effect being mediated through μ receptors, with minimal effect on κ (kappa) and σ (Sigma) receptors. It activates the monoaminergic receptors of the descending spinal inhibitory pathway of pain. It also inhibits the synaptosomal nor-adrenaline and serotonin uptake and may also contribute to its analgesic effect.

In the present study, we found that clonidine is as effective as tramadol in treating post–spinal. anaesthesia shivering, but the time interval from the commencement of treatment to cessation of shivering is quite less with clonidine (3.02±0.56 minutes) than with tramadol (6.1±1.0 minutes)

(P=.000001) . The response rate was also higher in the clonidine
group than in tramadol group, but the difference was not statistically significant (P=.03).
The complications were found to be higher in case of tramadol compared to clonidine. In the present study.The incidence of nausea was higher in tramadol group compared to clonidine group. Similar differences were noted between the two groups in relation to vomiting
and dizziness. In case of group C, 15 (33.3%) patients had sedation of grade 2; while in group T, it was 10 (22.2%). Two patients of group T had recurrence of shivering in postoperative period, while no patient in clonidine group suffered recurrence of shivering. These findings were similar to the findings of other researchers who compared clonidine with other drugs having anti-shivering properties.[23-27] Bradycardia occurred in 3 patients of group C, while one patient of group T suffered from bradycardia. Hypotension occurred in 3 patients of group C. On overall analysis, higher complication rates were noted in group T patients compared to group C patients.
No patient in either group had sedation of grade 3 or 4. One patient of group C had dry mouth, which was not present in groupt.Shukla et al compared same doses of tramadol and clonidine in nonparturients.Our study results are consistent with these study results.[26]

Conclusion

Clonidine 50 µg is more effective than Tramadol 50 mg, in the treatment of post spinal shivering. Also the side effects were fewer with clonidine, compared to with tramadol. Our study has limitations of small sample size, hence, further controlled large sample-sized studies with different doses of clonidine are required to confirm the optimal dose and the results of this study

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