Original Article

Effectiveness of Addition of Intrathecal Tramadol with Hyperbaric Bupivacaine in Prevention of Shivering in Parturients Undergoing Cesarean Section Under Spinal Anesthesia: A Randomized Placebo-controlled Study

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Abstract

Context: Intravenous (IV) tramadol has been in use for the treatment of postanesthetic shivering. **Aims:** To assess the efficacy of addition of tramadol to bupivacaine in subarachnoid block to reduce the incidence of shivering. **Settings and Design:** The study was conducted as a single-blind study in a 350-bedded teaching hospital. **Materials and Methods:** One hundred parturients undergoing cesarean section were randomly divided into two groups of 50 each. Group T received 0.2 mL (10 mg) of tramadol with 2 mL of 0.5% bupivacaine. The presence of shivering was noted intraoperatively and postoperatively. **Statistical Analysis Used:** Student's *t*-test (two-tailed, independent) was applied for continuous variables and Chi-square/Fisher's exact test was applied for categorical variables between the two groups. **Results:** Shivering was noted in 66% of the patients in Group NS as against the 16% noted in Group T with a majority of the cases (88%) noted in the intraoperative period. The mean duration to the two-segment regression was 135 ± 26 min in Group T versus 104 ± 22 min in Group NS and duration to 1-grade motor block regression was 128 ± 21 min in Group T versus 103 ± 18 min in Group NS. The analgesic effect of the block lasted for a mean duration of 232 min in Group T and 176 min in Group NS while nausea and vomiting were increased in group T versus NS. **Conclusions:** Tramadol (10 mg), along with bupivacaine given intrathecally plays a significant role in reducing the incidence of anesthesia-induced shivering in parturients while prolonging both the sensory and motor components of the subarachnoid block.

Key words: Cesarean section, intrathecal tramadol, postanesthetic shivering, spinal anesthesia (SA)

Introduction

Postanesthetic shivering can be defined as spontaneous, involuntary, rhythmic, oscillating, tremor-like muscle hyperactivity after general anesthesia (GA) or regional anesthesia.[1] Shivering increases metabolic heat production by up to 600% and is commonly associated with spinal anesthesia (SA) in patients undergoing cesarean section, occurring in up to 45–85%.[2]

Shivering increases the oxygen consumption, lactic acidosis, and carbon dioxide production, which may be deleterious in patients with impaired cardiovascular reserve or a limited respiratory capacity. It can also increase the intraocular and intracranial pressures. In addition, it interferes with the monitoring of electrocardiogram, noninvasive blood pressure, and oxygen saturation. Due to shivering and the associated thermal discomfort and the aggravation of postoperative pain by stretching of surgical incisions, the quality of patient recovery suffers. Parturients are low on pulmonary reserve and have an inherently high rate of metabolism[3,4] and hence, may be adversely affected by it.

Antishivering measures taken by the anesthesiologists include pharmacological (tramadol, pethidine, clonidine, ketamine, etc.) and nonpharmacological measures (forced air warmers, fluid warmers, warming mattresses, and warming blankets).

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Tramadol has been used for the prevention and treatment of shivering by intravenous (IV) route in multiple studies.[5,6] It is easily available, owing to lesser government regulation,[7] even in setups of a smaller scale. These studies have shown its effectiveness as a good method to control shivering at the cost of few side effects such as nausea, and vomiting, which can be distressing to the patients and require the use of antiemetic medications. We undertook this study to evaluate primarily the antishivering effects of tramadol and look at its side effects profile when given intrathecally while restricting ourselves to lower segment cesarean section (LSCS) cases in order to keep a standardized surgical procedure and a standard volume of the injected drug, facilitating easy comparison between patients.

Materials and Methods

Approval for the study was obtained from the institutional ethical committee and a written informed consent was obtained from all the participants of the study. The study was designed as a single-blinded, randomized placebo-controlled trial with patients and controls being selected from a secondary care teaching hospital in Bangalore, Karnataka, India. Because of the practical difficulties of blinding in emergency cases and the inherently low bias because of objective variables, a single-blinded model was used. All American Society of Anesthesiologists (ASA) Grade 1 or 2 parturients posted for elective and emergency LSCS were included in the study. Acute emergency indications for LSCS such as severe fetal distress or meconium-stained amniotic fluid, patients not consenting or having contraindications for SA, patients in whom there was a need for conversion to GA, short statured patients with a height below 145 cm, patients with severe preeclampsia and eclampsia, cardiorespiratory, neurological, or psychiatric illness, and allergy to opioids or local anesthetics were excluded from the study.

All patients received antiaspiration prophylaxis in the form of IV ranitidine 50 mg and IV metoclopramide 10 mg 30 min before being wheeled into the operation theater (OT) in the left lateral position. All parturients received 8 mL/kg of ringer lactate through an 18G IV cannula (B Braun Velsungen AG, Mebungen, Germany) as preloading. Based on the random numbers generated by the online generator, the block randomization technique was adopted to assign the patients into two groups of 50 each. Allocation concealment was achieved by keeping the block of four numbers in opaque sealed envelopes. Patients in Group T received 10 mg (0.2 mL) of preservative-free tramadol hydrochloride (Kamadol 50), along with 2 mL of 0.5% hyperbaric bupivacaine while the placebo group; Group NS received 0.2 mL of normal saline, along with 2 mL of 0.5% hyperbaric bupivacaine. After recording baseline values on the standard multipara monitors, the drug was injected intrathecally with a 26G Quincke needle (BD Spinal needle (BD India Pvt Ltd, New Delhi, India)) at L_{3-4} or L_{4-5} interspace. Immediately after, the patients were placed supine with a 15° lateral tilt using a wedge under the right hip. The OTs were maintained at a constant humidity (70%) and an ambient set temperature of around 20°C to 23°C with a side flow of cooled air supplied by the air-cooled chiller (Blue Star chiller, Bangalore, India) from the centralized air handling unit. The humidity and temperature in the operation theater were crosschecked with the dry and wet bulb type mercury thermometers (Dimple Thermometers, Delhi, India). Initially, the air-conditioning in the operation theater was switched off. It was turned on soon after the baby was taken out of the OT after initial assessment by the pediatrician. Oxygen was administered to all the patients at a rate of 5 L/min with a Oxygen Face Mask (Medicare Heathcare products, Agra, India), and the patients were covered with one layer of surgical drapes over the chest, thigh, and legs and one long sheet covering both the upper limbs. No methods of active rewarming (such as forced air-warmers) were used prophylactically. IV fluids (Ringer's lactate) and drugs including the prepping fluids were used at room temperature. After the delivery of the baby, 5 units of oxytocin was administered intramuscular (IM) infusion followed by a slow IV infusion of 10 units of oxytocin.

The highest level of sensory block was assessed by the loss of sensation to pinprick with a 24G Hypodermic needle (Hindustan Syringes, Ballabgarh, Faridabad, India) and the level of sensory block was checked every 15 min till a regression by two dermatomes was noted. Level of motor block was assessed as per the Bromage Scale (as in Table 1).[8] In the recovery, onset time of regression of motor block as evidenced by the ability to move her feet was assessed.

The measurements of heart rate, oxygen saturation, and blood pressure were noted from the multipara monitor (Philips MP40 (Philips Medizin Systema, Boablingen, Germany)) every 5 min till the delivery of the baby and every 15 min after that. The occurrence of hypotension (systolic blood pressure <90 mmHg or <20% of the baseline), bradycardia (<50 bpm) and oxygen desaturation (<92%) were noted and treated. For hypotension, a 2 mL/kg bolus of fluid infusion and incremental doses of ephedrine 6 mg IV were administered. Bradycardia was treated with atropine 0.6 mg IV. Oxygen desaturation was treated with oxygen through face mask at 6 L/min. The incidence of shivering, nausea, vomiting, and sedation were recorded. The grade of shivering was recorded according to a grading system used by Wrench[9] as in Table 2.

If there was shivering, nonpharmacological methods such as forced air warmer and blankets were used, along with pharmacological measures such as IV injection of pethidine 20 mg or IV tramadol 50 mg as rescue therapy. For treatment of nausea/vomiting, IV ondansetron 0.1 mg/kg was administered. No antiemetic prophylactic medications were administered.

The level of sedation was graded as per the following scale used by Campbell DC *et al*.[10] as (1) wide awake (2) drowsy (3) arousable (4) nonarousable.

The pediatrician attending the cesarean section documented the Apgar scores of the neonate at 1 min and 5 min after delivery. At the end of the surgery, 100 mg diclofenac suppository was inserted as per institution policy to all the patients. Postoperatively, in the recovery area, the time to regression of

the motor block by 1 level on the Bromage scale was noted. The time to request the first rescue analgesic was also recorded and injection pentazocine 30 mg IM was given as a rescue analgesic.

Sample size estimation was done according to the methods suggested by Kelsey and Fleiss[11,12] with power of 80% and two-sided significance level of 95%. The required sample size was 49 patients in each group. We planned to include 105 patients to account for exclusions and dropouts. The analysis was performed in the Statistical Package for the Social Sciences (SPSS) version 15 (SPSS Inc., Chicago, IL, USA), SAS 9.2 (SAS Institute Inc., Cary, North Carolina, USA), MedCalc 9.0.1 (MedCalc Software bvba, Ostend, Belgium). Results on continuous and categorical measurements are presented as mean ± standard deviation (SD) (minimum-maximum) and number (%), respectively. Student's *t*-test (two-tailed, independent) was applied for continuous variables and Chi-square/Fisher's exact test was applied for categorical variables between the two groups. A P value of < 0.05 was considered as statistically significant while those <0.01 were strongly significant statistically.

Results

In total, 104 patients were enrolled into the study. In one patient in each group, the level of SA was insufficient to perform the surgery due to which they had to be given GA. Two other patients, one in each group, experienced pain midway through the procedure that required supplementing with other analgesic agents. These four patients were excluded from the study. Thus, 50 patients received intrathecal tramadol and 50 patients received placebo. Demographically, both groups were well-distributed as shown in Table 3.

Shivering was noted in 66% of the patients in Group NS as against the 16% noted in Group T with majority of the cases (88%) noted in the intraoperative period [Table 4]. The mean duration to two-segment regression was 135.88 ± 26.13 min in Group T versus 104.48 ± 22.37 min in Group NS (as shown in Table 5) and duration to 1-grade regression in motor block was 128.76 ± 21.15 min in Group T versus 103.26 ± 18.23 min in Group NS. The analgesic effect of the block lasted for a mean duration of 232.18 min in Group T and 176.56 min in Group NS.

The adverse effect profile [Table 6] showed an increased incidence of nausea and vomiting in Group T ($P > 0.001$) while the 5 min Apgar score was higher in Group T ($P = 0.019$). Other variables were not statistically significant.

Table 1: Bromage scale for motor block

Grade	Criteria	Degree of block
I	Free movement of legs and feet	Nil (0%)
II	Just able to flex knees with free movement of feet	Partial (33%)
III	Unable to flex knees but with free movement of feet	Almost complete (66%)
IV	Unable to move legs or feet	Complete (100%)

Table 2: Wrench's grading for sedation

Grade 0	No shivering
Grade 1	One or more of the following: Piloerection, peripheral vasoconstriction, peripheral cyanosis but without visible muscle activity
Grade 2	Visible muscle activity confined to one muscle group
Grade 3	Visible muscle activity in more than one muscle group
Grade 4	Gross muscle activity involving the whole body

Table 3: Demographic variables

	Group T (n=50)	Group NS (n=50)
Mean age (in years)	26.28±4.15	27.58±3.89
Mean OT† temp (in °C)	22.49±0.77	22.51±0.75
ASA‡ 1	36 (72%)	32 (64%)
ASA 2	14 (28%)	18 (36%)

†OT: Operation theater, ‡ASA: American Society of Anesthesiologists

Discussion

Shivering is primarily caused by perioperative hypothermia due to the neuraxial anesthesia-induced peripheral vasodilation, which facilitates core-to-peripheral redistribution of heat causing warming of the cool peripheries at the expense of the core compartment,[13] which is sensed by the hypothalamic thermosensors that activate the thermoregulatory responses to increase heat production, prominently by shivering. This muscle activity may be increased even with normothermia, meaning that in addition to hypothermia, uninhibited spinal reflexes, sympathetic overactivity, postoperative pain, adrenal

Table 4: Shivering related variables

Shivering	No (%)		*P* value
	Group T	Group NS	
Shivering	8 (16)	33 (66)	<0.001
Time of occurrence of shivering			
Intraoperative	4 (50)	29 (87.9)	0.033
Postoperative	4 (50)	4 (12.1)	0.033
Grade of shivering			
1/2/3/4	0/50/50/0	12.1/18.2/51.5/18.2	0.279

Table 5: Variables of subarachnoid block

	Group T	Group NS	*P* value
Highest level of sensory blockade (T−)	4.80±1.09	5.04±0.99	0.251
Time to highest sensory level (mins)	5.46±2.22	6.22±2.31	0.097
Time to 2-segment regression (min)	135.88±26.13	104.48±22.37	<0.001
Time to wearing off of motor block (min)	128.76±21.15	103.26±18.23	<0.001
Time for first postoperative analgesic request (min)	232.18±80.55	176.56±47.39	<0.001

Table 6: Adverse effect profile

Side effects	No (%)		*P* value
	Group T	Group NS	
Nausea	29 (58%)	12 (24%)	<0.001
Vomiting	20 (40%)	10 (20%)	<0.001
Pruritus	0	0	-
Sedation score (1/2/3/4)	56/28/16/0	54/40/6/0	0.87
Hypotension	14 (28%)	21 (42%)	0.141
Bradycardia	3 (6%)	0	0.242
Mean Apgar score			
1 min	7.74±0.80	7.50±1.09	0.214
5 min	8.92±0.34	8.66±0.69	0.019
Use of uterotonic agents			
Nil	43 (86%)	46 (92%)	0.537
Methylergometrin	4 (8%)	3 (6%)	
Carboprost	3 (6%)	1 (2%)	

suppression, pyrogen release, and respiratory alkalosis could contribute to the origin of shivering.[14]

Other than being a weak opioid agonist, tramadol is also an inhibitor of the reuptake of 5-hydroxytryptamine and norepinephrine in the spinal cord. This facilitates 5-hydroxytryptamine release, which influences thermoregulatory control.[15]

The results of our study showed a significant fourfold decrease in the incidence of shivering in the tramadol group (8%) as compared to the placebo group (66%) with increased incidence of grade 3 or 4 shivering in the placebo group. This was in line with the study by Subedi *et al*.[16] where the incidence of shivering in the parturients receiving tramadol intrathecally was significantly lower (5%) than those receiving fentanyl (32%).

The tramadol group had a significant prolongation of the sensory block (duration for two-segment sensory block regression) by 30 min ($P < 0.001$) while the duration of motor block (time required for motor block to regress to Bromage grade III from grade IV) was also prolonged by about 25 min ($P < 0.001$) with a significant delay in the call to the ward nurse for postoperative analgesia by 55–60 min in the tramadol group ($P < 0.001$). A higher mean sensory level (T4.8) and a faster onset time (by 30 s) were also noted.

In a similar study conducted by Subedi *et al*.,[17] the maximum sensory block height attained in the tramadol group was around T2 while the time to maximum cephalad spread of the block was 8 min. The time required for the block to regress by two segments was 80 min and motor block regression took 120 min. The study by Chakraborty *et al*.[18] for gynecological surgeries also found that those receiving tramadol were pain-free for 380 ± 11.82 min versus 210 ± 10.12 min in the controls.

The antinociceptive effect of tramadol at the spinal level can be attributed to the increase in norepinephrine and serotonin in the spinal cord causing activation of descending inhibition, along with its effects on the opioid receptors,[17,19-21] in addition to the indirect activation of spinal alpha 2-adrenoceptors[22] and the galaninergic system.[23] In addition to the analgesic effects, there is also a central neural blocking effect[24] of intrathecal tramadol that is manifested as suppression of sensory and motor conductions in the spinal cord. This local anesthetic-like activity of the tramadol might have potentiated the action of bupivacaine, possibly explaining the higher dermatomal segmental block, longer regression time, and prolonged analgesic effect seen.

The incidence of intraoperative nausea in our study was 58% and vomiting was present in 40% of the patients. In comparison, in the study by Subedi *et al*.[17] intraoperative nausea was 26% and vomiting was present in 18% of the patients while in the study by Verma *et al*.,[25] nausea was seen in 10% of the patients and 6.6% had vomiting. The increased baseline (placebo group) incidence could be because the pregnant population is inherently more prone to vomiting,[26] with some studies quoting an incidence of up to 66% intraoperatively during cesarean section.[27,28] Our study witnessed a 20–25% incidence of nausea and vomiting in the placebo group, probably due to the combined effects of use of uterotonic agents that are known to induce nausea, vomiting as well as the ensuing hypotension in many of the patients. Lussos *et al*. suggested that intraoperative nausea and vomiting after delivery were related to the surgical manipulation of the uterus, abdominal viscera, and peritoneum, even in the presence of adequate sensorimotor blockade.[29] However, in our study the uterotonic agents and hypotensive episodes were distributed equally in both the groups. The ability of tramadol to increase the 5-HT levels by reducing its uptake may contribute to its proemetic property. These episodes were observed to be amenable for treatment with antiemetic agents such as ondansetron.

There was no incidence of pruritus in any of the patients in our study. There was a trend toward slightly higher grades of sedation with tramadol, which was not statistically significant. In the study by Rao ZA *et al*.,[30] none of the patients who received epidural tramadol for labor analgesia were sedated while in the study by Subedi A *et al*.,[17] 8% of the parturients with tramadol were drowsy. In the study by Verma *et al*. on orthopedic patients,[26] most of the patients receiving tramadol were awake and alert. The increased incidence of sedation in both the groups could have a possible attribution to the fact that there were parturients who were in labor for a prolonged duration and were posted for failure to progress in labor, prolonged labor, and failed induction. In addition, few of the surgeries were performed at night-time; thus, exhaustion and disturbance in circadian rhythm may have had additive effects in both the groups. Tramadol being considered a weak μ-receptor agonist may cause a mild degree of sedation; however, it has an inherently lower ability to cause sedation unlike pure agoinsts such as morphine or fentanyl.

There were no adverse effects of tramadol on the neonatal Apgar scores at 1 min and 5 min after delivery with comparable but higher scores in the tramadol group (mean of 7.6 and 8.92)

than in the placebo group (7.5 and 8.6). In comparison, Rao ZA *et al*.[31] had 100% newborns with Apgar scores ≥9 after 5 min when they used tramadol epidurally for labor analgesia. This was in line with the view expressed in the pharmacokinetic study in parturients receiving tramadol for labor analgesia by Claahsen *et al*. that neonates possess adequate capacity to hepatically metabolize tramadol.[31]

Regarding the contractility of the uterus after delivery, the requirement of additional uterotonic agents (methyergometrine or carboprost) as deemed necessary by the operating surgeons, in addition to the standard oxytocin dose IV bolus 5 units and 10 units by infusion, was comparable in both the groups; however, there was a slight increase in the usage of additional utertonic agents in the tramadol group, which was of no statistical significance.

Based on our study, we can conclude that tramadol (10 mg), along with bupivacaine given intrathecally plays a significant role in reducing the incidence of anesthesia-induced shivering in parturients while prolonging both the sensory and motor components of the subarachnoid block. The incidence of side effects such as nausea and vomiting is higher in those receiving tramadol with no major differences in the hemodynamics at most time intervals. Nausea and vomiting were amenable to treatment with $5HT_3$ blockers.

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Conflicts of interest

There are no conflicts of interest.

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