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Effect of Tramadol for Prevention of Shivering after Spinal Anesthesia for Cesarean Section

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Abstract: Shivering during spinal anesthesia in obstetric patients is one of the leading causes of discomfort for those patients. Tramadol is effective in the prevention and treatment of shivering after general anesthesia. The aim of this placebo-controlled study, was to investigate whether 1 mg kg^{-1} tramadol i.v. administered after spinal anesthesia would reduce the incidence and severity of shivering in patients undergoing cesarean section. In a randomized and double-blind clinical trial 70 healthy obstetric patients were scheduled for cesarean section under spinal anesthesia. Immediately, after spinal anesthesia 35 patients received 1 mg kg^{-1} tramadol in saline and 35 patients received saline normal. An anesthesiologist blind to the solution injected recorded incidence and intensity of shivering and pain and other parameters. The incidence of shivering was significantly lower in patients, who received tramadol than those who received placebo (28.57% v.s 65.71; $p<0.0001$). In the placebo group 26 (74.28%) patients had postoperative pain, compared to 4 (11.42%) in the study group ($p<0.0001$). There was no difference in the incidence of pharmacologic side effects. The results of this study revealed that tramadol 1 mg kg^{-1} i.v. is effective in prevention of shivering after spinal anesthesia for cesarean section.

Key words: Cesarean section, spinal anesthesia, shivering, tramadol, Iran

INTRODUCTION

Neuraxial anesthesia may impair thermoregulatory control (Miller, 2005). Shivering during neuraxial anesthesia is a common problem and up to 56.7% incidence of shivering during regional anesthesia has been reported (Hong and Lee, 2005; Sagir *et al*., 2007). Intra-operative hypothermia has been reported in parturients receiving spinal anesthesia, so the incidence of shivering in pregnant women is greater (Miller, 2005; Hui *et al*., 2006).

Most post-anesthetic shivering-like tremor is a normal thermoregulatory shivering in response to core hypothermia or is caused by the release of cytokines by the surgical procedure. Non-thermoregulatory shivering, occurring in normo-thermic patients is caused by other etiologies such as postoperative pain (Mathews *et al*., 2002).

Shivering is very unpleasant and physiologically stressful for the patients and may interfere with electrocardiogram, blood pressure and pulse oxygen saturation (Tsai and Chu, 2001). In addition, postoperative shivering is a potentially serious complication, increases oxygen consumption 100-600% in proportion to intra-operative heat loss, increases intracranial pressures and aggravates wound pain by stretching incisions (Mathews *et al*., 2002; Tsai and Chu, 2001; Bilotta *et al*., 2002). The best way to avoid the postoperative shivering-induced increase in hemodynamic and metabolic demands is to prevent shivering. One of these is that adequate treatment of postoperative pain will ameliorate, non-thermoregulatory tremor (Horn, 1999).

Tramadol, a synthetic opioid of the aminocyclo-hexonal, is a unique anesthetic that at multiple sites with low risk of respiratory depression, tolerance and dependence (Hui *et al*., 2006). Tramadol has been used in preventing pain and shivering after general anesthesia (Hui *et al*., 2006; Mathews *et al*., 2002; Tsai and Chu, 2001). There are a few studies regarding the effect of tramadol in prevention of shivering after neuraxial anesthesia especially in parturients.

This randomized, double-blind and placebo-controlled clinical trial was performed to evaluate the effect of tramadol 1 mg kg^{-1} administered after spinal anesthesia to prevent of postoperative shivering in parturients during elective cesarean section.

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MATERIALS AND METHODS

After obtaining approval from institutional ethics committee and written informed consent, 70 obstetric patients (ASA physical status I or II, aged 18-40 year) scheduled for cesarean delivery under spinal anesthesia with no prior premedication, were included in this randomized, double-blind and placebo-controlled study. Excluded were parturients with hyperthyroidism, cardiopulmonary disease, psychological disorder and with initial body temperature >38 or <36°C.

Before beginning regional anesthesia, standard monitoring was established and patients, were given intravenous lactated ringer's solution 7 mL kg^{-1} followed intra-operatively by 15 mL kg^{-1} in continuous infusion (at room temperature, 23-25°C). Spinal anesthesia was instituted at the L_{3-4} or L_{4-5} interspaces, with 5% lidocaine, 1 mL (50 mg) plus fentanyl, 10 μg mL^{-1} (total intrathecal volume was 2 mL) using a 25 Quincke spinal needle. Oxygen 5 L min^{-1} was administered through a mask during anesthesia and patients were covered with drapes but not actively warmed. Just after spinal anesthesia, the patients were randomly sequenced (by a computer-generated randomization) allocated to receive saline (placebo group, n = 35) or tramadol (Tralgidol, OSVAH pharma. Co. Tehran, Iran) 1 mg kg^{-1} (study group, n = 35). The study solutions, were diluted to a volume of 5 mL and were given low intravenous over 2-3 min injected. The study solutions were presented as codes syringes by an anesthesiologist who was not involved in the management of the patients. The dosage of tramadol was chosen according to previous studies (Mathews *et al*., 2002). An investigator, blind to the nature of the study solutions, recorded the body temperature from the axillary's area and the hemodynamic parameters, before establishing regional anesthesia, as a baseline and 3 min after spinal anesthesia, 3 min after tramadol injection, 15 min after beginning of operation and in the PACU. Intra-operative hypotension ≥20% from baseline was treated with an i.v. bolus of ephedrine 5 mg and a further i.v. infusion of normal saline or ringer lactated solution. In addition the same investigator recorded the neonatal Apgar scores at 1 and 5 min and the frequency and intensity of shivering and pain, sedation levels and side effects in the PACU. Shivering was graded on following scoring (Mathews *et al*., 2002):

0 = No shivering.
1 = Mild fasciculation of face or neck and ECG disturbances in the absence of voluntary activity of the arms.
2 = Visible tremor involving >1 muscle group.
3 = Gross muscular activity involving the entire body.

Pain was graded on a Numerical Analogous Scale (NAS) 0-3 (0 = none, 3 = sever pain) and degree of sedation on a 5-point scale where 0 = alert, 1 = arouse to voice, 2 = arouse with gentle tactile stimulation, 3 = arouse with vigorous tactile stimulation and 4 = no awareness (Mathews *et al*., 2002).

If the patients shivered according to at least 2, or had pain score ≥2, i.v. petidine 0.25-0.5 mg kg^{-1} was administered. Side effects such as respiratory depression (respiratory rate <8/min), nausea and vomiting were recorded. If patients had nausea and vomiting, i.v. metoclopramide, 5 mg was injected.

Statistical power calculations (α = 5%, β = 10%) based on preliminary data suggested that a group size of 35 should detect a difference of at least 33% in postoperative shivering comparing the tramadol group with placebo group (Bilotta *et al*., 2002). The SPSS 13.0 program (SPSS Inc., Chicago, IL) was used to analyze the statistical data. Patient characteristics were compared using Student t-test. The incidence of shivering and pain and side effects were statistically tested with the χ^2 test $p<0.05$ was considered statistically significant.

RESULTS

There were no significant differences among the 2 groups with respect to age, weight, cause of cesarean section, duration of surgery and anesthesia, volume of i.v. fluid at intra-operative and Apgar scores of babies (Table 1).

There was no significant difference between the 2 groups with regard to Mean Arterial Pressure (MAP) and Heart Rate (HR) during anesthesia. Furthermore no significant differences were found for MAP and HR

Table 1: Demographic data in the 2 groups

	Group		
Parameter	Study group (n = 35)	Placebo group (n = 35)	p-value
Age (year)	27.26±4.13	30.03±3.80	0.86
Weight (kg)	76.09±7.98	82.49±11.90	0.10
Duration of surgery (min)	58.91±11.15	58.60±7.20	0.88
Cause of cesarean section (%)			0.10
Repeat of C.S	21(60)	29(82.85)	
CPD	5(14.28)	2(5.71)	
Other	9(25.71)	4(11.42)	
IV fluid (mL)	1938.57±201.49	2232.85±256.12	0.26
Apgar scores			
1 min	8.80±1.34	8.90±1.15	0.75
5 min	9.2±0.27	9.40±0.46	0.22

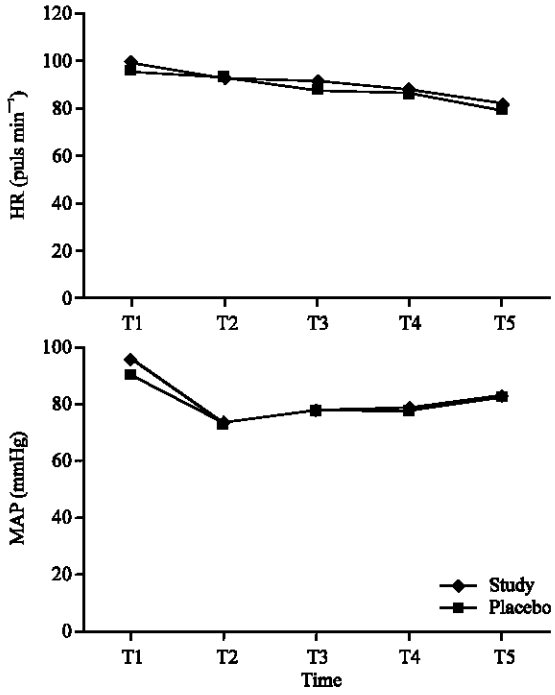

Fig. 1: Heart rate and mean arterial pressure of the 2 groups. T1 = base value, T2 = 3 min after spinal anesthesia, T3 = 3 min after study solutions injection, T4 = 15 min after beginning of operation, T5 = PACU period p>0.05 at all times

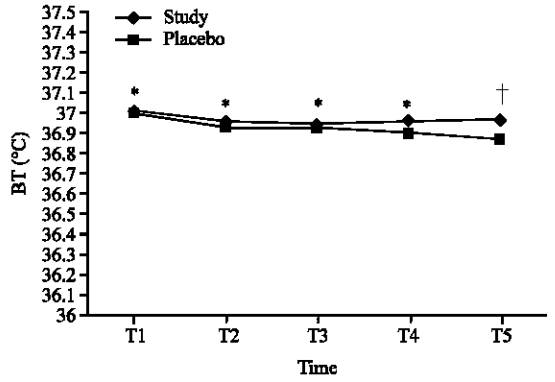

Fig. 2: Change in peripheral body temperature with time. T1 = base value, T2 = 3 min after spinal anesthesia, T3 = 3 min after study solutions injection, T4 = 15 min after beginning of operation, T5 = PACU period *p>0.05; † p = 0.004

values, within the groups after administration of study solution when compared with pre-injection solution's values (Fig. 1).

Figure 2 was shown that after spinal anesthesia the axillary's body temperature measures in some patients of the placebo group decreased (p = 0.004, a comparison with study group in the PACU).

Table 2: Post-operative data in the 2 groups

Parameter	Group: Study group (n = 35)	Group: Placebo group (n = 35)	p-value
Incidence of shivering (%)			<0.0001
Grade 0	25(71.42)	12(34.28)	
Grade 1	8(22.85)	13(37.14)	
Grade 2	2(5.71)	10(28.57)	
Grade 3	0	0	
Incidence of pain			<0.0001
Score 0	31(88.57)	9(25.71)	
Score 1	2(5.71)	13(37.14)	
Score 2	2(5.71)	13(37.14)	
Score 3	0	0	
Postoperative complications (%)			
Nausea	1(2.85)	4(11.42)	0.35
Respiratory deportation	0	0	1.00
Sedation level			0.67
0	31(88.57)	33(94.28)	
1	4(11.42)	2(5.71)	

Postoperative outcomes recorded in PACU are shown in Table 2. Grade ≥2 shivering was not seen in any patients. Shivering was seen in the study patients lower than the placebo group (p<0.0001). The incidence and intensity of pain was shown in Table 2, too. Patients who had higher pain scores, the incidence of shivering were higher (p<0.0001).

Nausea and vomiting occurring during PACU were not significantly different between two groups (p = 0.35). Sedation level recorded in PACU was not a significantly different between the two groups. None of the patients in either groups, had sedation level ≥2. Respiratory depression did not occur in any patients.

DISCUSSION

Patients who received tramadol presented a larger reduction of pain levels and incidence of shivering in the PACU. Furthermore, tramadol did not increase the incidence of nausea and vomiting throughout the anesthesia and PACU. Overall incidence of shivering after neuraxial anesthesia was 33.28% in this study, this is similar to the results in previous studies (Tsai and Chu, 2001; Bilotta *et al*., 2002).

There are several possible mechanisms for shivering associated with spinal anesthesia. Internal redistribution of core temperature, loss of thermoregulatory vasoconstriction below the level of the blockade and decrease of vasoconstriction threshold have been suggested to explain shivering under spinal anesthesia especially in parturients (Miller, 2005; Hong and Lee, 2005; Sagir *et al*., 2007; Hui *et al*., 2006).

Tramadol is an atypical opioid analgesic. Its opioid action is preferentially mediated via the μ-receptor with minimal effects at K. and Δ-binding sites. Tramadol also, activates the monominergic receptors of the descending neuraxial inhibitory pain pathway. Tramadol inhibits noradrenalin and serotonin reuptake. This inhibitory action contributes substantially to tramadol's analgesic action. The anti-shivering action of tramadol is probably mediated via its opioid or serotonergic and noradrenergic activity or both (Mathews *et al*., 2002; Tsai and Chu, 2001; Bilotta *et al*., 2002). Horn (1999) suggested that adequate treatment of postoperative pain will decrease non-thermoregulatory tremor. So, frequency of shivering during spinal anesthesia in his study in patients, who received analgesia was lower than that reported in the control group.

In a systematic search for full reports of randomized comparisons of prophylactic, parentral and single dose anti-shivering interventions with inactive control (placebo or no treatment), tramadol 35-220 mg was more effective than control. In addition, it has Relative Benefits (RB) compared to meperidine or clonidine for shivering treatment (Kranke *et al*., 2004).

Chan *et al*. (1999) showed that tramadol 0.25-0.5 mg was effective (0.80, 92%, respectively) in the treatment of intraoperative shivering during regional anesthesia for cesarean section without side effects on neonates. Other investigations have revealed that that tramadol is effective for treatment of post-regional anesthetic shivering (Tsai and Chu, 2001; Bilotta *et al*., 2002).

In this study, was observed that axillary's temperatures of the patients who received tramadol were higher than those in the placebo. Compensatory cutaneus vasoconstriction occurs above the level of regional block and thermoregulatory vasoconstriction may also decrease skin temperatures. It could be the tramadol interferes with this compensatory cutaneous vasoconstriction (Hong and Lee, 2005).

Throughout the study, there were no differences among 2 groups regarding hemodynamic values. Tramadol is associated peripheral vasodilation, but it can be minimized by injecting the drug slowly over minuets or by limiting the size of the bolus dose (Mathews *et al*., 2002). Sedation also was not clinically or statistically significant and there was no respiratory depression in any of the patients of 2 groups. Tramadol has a decreased incidence of central depressive effects, so tramodol should be consider superior to meperidine for the treatment of shivering. The safety of tramadol compared to meperidine or morphine was shown in studies by Tsai and Chu (2001), Krancke *et al*. (2004) and Bhatangar *et al*. (2001). Adverse side effects, nausea and vomiting, in particular, are dose dependant and therefore considerably more likely to appear if the loading dose is higher (Mathews *et al*., 2002; Tsai and Chu, 2001; Bilotta *et al*., 2002; Horn, 1999; Kranke *et al*., 2004; Chan *et al*., 1999; Bhatnagar *et al*., 2001). The 1 mg kg^{-1} dose of tramadol in this study was relatively small and it was administered as prophylactically so did not increase nausea and vomiting compared to the control group.

A limitation of this study is that we could not measure the body core temperature measurement. Another limitation is that we assessed the effectiveness of an anti-shivering drug for prevention and we did not use of other pharmacologic methods. Further, studies are needed to compare the effectiveness of various drugs in preventing shivering in parturients undergoing neuraxial anesthesia.

CONCLUSION

Administration of a 1 mg kg^{-1} tramadol is effective in prevention of shivering after spinal anesthesia for cesarean section.

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