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Original article

Comparison of the efficacy of nalbuphine, tramadol, ondansetron and placebo in the treatment of postanesthetic shivering after spinal anesthesia for cesarean delivery

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Background: Use of meperidine for the treatment of post-anesthetic shivering (PS) after neuraxial opioids is limited by risk of respiratory depression.
Objective: To compare the efficacy of tramadol, nalbuphine, ondansetron and a placebo in the treatment of PS after spinal anesthesia in cesarean section patients.
Methods: Two hundred eighty parturients who developed moderate to severe shivering and required treatment after cesarean delivery under spinal anesthesia with bupivacaine and intrathecal morphine 0.2 mg were randomized into 4 groups. Group T, Group N, Group O and Group P were given tramadol 0.5 mg/kg, nalbuphine 0.05 mg/kg, ondansetron 0.1 mg/kg and normal saline 5 mL IV, respectively. The patients were evaluated at 15 minutes after treatment and were observed for a recurrence of PS within 4 hours in a double-blinded fashion.
Results: The treatment success rate (no or mild shivering) of PS in groups T, N, O and P were 88, 81, 61 and 36 %, respectively ($p<0.001$). The treatment success rate of groups T vs P, N vs P, O vs P, T vs O and N vs O were significantly different ($p<0.001$, 0.001, 0.003, <0.001, and 0.009, respectively). The success rate between groups T vs N was not significantly different ($p=0.223$). Recurrence rate of PS in groups T, N, O and P were 14 %, 15 %, 11 % and 28 %; $p=0.329$. Other side effects such as pruritus, nausea/vomiting, and dizziness were few and treatable.
Conclusion: Tramadol, nalbuphine and ondansetron were efficacious in the treatment of PS after intrathecal morphine in cesarean section patients with low recurrence rates. Tramadol and nalbuphine were superior to ondansetron in the treatment of PS.

Keywords: Nalbuphine, ondansetron, respiratory depression, shivering, spinal anesthesia, tramadol.

Spinal anesthesia is a safe and popular anesthetic technique for cesarean section because of its rapid onset, the low dose of local anesthetic used and postoperative analgesia provided by intrathecal morphine [1]. However, post-anesthetic shivering (PS) develops in up to 39 % of parturients receiving spinal anesthesia [2]. It may also increase metabolic rate by up to 400 %, induce arterial hypoxemia and lactic acidosis, increase intraocular pressure and cause artefacts in monitors [3, 4]. Among the pharmacological methods of controling shivering, meperidine is often recommended for PS [5-8]. This special antishivering activity may be mediated in part by activation of the kappa opioid receptors [9]. However, the effectiveness of meperidine in the treatment of shivering after neuraxial opioids is limited by the risks of respiratory depression and sedation [8, 10]. Tramadol has been shown to be effective in the treatment of shivering under regional anesthesia in cesarean delivery patients [11]. Nalbuphine and ondansetron, drugs used for the prevention of intrathecal morphine induced pruritus, are also effective in treatment or prevention of PS [7, 12, 13]. We therefore undertook a prospective, randomized, double-blind study to compare the efficacy of tramadol, nalbuphine, ondansetron, and a placebo in the treatment of postanesthetic shivering after intrathecal morphine in cesarean delivery patients.

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Methods

After approval was obtained from the institutional ethics committee and written informed consent was obtained from each patient, this prospective, randomized, double-blind study was performed at King Chulalongkorn Memorial Hospital, a 1500-bed university hospital. ASA class I or II parturients scheduled for cesarean delivery under spinal anesthesia were recruited into this study. Patient who had a known allergy to nalbuphine, tramadol, ondansetron, morphine, or bupivacaine and those with a history of any disease associated with shivering, neurobehavior, or contraindication to regional anesthesia were excluded.

Without premedication, all patients were hydrated with 500 to 1,000 ml of normal saline before the administration of spinal anesthesia. The block was then performed with the patients in the left lateral position at either the L2-3 or L 3-4 interspace by use of a 27 gauge Quincke spinal needle. Once the free flow of cerebrospinal fluid had been demonstrated, 2.2 ml of 0.5 % hyperbaric bupivacane and 0.2 ml (0.2 mg) of preservative-free morphine, mixed in the same syringe, were injected. The parturient was then immediately placed in the supine position with left uterine displacement, and supplemental oxygen was delivered through a face mask at 5 L/min. IV fluid and ephedrine were administered as needed to maintain the systolic blood pressure within 30 % of its preoperative value, or systolic blood pressure $\geq$100 mmHg. After a satisfactory spinal block was verified by loss of sensation to cold or pinprick, cesarean delivery was performed. All loading fluids and drugs were to be given at room temperature. The operating room temperature was kept at 25 °C. The attending anesthesiologists recorded the amounts of preoperative fluid, intraoperative fluid and duration of surgery.

After cesarean delivery, patients were observed in the postanesthesia care unit for 2 hours. Vital signs were recorded every 15 minutes, according to the institutional monitoring protocol. The patients were observed for shivering by the first author. The patients whose shivering score >2 (1=no shivering ; 2=mild shivering, treatment not necessary; 3= moderate shivering, treatment necessary; 4=severe shivering, treatment necessary) [14] as determined by the same investigator were assigned to receive one of the following treatments via the IV route: Group 1=0.5 mg/kg tramadol in saline 5 mL, Group 2=0.05 mg/kg nalbuphine in saline 5 mL, Group 3=0.1 mg/kg ondansetron in saline 5 mL, and Group 4=saline 5 mL. The randomization sequence was selected according to a random number table and was written on a paper enclosed in a sealed envelope. Randomly allocated coded syringes were prepared by a nurse anesthetist not involved in the study and were administered in a double-blind fashion. Fifteen minites after treatment, the patients were assessed by the same investigator. In the absence of a positive response (shivering score of 3 or 4), the result was considered a failure of treatment and shivering was treated by 20 mg propofol intravenous injection. If the treatment was successful (shivering score of 1 or 2), the patients were evaluated every 15 minutes for 2 hours according to the protocol of the post-anesthesia care unit and followed up to 4 hours to determine the duration of the anti-shivering response and recurrence of shivering. At the same time, while the patient was evaluated for shivering evaluation of other side effects was done by a 4-point sedation rating scale (1=fully awake; 2=somnolent, responds to call; 3=somnolent, responds to tactile stimulation; 4=asleep, responds to painful stimulation) [15]; a 4-point pruritus rating scale (1=no pruritus; 2=minimal pruritus, treatment not necessary; 3=moderate pruritus, treatment necessary; 4=severe pruritus and scratching, treatment necessary) [15]; a 4-point nausea and vomiting rating scale (1=no nausea or vomiting; 2=queasy; 3=severe nausea; 4=vomiting) and a verbal numeric pain scale (0=no pain, 10=worst imagination pain). Ten milligrams of metoclopramide was administed for nausea and vomiting as required. Chlorpheniramine 10 mg intravenously was prescribed for pruritus as needed. After drug administration, blood pressure, heart rate, body temperature, dizziness, extrapyramidal effect and respiratory depression were recorded.

Power analysis was performed to determine the size of the treatment groups. Allowing for the probability of type II error of 0.1 and type I error of 0.05 (considering the success rate of the nalbuphine group of 60 %, ondansetron group of 60 %, and tramadol group of 85% from pilot study), a sample size of 70 in each group was calculated as being required. Statistical analysis of the results was performed by using analysis of variance for continuous data, Kruskal-wallis 1-way ANOVA for ordinal data, the X^2 test (Fisher exact test if necessary) for binary data, P value <0.05 and a Bonferroni corrected P value for multiple comparison of <0.01 were considered to be significantly different.

Results

Eight hundred thirty-six parturients undergoing cesarean section under spinal anesthesia with intrathecal morphine provided an event rate of postanesthetic shivering of 45.0 %. Among 376 cases with mild to severe shivering (shivering score 2-4), 280 cases (33.5 % of all shivering) of parturients who suffered with moderate to severe shivering (shivering score 3, 4) were allocated to the tramadol group (n=71), nalbuphine group (n=70), ondansetron group (n=70) and placebo group (n=69). All groups were comparable regarding demographic characteristics, peri-operative data and onset of post-anesthetic shivering as shown in **Table 1**. The onsets of postanesthetic shivering were between 20 to 180 minutes after neuraxial administration of local anesthetics.

The treatment success rates for moderate to severe degrees of post-anesthetic shivering in the tramadol, nalbuphine, ondansetron and placebo group were 88.7 % (63 in 71 patients), 81.4 % (57 in 61.4 % (43 in 70 patients), and 36.2 % (25 in 69 patients); p<0.001 by the Chi-square test as shown in **Table 2**. The success rate of treatment of moderate to severe degree of PS between tramadol and placebo groups, nalbuphine and placebo groups, ondansetron and placebo groups, tramadol and ondansetron groups, and nalbuphine and ondansetron groups were considered statistically significantly different; p=<0.001, p=0.001, p=0.003, p<0.001 and p=0.009 respectively. There was no statistically significant difference in the treatment success rate of PS between the tramadol and nalbuphine groups (p=0.223).

Among the successfully treated patient, 9 of 63 patients (14.3 %) in the tramadol groups, 9 of 57 patients (15.8 %) in the nalbuphine groups, 5 of 43 patients (11.6%) in the ondansetron groups and 7 of 25 patients (28.0 %) in the placebo groups revealed the recurrence of moderate to severe PS (shivering score 3, 4) within 4 hours after the administration of antishivering drugs (p=0.329).

Postoperative side-effects including pruritus, nausea, vomiting and dizziness were shown in **Table 3**. Four patients (80 %) with pruritus score ≥3 were successfully treated by chlorpheniramine 10 mg intravenously. After failure of treatment of pruritus an other patient was successfully treated by IV 20 mg of propofol. All patients who had nausea/ vomiting on a scale ≥2 were successfully treated with metoclopramide 10 mg intravenously. There was no patient with sedation score >2, or verbal numeric pain score >5 in any of the groups after administration of the study drugs. None of our patients experenced extrapyramidal effects or respiratory depression in the postanesthesia care unit.

Table 1. Demographic characteristics, base line characteristics and onset of postanesthetic shivering.

	Tramadol n=71	Nalbuphine n=70	Ondansetron n=70	Placebo n=69
Age (years)	29.92 (5.15)	29.93 (5.3)	31.11 (5.53)	30.19 (4.79)
Weight (kg)	68.69 (9.39)	65.73 (8.78)	67.17 (9.92)	69.73 (10.09)
Height (cm)	157.12 (5.27)	155.9 (5.89)	155.37 (5.18)	155.89 (4.82)
Temperature in PACU (°C)	23.30 (0.50)	23.21 (0.43)	23.36 (0.51)	23.29 (0.40)
Body temperature after entering PACU (°C)	36.37 (0.43)	36.51 (0.45)	36.40 (0.38)	36.55 (0.38)
Preoperative fluid (cc)	639 (194)	585 (172)	585 (210)	610 (201)
Intraoperative fluid (cc)	885 (300)	854 (351)	866 (265)	897 (312)
Duration of anesthesia (min)	53 (17.33)	51.64 (14.93)	48.36 (13.85)	52.24 (15.57)
Onset of shivering (min)	81.43 (38.03)	74.95 (34.92)	75.42 (34.71)	76.56 (35.72)

Value are expressed as means (SD).

Table 2. Successful treatment and recurrence rates of moderate to severe PS.

	Tramadol Group T	Nalbuphine Group N	Ondansetron Group O	Placebo Group P	P value
Success rate*, **	63/71 (88.7 %)	57/70 (81.4 %)	43/70 (61.4 %)	25/69 (36.2 %)	<0.001
Recurrence after success	9/63 (14.3 %)	9/57 (15.8 %)	5/38 (11.6 %)	7/25 (28.0 %)	0.329

Values shown as frequency/n (%); *T *(vs)* P, N *(vs)* P, O *(vs)* P, T *(vs)* O, N *(vs)* O = <0.001, 0.001, 0.003, <0.001, 0.009; **T *(vs)* N = 0.223

Table 3. Pruritus, nausea / vomiting and dizziness after treatment of PS among study groups.

	Tramadol Group T n=70	Nalbuphine Group N n=70	Ondansetron Group O n=71	Placebo Group P n=69	P value
Pruritus rating scale					0.789
1 no	59 (83.1 %)	64 (91.4 %)	59 (84.3 %)	60 (87.0 %)	
2 mild	10 (14.1 %)	6 (8.6 %)	9 (12.9 %)	8 (11.6 %)	
3 moderate	2 (2.8 %)	0 (0.0 %)	2 (2.9 %)	1 (1.4 %)	
4 severe	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	
Nausea/vomiting scale					0.361
1 no	69 (97.2 %)	67 (95.7 %)	69 (98.6 %)	66 (95.7 %)	
2 queasy	1 (1.4 %)	3 (4.3 %)	1 (1.4 %)	0 (0.0 %)	
3 severe nausea	1 (1.4 %)	0 (0.0 %)	0 (0.0 %)	2 (2.9 %)	
4 vomiting	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (1.4 %)	
Dizziness	1 (1.4 %)	1 (1.4 %)	4 (5.6 %)	1 (1.4 %)	0.266

Values are shown as frequency (%)

Discussion

The mechanism of shivering under regional anesthesia is not fully understood. Possible contributing factors are a decrease in core temperature and misinformation from receptors. A decrease in core temperature may be due to: 1) sympathetic blockade which results in peripheral vasodilation, an increase in cutaneous blood flow, and subsequent increased heat lost via the skin [16]; 2) a cold operating room, or the rapid infusion of crystalloid solutions at room temperature [17]; or 3) the direct effects of cold anesthetic solutions upon the thermosensitive structures within the spinal cord. Treatment modalities have included covering the patient with a blanket, application of radiant heat and warming the operating room suite. The use of warm local anesthetic solution [18] or warm intravenous fluids has met with varying degrees of success [19]. Our study was designed to standardize these possible confounding factors while reflecting the usual practice in our institution. Operating room temperature was held constant at 25 °C, intravenous fluids and drugs were administered at room temperature and a blanket was used for all parturients to cover the upper part of the body. Body temperature was also recorded at entering the post-anesthesia care unit. All parturients received 0.2 mg of intrathecal morphine for postoperative pain relief. Pethidine has been shown to be one of the most effective treatments of PS but its disadvantage is interaction with intrathecal morphine leading to respiratory depression. Therefore, the aim of this study was to find alternative medications for treatment of PS in this group of patients.

The incidence of PS after neuraxial analgesia in this study was 44.9 % which was in accordance with previous studies [1, 11, 20]. Our study demonstrated that 0.5 mg/kg tramadol, 0.05 mg/kg nalbuphine and 0.1 mg/kg ondansetron successfully treated shivering in parturients undergoing cesarean section under spinal anesthesia. Tramadol and nalbuphine were more efficacious in the treatment of PS but we could not demonstrate any statistical difference in response between tramadol and nalbuphine.

Tramadol is an analgesic with agonist properties on opioid receptors. It also activates the mono-aminergic receptors of the descending spinal inhibitory pathway of pain. The main opioid effect of tramadol is mediated via the μ-receptor, with minimal effect at K, or δ binding sites [21]. Tramadol also inhibits in vitro synaptosomal noradrenaline and serotonin uptake, which contributes to its analgesic effects [21]. The antishivering effect of tramadol is more likely mediated via receptors other than the μ-receptor, in particular the K-receptor. Nalbuphine, a semisynthetic opioid, also has the characteristics of μ-antagonist and K-agonist activity [22]. Ondansetron, a 5-HT_3 receptor inhibitor, has a specific antishivering effect, but given the variety of neurotransmitter systems known to be involved in regulating shivering, an inhibitory effect at the 5-HT_3 receptor probably results from a generalized thermoregulatory inhibition at the level of the hypothalamus where the bulk of thermoregulatory control occurs [23]. In our study, 0.1 mg/kg of IV ondansetron was less than the dosage of 8 mg ondansetron use in a previous study for prevention of

PS after general anesthesia. The recurrence rates of PS within 4 hours after successful treatment of all three groups were not significantly different. Other side effects such as pruritus, nausea, vomiting and dizziness were not different. However the incidence of intrathecal morphine-induced pruritus in this study was lower than that in previous studies [12, 15]. A possible explanation was that nalbuphine and ondansetron had been used for the prevention and treatment of intrathecal morphine induced pruritus [12, 15], and there was a variation of incidence of intrathecal morphine- induced pruritus. There was no respiratory depression or other serious side effect occuring in any of the patients.

In this study, the dose of drug administration was based on patient weight, a standard dose being given to all patients. The dose of 0.5 mg/kg pethidine was chosen as an effective dose for treatment of postanesthetic shivering in obstetric patients [11]. The doses of 0.05 mg/kg of the nalbuphine and 0.1 mg/kg of ondansetron were chosen by modification of the dosage of drugs administered for the treatment and prevention of postanesthetic shivering in nonobstetric patients in previous studies [7, 13]. We chose shivering rating scales according to Schwarzkopf KR et al study [14] that is usually used in our institution for the measurement tool for primary outcome. We also tested for inter-rater agreement (weighted kappa = 0.94) in a pilot study which was considered as very good agreement.

In conclusion, the IV administration of tramadol (0.5 mg/kg), nalbuphine (0.05 mg/kg) and ondansetron (0.1 mg/kg) were superior to a placebo for treatment of postanesthetic shivering after intrathecal morphine for cesarean section patients. Moreover, tramadol (0.5 mg/kg) and nalbuphine (0.05 mg/kg) were more efficacious than ondansetron (0.1 mg/kg). The recurrence rates after treatment were low and not different. The side effects were few, minor and treatable.

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