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Comparison of efficacy between Nalbuphine, Tramadol and Ondansetron in treatment of postanesthetic shivering after spinal anesthesia for cesarean delivery

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Rationale and background : *Spinal anesthesia is a safe and increasingly a popular technique for elective cesarean section, because of its rapid onset, low dose of local anesthetic used and postoperative analgesia provided by intrathecal morphine. Addition of morphine to intrathecally injected local anesthetics provides effective, long-lasting postoperative analgesia following cesarean section. However, a common side effect after intrathecal administration of local anesthesia includes shivering.*

Objective : *To compare the efficacy among 0.05 mg/kg Nalbuphine, 0.1 mg/kg Ondansetron, and 0.5 mg/kg Tramadol in the treatment of postanesthetic shivering in cesarean section patients after intrathecal morphine.*

Design : *Randomized, double-blind controlled trial.*

Setting : *King Chulalongkorn Memorial hospital, which is a tertiary care center.*

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- Method** : *Two hundred and twenty-five parturients who had moderate to severe shivering were randomly allocated into three groups through simple randomization. Group 1 (n=75) received 0.05 mg/kg Nalbuphine; group 2 (n=74) 0.1 mg/kg Ondansetron; and, group 3 (n=76) 0.5 mg/kg Tramadol. The success rates of treatment of shivering and other adverse effects were determined at 15 minutes after the administration of the study drugs. Statistical analysis of the results was performed with Chi-square test and Kruskal-Wallis 1 way ANOVA with Bonferroni's correction for multiple comparisons. The priori p value of 0.05 was considered significant.*
- Result** : *The success rates of treatment of shivering in Nalbuphine, Ondansetron and Tramadol groups were 81.3 %, 62.2 % and 88.2 % respectively. (p-value <0.001). The success rates between Nalbuphine and Ondansetron groups, Tramadol and Ondansetron groups were statistically significantly different (p-value = 0.009 and p-value < 0.001, respectively). The success rates between Nalbuphine and Tramadol groups were not statistically significantly different (p-value = 0.243). The recurrence rate of moderate to severe shivering within four hours after the first successful treatment in Nalbuphine, Ondansetron and Tramadol groups : were 14.8 %, 13.0 % and 13.4 % respectively. These were not statistically significantly different (p-value = 0.963). Other side effects such as pruritus, nausea/vomiting, pain, and dizziness were few, minor and not significantly different.*
- Conclusion** : *Nalbuphine 0.05 mg/kg and Tramadol 0.5 mg/kg were superior to Ondansetron 0.1 mg/kg in the treatment of postanesthetic shivering after intrathecal morphine for cesarean section patients. The recurrence rates after treatment were low and side effects were few and minor.*
- Keywords** : *Nalbuphine, Ondansetron, Tramadol, Intrathecal morphine, Shivering, Cesarean delivery.*

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เดชา ทำดี, อรุณช เกี้ยวข้อง, สมรัตน์ จารุลักษณะนันท์. การศึกษาเปรียบเทียบประสิทธิผลของนาบูพีนออนแดนซีตรอน และ ทรามาดอล ในการรักษาอาการสั่นภายหลังได้รับมอร์ฟินเข้าช่องไขสันหลังในผู้ป่วยทำการผ่าตัดคลอดทางหน้าท้อง. จุฬาลงกรณ์เวชสาร 2549 ธ.ค.; 50(12): 851 - 62

ความเป็นมาและเหตุผล : การให้ยาระงับความรู้สึกทางไขสันหลังเป็นที่ยอมรับว่ามีความปลอดภัย และได้รับความนิยมเป็นอย่างมาก เนื่องจากสามารถระงับความรู้สึกได้เร็ว ใช้ยาชาปริมาณน้อยอีกทั้งยังสามารถให้มอร์ฟินในน้ำไขสันหลัง ซึ่งช่วยระงับอาการปวดภายหลังการผ่าตัดคลอดเด็กทางหน้าท้องได้เป็นระยะเวลานาน แต่อาการข้างเคียงที่อาจเกิดขึ้นคือผู้ป่วยจะมีการสั่นภายหลังได้รับยาระงับความรู้สึกเข้าช่องไขสันหลัง

วัตถุประสงค์ : เพื่อเปรียบเทียบประสิทธิผลของการใช้นาบูพีน 0.05 มิลลิกรัมต่อกิโลกรัม ยาออนแดนซีตรอน 0.1 มิลลิกรัมต่อกิโลกรัม ยาทรามาดอล 0.5 มิลลิกรัมต่อกิโลกรัม ฉีดเข้าทางหลอดเลือดดำเพื่อรักษาอาการสั่นภายหลังได้รับมอร์ฟินเข้าช่องไขสันหลังในผู้ป่วยผ่าตัดคลอดทางหน้าท้อง

รูปแบบการทดลอง : การศึกษาเปรียบเทียบโดยการสุ่มและปกปิดสองทาง

สถานที่ทำการวิจัย : โรงพยาบาลจุฬาลงกรณ์ ซึ่งเป็นโรงพยาบาลระดับตติยภูมิขนาด 1,500 เตียง

วิธีการศึกษา : แบ่งผู้ป่วยหลังการผ่าตัดคลอดเด็กทางหน้าท้องที่ได้รับมอร์ฟินเข้าช่องไขสันหลัง ที่มีอาการสั่น ระดับปานกลางขึ้นไป 225 คน โดยการสุ่มเป็น 3 กลุ่ม กลุ่มแรกได้รับยานาบูพีน 0.05 มก./กก. กลุ่มที่ 2 ได้รับยา ออนแดนซีตรอน 0.1 มก./กก. กลุ่มที่ 3 ได้รับยาทรามาดอล 0.5 มก./กก. ฉีดเข้าทางหลอดเลือดดำประเมินผลการรักษาอาการสั่นและผลข้างเคียงอื่น ๆ ที่ 15 นาทีภายหลังการบริหารยา และวิเคราะห์ข้อมูลผลการรักษาโดยใช้สถิติไคสแควร์และ Kruskal-Wallis และการปรับค่าแบบ Bonferroni สำหรับการเปรียบเทียบหลายครั้ง ค่า p-value < 0.05 ถือว่ามีนัยสำคัญทางสถิติ

- ผลการศึกษา** : ยานาลูฟิน ยาออนแดนซีตรอน ยา ترامาดอล ฉีดเข้าทางหลอดเลือดดำมีประสิทธิภาพในการรักษาอาการสั่นในผู้ป่วยผ่าตัดคลอดทางหน้าท้องที่ได้รับมอร์ฟินเข้าช่องไขสันหลังเท่ากับ 81.3 %, 62.2 % และ 88.2 % ตามลำดับ ($p\text{-value} < 0.001$) ประสิทธิภาพของยานาลูฟินสูงกว่าออนแดนซีตรอน, ترامาดอลสูงกว่าออนแดนซีตรอนอย่างมีนัยสำคัญทางสถิติ ($p\text{-value} = 0.009$ และ $p\text{-value} < 0.001$ ตามลำดับ) ประสิทธิภาพของยานาลูฟินและยา ترامาดอลไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p\text{-value} = 0.243$) โดยมีอัตราการเกิดการสั่นซ้ำภายใน 4 ชั่วโมงหลังการรักษาครั้งแรกสำเร็จ ของยานาลูฟิน ยาออนแดนซีตรอน และยา ترامาดอล เท่ากับ 14.8 %, 13.0 % และ 13.4 % ตามลำดับ ซึ่งไม่แตกต่างกัน ($p\text{ value} = 0.963$) สำหรับอัตราการเกิดอาการข้างเคียงอื่น ๆ ได้แก่ อาการคลื่นไส้หรืออาเจียน อาการปวด อาการคัน และอาการมึนงง หลังการฉีดยาพบน้อยและไม่รุนแรง อีกทั้งไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ
- สรุป** : ยานาลูฟิน 0.05มก./กก. และยา ترامาดอล 0.5 มก./กก. ฉีดเข้าทางหลอดเลือดดำมีประสิทธิภาพสูงกว่ายาออนแดนซีตรอน 0.1 มก./กก ในการรักษาอาการสั่นภายหลังได้รับมอร์ฟินเข้าช่องไขสันหลังในผู้ป่วยผ่าตัดคลอดทางหน้าท้อง และมีอัตราการเกิดอาการสั่นซ้ำต่ำ โดยเกิดอาการข้างเคียงในอัตราต่ำและไม่รุนแรง
- คำสำคัญ** : นาลูฟิน, ออนแดนซีตรอน, ترامาดอล, มอร์ฟินเข้าช่องไขสันหลัง, อาการสั่น, ผ่าตัดคลอดทางหน้าท้อง

Nowadays, spinal anesthesia is a safe and increasingly a popular technique for elective cesarean section, because of its rapid onset, low dose of local anesthetic used and postoperative analgesia provided by intrathecal morphine.^(1, 2) Addition of morphine to intrathecally injected local anesthetics provides effective, long-lasting postoperative analgesia following cesarean section. However, the common side effect after intrathecal administration of local anesthesia includes shivering. The incidence of shivering post regional anesthesia is between 33 % - 66 %.^(1- 5)

Postanesthetic shivering is distressing for some patients and may exacerbate postoperative pain, increase intracranial pressure, and induce cardiopulmonary complication.⁽⁶⁾ Shivering may also interfere with the monitoring of electrocardiogram, blood pressure, and pulse oxygen saturation. It increases oxygen consumption, lactic acidosis, and carbon dioxide production. Thus it may cause distress in patients with a low cardiopulmonary reserve.⁽⁷⁾ Although postanesthetic shivering in obstetric patients is sometime distressing, it is not a cause of morbidity in young patients. However, postanesthetic shivering is one of the most common troublesome side effects in the postanesthetic care unit.

Many drugs have been used to treat postanesthetic shivering including clonidine, nalbuphine, meperidine, tramadol, ketaserin, propofol, nefopam, physostigmine, fentanyl, alfentanyl, sufentanil, doxapam, dexamethazone, and metamizol. Meperidine is an effective treatment for shivering than equianalgesic doses of other μ -opioids agonists. This special anti-shivering activity may base on its K-receptor activity. However, the effectiveness of opioids

in the treatment and prevention of shivering after neuraxial opioids is limited by the risk of respiratory depression, sedation, pruritus, and nausea.⁽⁸⁾ There are also side effects when other drugs are administered and the ideal drugs for postanesthetic shivering have not been found. We, therefore, undertook a prospective, randomized, double-blind study to compare the efficacy among Nalbuphine, Tramadol, and Ondansetron in the treatment of postanesthetic shivering after intrathecal morphine in cesarean delivery patients.

Methods

After receiving approval from the research ethics committee and inform consent was obtained from each patient, this prospective, randomized, double-blind study was performed at King Chulalongkorn Memorial Hospital, a 1,500 -bed university hospital. ASA class I or II parturients who were scheduled for cesarean delivery under spinal anesthesia were recruited for this study. Patients who had a known allergy to Nalbuphine, Tramadol, Ondansetron, or morphine, and those with history of any disease associated with shivering, neurobehavior, or some 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 the L 3-4 interspace by 25 or 27- gauge Quincke spinal needle. Once free flow of cerebrospinal fluid was secured, 2.2 ml of 0.5 % hyperbaric bupivacaine 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 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 mm Hg. After a satisfactory spinal block was verified by loss of sensation to cold or pinprick, cesarean delivery was performed.

After cesarean section, parturients who were observed of shivering while in the post anesthesia care unit (PACU) (2 hours after completion of the cesarean section) were evaluated by the investigator. 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) as determined by the investigator were assigned to receive either 0.05 mg/kg Nalbuphine or 0.5 mg/kg Tramadol or 0.1 mg/kg Ondansetron according to randomization sequence. Fifteen minutes after treatment, the patients was assessed by the same investigator. In the absence of a positive response (shivering score of 3 or 4) the result was considered failure of treatment and shivering was titrately treated by 20 milligrams propofol intravenous injection. If the treatment was successful, the patient was evaluated every 15 minutes for 2 hours according to the protocol of postanesthetic care unit and followed up for 4 hours to determine the duration of the anti-shivering effect and recurrence of shivering. At the same time the patient was evaluated for shivering, the level of sedation was assessed using a 4-point sedation rating scale, the pruritus was assessed by

4-point rating scale, nausea and vomiting were assessed by 4-point rating scale, and the pain level was assessed by verbal numeric pain scale (0 = no pain, 10 = worst imaginable pain). Ten milligrams of metoclopramide was administered for nausea and vomiting as required. Chlorpheniramine 10 mg intravenously was prescribed for pruritus as needed. After each 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 the probability of type II error of 0.1 and type I error of 0.05 (considering the success rate of Nalbuphine group of 60 %, Ondansetron group of 60 %, and Tramadol group of 85 % from a pilot study), a sample size of 68 in each group and with 10 % drop out rate ; therefore, 75 patients per group was calculated as required. Statistical analysis of the result was performed with X^2 test (fisher exact test if necessary) for binary data, and Kruskal-Wallis 1-way ANOVA for ordinal data, with Bonferroni's correction for multiple comparisons. The priori P value < 0.05 was considered significant.

Results

Seven hundred and thirty-six parturients who underwent cesarean section under spinal anesthesia with intrathecal morphine provided the event rate of postanesthetic shivering of 51.09 %. Among them, 376 cases had mild to severe shivering (shivering score 2 - 4); 255 cases (30.57 %) with moderate to severe shivering (shivering score ≥ 3) were allocated to the Nalbuphine group (n = 75), Tramadol group (n = 76) and Ondansetron group (n = 74). All groups were

comparable regarding demographic characteristics, base line data and onset of postanesthetic shivering as shown in Table 1. The onsets of postanesthetic shivering were 20 to 180 minutes after neuraxial administration of local anesthetics.

The success rates of the treatment for moderate to severe degree of postanesthetic shivering in Nalbuphine, Ondansetron and Tramadol groups were 81.3 % (61 in 75 patients), 62.2 % (46 in 74 patients) and 88.2 % (67 in 76 patients) respectively. The result was considered statistically significant (p-value < 0.001) by Chi-square are test. The success rates between Nalbuphine group and Ondansetron

group, Tramadol group and Ondansetron group were statistically significant (p-value = 0.009, p-value < 0.001 respectively) by Chi-square test with Bonferroni correction for multiple comparisons. The success rate between Nalbuphine and Tramadol was not statistically significantly different (p-value = 0.243) as shown in table 2. Among the successfully treated patients, 9 of 52 (14.8 %) in the Nulbuphine group, 6 of 40 (13.0 %) in Ondansetron group and 9 of 58 (13.4 %) in Tramadol group reported the recurrence of moderate to severe shivering (shivering score ≥ 3) within 4 hours after the administration of study drug (p-value = 0.963).

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

| | Nalbuphine N = 75 | Ondansetron N = 74 | Tramadol N = 76 |
|--|----------------------|-----------------------|--------------------|
| Age (years) | 30.12 (5.36) | 31.00 (5.49) | 30.03 (5.18) |
| Weight (kg) | 60.60 (9.35) | 67.40 (9.75) | 68.53 (9.40) |
| Height (cm) | 155.81 (5.97) | 155.27 (5.14) | 157.10 (5.22) |
| Temperature in PACU ($^{\circ}$ C) | 23.19 (0.43) | 23.35 (0.50) | 23.29 (0.49) |
| Body Temperature after entering PACU ($^{\circ}$ C) | 36.48 (0.45) | 36.39 (0.38) | 35.37 (0.43) |
| Preoperative fluid (mL) | 590 (173) | 588 (205) | 635 (194) |
| Intraoperative fluid (mL) | 856 (345) | 864 (262) | 879 (297) |
| Duration of anesthesia (min) | 52.67 (15.43) | 48.38 (13.50) | 52.83 (16.90) |
| Onset of shivering | 74.95 (34.92) | 74.88 (33.69) | 82.45 (37.80) |

Value are expressed as mean (SD)

Table 2. The treatment success rate of study drugs.

| | Nalbuphine group | Ondansetron group | Tramadol group | p-value |
|---------|------------------|-------------------|----------------|----------|
| Success | 61 (81.3 %) | 46 (62.2 %) | 67 (88.2 %) | < 0.001* |
| Failure | 14 (18.7 %) | 28 (37.8 %) | 9 (11.8 %) | |
| Total | 75 (100 %) | 74 (100 %) | 76 (100 %) | |

Value shown as number (%)

Using Chi-square test

Table 3. The recurrence rate of moderate to severe shivering with in 4 hours after first successful treatment.

| | Nalbuphine group | Ondansetron group | Tramadol group | p-value |
|----------------|------------------|-------------------|----------------|---------|
| Recurrence | 9 (14.8 %) | 6 (13.0 %) | 9 (13.4 %) | 0.963 |
| Non-recurrence | 52 (85.2 %) | 40 (87.0 %) | 58 (86.6 %) | |
| Total | 61 | 46 | 67 | |

Using Chi-square test

The number of patients who had pruritus score = 2 were 6, 9 and 10 after administration of Nalbuphine, Ondansetron and Tramadol, respectively; pruritus score = 3 were 0, 2, 2 after administration of Nalbuphine, Ondansetron and Tramadol, respectively which was not statistically significantly different (p value = 0.280). All patients with pruritus score ≥ 3 were successfully treated by chlorpheniramine 10 mg. intravenously. The number of patients who have nausea or vomiting score ≥ 2 were 3, 1 and 3 after administration of Nalbuphine, Ondansetron and Tramadol, respectively, which was considered non-statistically significantly different (p value = 0.565). Two patients in Tramadol group with moderate nausea/vomiting (nausea/vomiting score ≥ 3) were successfully treated by metoclopramide 10 mg. intravenously. There was no patient who had sedation score ≥ 2 or verbal numerical pain score > 5 in all groups after administration of Nalbuphine, Ondansetron and Tramadol. No extrapyramidal effect or respiratory depression or dizziness was observed in all groups of the patients.

Discussion

Spinal anesthesia is an increasingly popular anesthetic technique for elective cesarean section, because of its rapid onset, and postoperative

analgesia provided by intrathecal morphine. However, a common side effect after intrathecal administration of local anesthesia is shivering. In postanesthetic shivering patients, left ventricular systolic work index and oxygen consumption index may increase.⁽⁹⁾ Shivering in association with regional anesthesia was reported to resemble true thermogenic shivering.⁽⁴⁾ It is generally regarded as a nuisance rather than as a factor in morbidity although it has been reported to cause significant distress.⁽⁵⁾

This study revealed a 51.09 % incidence of mild to severe postanesthetic shivering with 30.57 % of postanesthetic shivering requiring treatment (shivering score ≥ 3), confirming previous studies.^(1, 2, 4, 5, 10, 11) Since postanesthetic shivering usually occurred within a few hours after spinal anesthesia, therefore we observed the patients for 2 hours in the postanesthesia care unit to enroll all patients with postanesthetic shivering.

The mechanism of shivering under regional anesthesia is not fully understood. Possible contributing factors are a decrease in core temperature. A decrease in core temperature may be due to sympathetic blockade, which results in peripheral vasodilatation, increased cutaneous blood flow, and subsequent increased heat lost via the skin.^(3, 6) Other reasons may be the low temperature

in the operating room,⁽⁶⁾ or the direct effects of cold anesthetic solutions upon thermosensitive structures within the spinal cord. Also, local anesthetics introduced into the extradural space might modify environmental thermal response, with resultant in appropriate thermal response to false information. Treatment modalities have included covering the patient with blankets, application of radiant heat and warming the operating room suite. The use of warm local anesthetic solution or warm intravenous fluid has met with varying degrees of success.⁽⁶⁾ Addition of various opioids extradurally also reduced the incidence of shivering. Moreover, several hypotheses have also been raised to explain the occurrence of postanesthetic shivering. These included postoperative pain, perioperative heat lost, the direct effect of certain anesthetics, hypoxia, hypercapnia or respiratory alkalosis, the existence of pyrogens, early recovery of spinal reflex activity and sympathetic over activity.⁽¹¹⁾

The study was designed to standardize these possible confounding factors while reflecting the usual practice in our institution. Postanesthesia care unit temperature was held about 22-25 °C, intravenous fluid and drugs were administered at room temperature and a blanket was used for all patients to cover the whole body. The body temperature was also recorded at the beginning of postanesthesia care unit. All patients received intrathecal morphine for postanesthetic analgesia. Demographic data such as age, weight and height were similar in all groups. The temperature of postanesthetic care unit and body temperature were also not different among three groups. The amount of intravenous, preoperative, intraoperative, postoperative fluid and duration of

surgery among three groups were also not different.

The measurement tool for postanesthetic shivering, sedation, nausea/vomiting, pruritus, and pain level was according to a previous study.^(12,13) As shivering is the primary outcome, we also tested for inter-rater agreement (weighted kappa = 0.94), which was considered as a very good agreement.

In this study, we were able to demonstrate that the success rate of treatment with 0.05 mg/kg Nalbuphine, 0.1 mg/kg Ondansetron and 0.5 mg/kg Tramadol were statistically significant different (p-value < 0.001). The success rate of treatment with Tramadol was significantly greater than Ondansetron : 88.2 % vs 62.2 % (p-value < 0.001) and the success rate of treatment with Nalbuphine was also significantly greater than Ondansetron: 81.3 %vs 62.2 % (p-value < 0.001) respectively. However, the success rate of Nalbuphine and Tramadol groups was not statistically significantly different (p-value = 0.160). Therefore, this study indicated that Tramadol and Nalbuphine were more effective than Ondansetron in the treatment of post spinal anesthetic shivering in the parturient undergoing cesarean section.

The success rates of Tramadol group and Nalbuphine group were corresponding to a previous study. Chan et al.⁽⁷⁾ showed that 80 % of parturient who develop shivering after regional anesthesia were successfully treated by 0.5 mg/kg Tramadol. Wang et al.⁽¹⁴⁾ showed that 0.05 mg/kg Nalbuphine was effective for treating postanesthetic shivering after general anesthesia with 80 % success rate. The success rate for treatment of postanesthetic shivering with Ondansetron in this study was 62.2 %, which was less effective than Tramadol

and Nalbuphine groups. Powell et al. performed a randomized, placebo controlled, double-blind study to evaluate the effect of Ondansetron given before the induction of anesthesia, the prevention success rate for shivering by 4 mg Ondansetron was 67 %⁽¹⁵⁾ which was comparable to the success rate of treatment of 62.2 % in our study.

Among the successfully treated patients, 9 of 52 (14.8 %) in the Nalbuphine group, 6 of 40 (13.0 %) in the Ondansetron group and 9 of 58 (13.4 %) in the Tramadol group reported recurrence of moderate to severe shivering (shivering score ≥ 3) within 4 hours after first successful treatment, which were not statistically significantly different (p -value = 0.963). From a recent systematic review of pharmacological treatment of postanesthetic shivering, there was a direct relationship between the length of observation period and the success rate of treatment of shivering. The relative risk for further shivering compared with placebo decreased overtime, i.e., the antishivering efficacy decreased with increases in length of the observation period.⁽¹⁶⁾ Therefore, this was the first study to observe long-term outcome of 4 hours after treatment. Moreover, there was no further reported of shivering in all three groups within 24 hours.

The pruritus rating score, nausea/vomiting rating score, and verbal numeric pain score in the three groups were not statistically significantly different. No patient in any group developed sedation after injection of the study drugs. Only two patients in the Tramadol group required metoclopramide as antiemetic after treatment. There were few patients with pruritus score ≥ 3 who were successfully treated by chlorpheniramine 10 mg intravenously. There was no patient who has sedation score 2 in all groups

after administration of study drugs. There were no extrapyramidal effect or respiratory depression, dizziness, respiratory depression and hallucination observed in all groups of the patients. Moreover, some reported side effects associated with Ondansetron such as headache, abdominal pain, and cardiac arrhythmias were not observed.

Pharmacologic drugs remain the most popular mode for treatment and prevention of shivering. Meperidine is a commonly used medication for controlling shivering in patients without neuraxial opioids administration. The mechanism of pharmacologic anti-shivering effect has yet to be fully elucidated. Intravenous pethidine controls shivering better than equianalgesic dose of pure μ -opioid agonist such as fentanyl, alfentanil, sufentanil, or morphine. The anti-shivering effects of pethidine are not reversed by small dose naloxone, which blocks most the μ -opioid receptors, but they are reversed by large dose of naloxone,⁽⁸⁾ which blocks both the μ -receptors and κ -receptors. These data suggest that the κ -opioid receptor may play a more important role than the μ -opioid receptors in the treatment of postanesthetic shivering. Nalbuphine, a semisynthetic opioid related to both naloxone and oxymorphone, has the characteristics of μ -antagonist and κ -agonist activity. It has high affinity to the κ -opioid receptors in the central nervous system.^(8, 15) Theoretically, Nalbuphine may have significant effect on postanesthetic shivering. In this study, we found that Nalbuphine demonstrated a potent antishivering effect on postanesthetic shivering. Tramadol is an analgesic with agonist properties on opioid receptors. Tramadol also activates the monoaminergic 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 the κ -receptor.⁽¹²⁾ In similar to pethidine used to treat postanesthetic shivering, Tramadol has a potent antishivering effect which its κ -receptors activity. Moreover, Tramadol inhibits the neuronal reuptake of norepinephrine and 5-hydroxytryptamine and facilitates 5-hydroxytryptamine releases. Another potent antinociceptive effect of Tramadol is significant decreasing α_2 -adrenoceptor antagonists, which is in this respect; Tramadol is similar to clonidine, a partial α_2 -adrenoceptor agonist that is also useful in the treatment of postanesthetic shivering.⁽¹⁷⁾ Therefore, the interaction of κ -opioid and α_2 -adrenoceptor mechanism working in a complementary on synergistic manner to produce antishivering effect seems to be a possible explanation. Ondansetron has been shown to produce a dose-dependent reduction in shivering by given before induction of general anesthesia.⁽¹⁵⁾ The possible explanation of its action is a specific 5HT₃ receptor antagonist which giving the variety on neurotransmitter system, known to be also involved in regulating shivering. An inhibitory effect at the 5-HT₃ receptors probably results from a generalized thermoregulatory inhibition at the level of hypothalamus, where the bulk of thermoregulatory control occurs.⁽¹⁵⁾

In contrast to some other drugs used to treat postanesthetic shivering, we found that our study drugs (Nalbuphine, Ondansetron, and Tramadol) have no serious effect on the cardiovascular system and other systems. Whereas, clonidine may be associated with significant hypotension, bradycardia, and sedation.⁽¹⁷⁾ Doxapram is associated with significant hemodynamic effects.⁽¹⁸⁾ Physostigmine increases the

heart rate and blood pressure, which may be detrimental to myocardial oxygen demand in some patients with coronary artery insufficiency.⁽¹⁹⁾ Pethidine increases the risk of respiratory depression, nausea/vomiting, and sedation than other opioids at equivalent dosages.⁽¹⁹⁾

Conclusion

This study showed that 0.05 mg/kg Nalbuphine and 0.5 mg/kg Tramadol were superior to 0.1 mg/kg Ondansetron in the treatment of postanesthetic shivering after intrathecal morphine for cesarean delivery. The recurrence rate among the three groups were not statistically significantly different. The side effects were few and minor.

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