A Comparison Between Ondansetron and Chlorpheniramine for the Prevention of Intrathecal Morphine-Induced Pruritus

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Abstract : **การเปรียบเทียบการป้องกันอาการคันจากการใส่มอร์ฟีนในช่องน้ำไขสันหลังโดยใช้ยา Ondansetron และ Chlorpheniramine**

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ที่มา : **ปัจจุบันการระงับความรู้สึกเฉพาะส่วนโดยการใช้การใส่มอร์ฟีนในช่องน้ำไขสันหลัง ในการผ่าตัดมีการใช้กันอย่างแพร่หลาย มีผลในการระงับปวดหลังผ่าตัดที่ดีและระยะเวลาระงับปวดนาน โดยเฉพาะในการผ่าตัดคลอดทางหน้าท้อง อย่างไรก็ดี การใส่มอร์ฟีนดังกล่าวอาจนำมาซึ่งผลข้างเคียงหลายอย่าง อาการคันเป็นอาการที่พบได้บ่อย จากรายงานอุบัติการณ์การเกิดอาการคันภายหลังการใส่มอร์ฟีนปริมาณต่ำเข้าช่องไขสันหลังพบประมาณร้อยละ 60 *วัตถุประสงค์ :* เพื่อศึกษาการป้องกันการเกิดอาการคันจากการใส่มอร์ฟีนในช่องน้ำไขสันหลังโดยการใช้ยา ondansetron เปรียบเทียบกับยา chlorpheniramine และ ยาหลอก *วิธีการ :* ผู้ป่วยเข้าร่วมการวิจัยจำนวน 97 ราย แบ่งเป็น 3 กลุ่ม โดยการแบ่งแบบ randomized, double blinded ในกลุ่ม A ได้รับน้ำเกลือ 2 มล. กลุ่ม B ได้รับยา ondansetron 2 มล. (4 มิลลิกรัม) และ กลุ่ม C ได้รับยา chlorpheniramine 2 มล. (10 มิลลิกรัม) *ผลการวิจัย :* ไม่พบความแตกต่างระหว่างยา ondansetron และ chlorpheniramine ในการป้องกันอาการคันที่เกิดจากการใส่มอร์ฟีนในช่องน้ำไขสันหลัง**

คำสำคัญ : *คัน มอร์ฟีนในช่องน้ำไขสันหลัง ยา ondansetron*

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Background

Low-dose intrathecal (spinal) morphine, first made popular more than a decade ago, has become established as an effective analgesic regimen after Caesarean section.[1-3] Unfortunately, the use of intrathecal morphine may be associated with high incidence of side effects. The incidence of pruritus is frequent after intrathecal morphine, especially after Caesarean section. The reported incidence of intrathecal opioid-induced pruritus was 60%.[4] This pruritus is often difficult to be treated and responded poorly to conventional treatments except for naloxone and propofol, the two most effective means available to control this side effect.[5-6] In naloxone treatment, a tendency toward poorer quality of analgesia and pulmonary edema has been described. In Ramathibodi hospital Chlorpheniramine (CPM) is a common drug used to treat intrathecal morphine-induced pruritus.

Recently ondansetron has been well recognized in the treatment of pruritus after neuraxial opioid administration in the orthopedic and obstetric patients.[7-8] Borgeat A, et al. studied the efficacy of ondansetron 8 mg on morphine-induced pruritus compared with placebo in patients scheduled for orthopedic surgery. The treatment success rate was significantly greater in the ondansetron group (70%) when compared with the placebo (30%) (P value < 0.05). Ondansetron can also treat and prevent episodes of nausea and vomiting.[9] Because ondansetron provides significant antipruritus effect, it may also be effective in the prevention of pruritus following intrathecal morphine. The aim of the study was to evaluate the prophylactic effect of intravenous ondansetron compared with intravenous Chlorpheniramine (CPM) following intrathecal morphine for postoperative analgesia in caesarean section patients.

Method

We studied 97 parturients, ASA physical status I-II, aged 20-45 years, body weight ≤ 90 kg, scheduled for Ceasarean section under spinal anesthesia. All of parturients were enrolled in this randomized double blinded, placebo-controlled study.

No premedication was given. Surgical analgesia to T4 dermatome level was provided by a dose of 0.5% hyperbaric bupivacaine 2-2.2 ml added with morphine 0.2 mg. We prepared morphine 0.2 mg by mixing morphine 10 mg (1 ml) with normal saline solution to make up the total volume of 10 ml. Insulin syringe was used for drawing out this solution only 0.2 ml mixed with 0.5% heavy marcaine in plastic syringe 2.5 ml.

Exclusion criteria were known allergy to ondansetron, history of any disease associated with pruritus, history of receiving opioids and antihistamine medication within 48 hours before surgery, history of steroid use, complaint of pruritus before surgery, patients with contraindication to regional anesthesia, increased in liver enzyme (alamaminotransferase or aspartate aminotransferase more than two times the normal range) and increased serum creatinine only increasing of laboratory value was valuable.

Patients were allocated randomly to receive one of three preventive regimens ; A 2 ml normal saline, B 2 ml (4 mg) ondansetron (Onsia®) and C 2 ml (10 mg) CPM. Patients and anesthesiologists involved in intraoperative care and investigators who collected postoperative data were unaware of patient group allocation. The study drugs were administered by intravenous injection immediately after delivery. Patients who received blood components for intraoperative massive blood loss were excluded from this study. Patients were observed postoperatively for 6 hours. Post operative data was collected at 1st hour and 6th hour after injection of drugs. Pruritus was assessed by using 5 points pruritus scale 1 = no pruritus, 2 = mild pruritus patients only feel pruritus but do not scratching skin, 3 = moderate pruritus with itching and scratching, 4 = severe pruritus with itching and scratching and 5 = intractable pruritus with scratching and itching. Pruritus was treated with naloxone 0.1 mg when pruritus scale was 3-5. This

rescue treatment was ordered by another anesthesiologist who was blinded of allocation group. The level of sedation was measured by using the Sedation Rating scale as 1 = fully awake, 2 = somnolence response to verbal stimuli, 3 = response to pain but not to verbal command and 4 = no response. The anesthetic level and Apgar scores were also recorded.

Sample size was predetermined by using a power analysis based on assumption that the total frequency of pruritus in the saline group would be 70% and the incidence of prevention pruritus in ondansetron group would be 70% based on the previous research[8], and $\alpha = 0.05$ and $\beta = 0.1$. The analysis $\eta = (Z\alpha + Z\beta)^2\ 2p(1-p)/D^2$ showed that 26 patients per group would be sufficient. Parametric data were analyzed by using unpaired t test ; the frequency of pruritus was analyzed by using χ^2 test. The pruritus scale was analyzed by using crosstab chi-square's test. A P value of point pruritus scale (0-2 mild pruritus, 3-5 moderate to severe pruritus) < 0.05 was considered statistically significant.

Results

There was no differences between groups in terms of age, weight, height, ASA physical status and type of emergency/elective surgery. The anesthetic level of all groups were the same, median T4 level (range from T1-T6). In addition, there were no differences between groups according to Apgar score and milligrams of ephedrine used. (Table 1)

The incidence of postoperative pruritus (pruritus score > 1) at 6th hour in ondansetron group was 62.9% (n = 22) and CPM was 62.5% (n = 20) which were not significantly different from that in placebo group (NSS group = 70%). (Table 2) Patients who had pruritus score > 2 were received naloxone as a rescue drug and the incidence of rescue treatments were not different in all groups. (Table 3) In NSS group, we found that 4 patients were received CPM before we evaluated pruritus score at 6th hour but we did not excluded these patients out of our study. There was only one patient in NSS group who had pruritus score > 2 at 6th hour and

Table 1 Patient demographics and operative characteristics

	NSS (n = 30)	Ondansetron (n = 35)	CPM (n = 32)	P value
Age (yr)	32 ± 6	32.9 ± 4	31.7 ± 4.8	0.61
Weight (kg)	67 ± 8.6	70.2 ± 9	72.39 ± 11.9	0.13
Height (cm)	155 ± 5.3	157 ± 5	156.9 ± 5	0.42
ASA status 1	19 (63.3%)	28 (80%)	23 (71.8%)	0.47
2	11 (36.7%)	7 (20%)	9 (28.2%)	
Elective	23 (76.7%)	34 (97.1%)	25 (78.1%)	0.91
Emergency	7 (23.3%)	1 (2.9%)	7 (21.9%)	
Anesthetic level : Median	T 4	T4	T4	0.56
Range	T2 - T6	T1 - T6	T3 - T6	
Apgar score at 5 minute				0.682
Score ≤ 9	1 (3.3%)	3 (8.6%)	2 (6.3%)	
Score 10	29 (96.7%)	32 (91.4%)	30 (93.8%)	
Ephedrine use (mg)	12.4 ± 11.9	10.17 ± 10.67	12.2 ± 11.61	0.668

Table 2 Postoperative pruritus score

	NSS (n = 30)	Ondansetron (n = 35)	CPM (n = 32)	P value
Pruritus score incidence at 1st hr.				
Score 2-5	7 (23.3%)	7 (20%)	4 (12.5%)	0.55
Pruritus score incidence at 6th hr.				
Score 2-5	21 (70%)	22 (62.9%)	20 (62.5%)	0.78

Table 3 Incidence of patients with postoperative pruritus score > 2 who received naloxone as a rescue drug.

	NSS (n = 30)	Ondansetron (n = 35)	CPM (n = 32)	P value
Pruritus score at 1st hr.				
Score 3-5 (naloxone received)	0	1 (2.9%)	1 (3.1%)	0.63
Pruritus score at 6th hr.				
Score 3-5 (naloxone received)	5 (16.7%)	4 (11.4%)	2 (6.3%)	0.43

Table 4 Postoperative sedation score

	NSS (n = 30)	Ondansetron (n = 35)	CPM (n = 32)	P value
Sedation score at 1st hr.				
Score 1-2	30 (100%)	35 (100%)	32 (100%)	*1
Score 3-4	0	0	0	
Sedation score at 6th hr.				
Score 1-2	30 (100%)	34 (97.1%)	32 (100%)	0.41
Score 3-4	0	1 (2.9%)	0	

(1* = no statistic are computed because sedation score at 1st hour is constant)

refused to receive the rescue drug. Patients' satisfaction of all groups was good except only one patient in ondansetron group who complained of too much nausea/vomiting. There were no significant differences sedation score at 1st or 6th hour in all groups. (Table 4)

There was neither complication from spinal

block nor detrimental effects of ondansetron on post delivery neonatal outcome.

Discussion

The incidence of intrathecal morphine induced pruritus in untreated patients in our study was high (70%) and similar to that reported in the literature (60%).[4] We demonstrated that 4 mg of ondansetron or 10 mg of CPM could not effectively prevent pruritus occurred after intrathecal morphine. The pruritus is refractory to conventional treatment, such as topical drug application and CPM. Several reports have shown promising result of ondansetron, a serotonin type 3 receptor antagonist.[7-9] Ondansetron is a lipophilic drug and may be excreted in breast milk, although there are no reports defining the concentration of this drug in breastfeeding mothers. So we chose only small dose of ondansetron (4 mg) as a research drug in our institution. We also included CPM in our research because it is a standard antipruritic treatment. Yeh HM, et al.[7] reported in their study that the use of 0.1 mg/kg intravenous ondansetron effectively for prophylaxis morphine 0.15 mg induced pruritus compared to CPM. In our study, we used only 4 mg ondansetron for prophylaxis morphine 0.2 mg induced pruritus which ondansetron dose might be inadequate for the prevention of postoperative intrathecal morphine induced pruritus. Further research may be required to find out whether ondansetron 8 mg will give a better result than ondansetron 4 mg and decrease dose of intrathecal morphine will effect the outcome of postoperative intrathecal morphine induced pruritus.

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A Comparison Between Ondansetron and Chlorpheniramine for the Prevention of Intrathecal Morphine-Induced Pruritus

Abstract

Low dose intrathecal morphine has been established as an effective analgesic regimen after Caesarean section. Unfortunately the use of intrathecal morphine may be associated with pruritus (incidence~60%). We evaluated the prophylactic effect of ondansetron on prevention of postoperative pruritus associated with 0.2 mg intrathecal morphine. Chlorpheniramine (CPM) and normal saline (NSS) were used as the controls. Ninety seven parturients (n = 30-35 in each three group) were enrolled in this randomized, double blinded and placebo-controlled study. After delivery, group A received NSS 2 ml., group B received ondansetron 2 ml (4 mg) and group C received CPM 2 ml (10 mg). Both ondansetron and CPM did not significantly reduce the incidence of pruritus associated with intrathecal morphine. We concluded that ondansetron 4 mg has no benefit for preventing pruritus in low dose intrathecal morphine.

Keywords : *pruritus, spinal morphine, ondansetron*