

Epidural Nalbuphine for Post Cesarean Epidural Morphine Induced Pruritus[†]

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Objective: The aim of the present study was to test the efficacy of epidural nalbuphine 5 mg for prevention of morphine-induced pruritus.

Material and Method: Parturients, ASA I-II scheduled for elective cesarean section under epidural anesthesia were randomized into 3 groups: the placebo group, N-5 group, and N-10 group received 4 ml epidural solution containing morphine 4 mg plus either saline, nalbuphine 5 mg, and nalbuphine 10 mg respectively. Pain score at rest and on movement, incidence and severity of pruritus, sedation score, and pethidine consumption were recorded for 24 hours.

Results: The 182 parturients were randomized into 60 in the placebo group, 61 in the N-5 group, and 61 in the N-10 group. The severity of pruritus was significantly lower at 3, 6, 9 and 12 h postpartum in the N-5 group and the N-10 group had a lower degree of pruritus at 3 and 6 h postpartum compared to placebo. The VAS pain scores at rest and on movement were significantly higher in the N-10 group at 3, 6, 9, 12 and 18 h postpartum compared to the placebo and significantly higher at 3 h, 6 h postpartum compared to the N-5 group ($p < 0.05$). Patient's satisfactions were high in all groups without any significant difference between groups.

Conclusion: Epidural nalbuphine 5 mg reduced severity of morphine induced pruritus for 12 h with statistically significant different advantages over epidural nalbuphine 10 mg without anti-analgesic effect. However, the difference is too small to convey into clinical significant advantage.

Keywords: Adverse effects, Analgesia, Epidural, Cesarean section, Morphine, Nalbuphine, Pruritus

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Epidural morphine provides good analgesia after cesarean section for approximately 18-24 h⁽¹⁾. However, the common side effects after epidural morphine including pruritus and vomiting happens frequently causing reduction in patient satisfaction⁽²⁾. Epidural nalbuphine provides moderate postoperative pain control with duration of action only 6.4-9.2 h, so it is not suitable to be used as a sole agent for post-operative pain control^(3,4). Mixed agonist-antagonist opioid effects of nalbuphine have been reported for prevention of pruritus after epidural morphine⁽⁵⁻⁷⁾.

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Duration of action of intravenous nalbuphine is shorter than the duration of epidural morphine induced pruritus and continuous intravenous infusion is needed to treat this side effect⁽⁶⁾. Epidural nalbuphine 10 mg reduce incidence of pruritus for 6 h⁽⁷⁾ with increasing incidence of agitation⁽⁸⁾. The purpose of the present study was to test the clinical efficacy of epidural nalbuphine 5 mg and 10 mg for prevention of morphine-induced pruritus. This trial was registered at www.clinicaltrials.gov (NCT00707824).

Material and Method

The present trial was registered at www.clinicaltrials.gov. After obtaining the ethic

committee of Siriraj Hospital's approval, 182 parturients, ASA I-II scheduled for elective cesarean section under epidural anesthesia were enrolled in the study. Patients were excluded from the present study if they have contra-indication for regional block, history of drugs or alcohol abuse, receiving opioids within 12 hours period, or body mass index ≥ 35 kg/m². After obtaining informed consent, all received epidural anesthesia using 2% lidocaine with epinephrine 1:200,000 via epidural catheter at L2-3 or L3-4 in a volume sufficient to achieve a T4 sensory level bilaterally.

After the umbilical cord was clamped, patients were assigned randomly to three groups. The placebo group, N-5 group, and N-10 group received 4 ml epidural solution containing morphine 4 mg plus either saline, nalbuphine 5 mg, and nalbuphine 10 mg respectively.

At the post anesthetic care unit, intravenous pethidine PCA were administered via an Abbott pump for pethidine 15 mg PCA dose with a 6 min lock out which continued to 24 hr postoperative period. Patients requesting treatment for itching received intravenous chlorpheniramine 10 mg every 4 hr as needed. Patients requesting treatment for nausea or vomiting were given intravenous metoclopramide 10 mg every 4 hr as needed. The observers blinded to the treatment group evaluated the level of sedation using 0-3 scale (0 = awakens to a voice alone, 1 = awakens to a voice and gentle touch, 2 = requires a vigorous touch to awaken, 3 = fails to arouse when touched vigorously). Respiratory rates were monitored and recorded every 1 h for 24 hr. Patients with somnolence (sedation score ≥ 2) or respiratory depression (RR ≤ 8 breath/min) received intravenous naloxone 0.1 mg every 5 min until sedation score < 2 or respiratory rate > 10 breath/min followed by continuous intravenous naloxone infusion at 1 μ g/kg/hr for 12 hr. During the 24-hour postoperative period, patients were assessed every 3

hours for incidence and severity of pruritus using 0-10 verbal analog scales. Intensity of pain at rest and on movement evaluated by using 0-10 verbal analog scale was also recorded at the same period. Severity of agitation was rated on a four-point scale: 1 = calm, 2 = not calm but could be easily calmed, 3 = not easily calmed, moderately agitated or restless, and 4 = combative, excited, or disoriented were evaluated by the observer at the same interval. Incidence of respiratory depression and sedation score were also evaluated at the same time. Patient's satisfaction for the quality of pain management and total dose of intravenous pethidine PCA were assessed at 24 hr.

The sample size was calculated by using the program sample size Fisher's exact for comparing event rates between two independent cohorts using control proportion 0.56, treated proportion 0.28, confidence level 0.95 and and power 0.8, the sample size was 48 patients in each group. Statistical analysis of the result was performed using one-way ANOVA test and Bon ferroni for continuous data. The Chi-Square test was used to compare categorical data. P-value < 0.05 was considered significant

Results

One hundred and eighty-two parturients were enrolled in the present study n = 60 in placebo group, n = 61 in N-5 group, and n = 61 in N-10 group. The groups were similar with respect to age, weight, height and ASA physical status (Table 1). The operative time in N-10 group was significantly longer than the placebo group (p = 0.004). The incidence of pruritus was 71.1% in placebo, 73.8% in N-5, and 82% in N-10 group which were not significantly different between the groups (Fig. 1). The severity of pruritus was significantly lower at 3 hr 6 h, 9 h and 12 h postpartum in the N-5 group compared to the placebo group. In addition, at 3 h and 6 h postpartum, the N-10 group had

Table 1. Patient characteristics, operative time, patient's satisfaction and chlorpheniramine treatment

Variables	Placebo (n = 60)	N-5 (n = 60)	N-10 (n = 60)	p-value
Age (yr)	29.72 \pm 4.68	31.07 \pm 5.17	31.26 \pm 5.00	0.179
Weight (kg)	69.27 \pm 7.12	68.51 \pm 8.52	68.21 \pm 8.71	0.766
Height (cm)	156.00 \pm 4.95	154.91 \pm 5.6	155.67 \pm 4.86	0.496
ASA I	27 (45%)	27 (44.3%)	26 (42.6%)	0.964
ASA II	33 (55%)	34 (55.7%)	35 (57.4%)	0.964
Operative time	51.90 \pm 14.82	55.25 \pm 11.01	59.87 \pm 13.33	0.004
Patient's satisfaction VAS score (0-10)	9.08 \pm 1.45	9.35 \pm 1.15	9.20 \pm 1.41	0.607
Chlorpheniramine treatment	15%	8.2%	3.3%	0.073

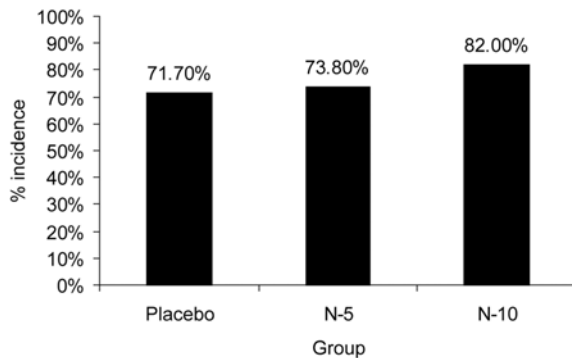


Fig. 1 Incidence of pruritus. Data represent in percentage in each group
N-5 = nalbuphine 5 mg, N-10 = nalbuphine 10 mg

lower degree of pruritus compared to placebo (Fig. 2). The VAS pain scores at rest and on movement were significantly higher in the N-10 group at 3 h, 6h, 9 h, 12 h and 18 h postpartum compared to the placebo and significantly higher at 3 h, 6 h postpartum compared to the N-5 group (Fig. 3, 4). The VAS pain score in the N-5 group was not significantly different from the placebo group. There were no differences in the PCA pethidine consumption between the groups (Fig. 5). No patient in the present study had sedation score ≥ 2 or respiratory rate ≤ 8 breath/min. There was no report of agitation in any groups. The requirement for chlorpheniramine was not different between the groups (Table 1). Patient's satisfactions was high in all groups without any significant difference between groups (Table 1).

Discussion

Pruritus was an unpleasant and common side effect after epidural or intrathecal morphine. Incidences of pruritus reported in the literature were 62-94%⁽⁹⁻¹¹⁾. In the present study the incidence of pruritus in control group with epidural morphine was 71.7%. The mechanism of pruritus after epidural morphine is not fully understood. Antihistamines are ineffective for therapy of pruritus so mechanism of action should not be histamine release effect of morphine⁽¹²⁾. Mu receptor antagonist as naloxone or nalbuphine has been reported as an effective treatment drug for pruritus leading to the hypothesis that mu opioid receptor stimulation was the leading cause for pruritus^(6,7,11). Nalbuphine, ondansetron and subhypnotic doses of propofol have been used effectively for treating pruritus^(11,13). Nalbuphine is a mixed agonist-antagonist opioid which has antagonist effect at mu receptor.

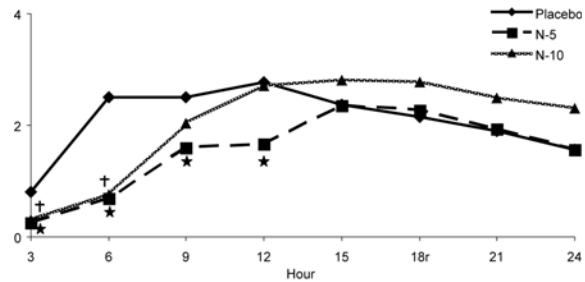


Fig. 2 Visual analog scale (VAS) of Severity of pruritus. VAS was lower in N-5 group at 3, 6, 9, and 12 hr and in N-10 group at 3 and 6 hr compare to placebo
★ Significantly different between N-5 and placebo
† Significantly different between N-10 and placebo

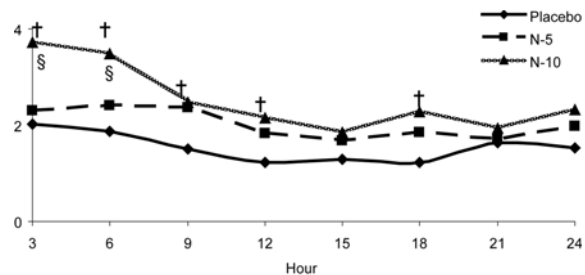


Fig. 3 Visual analog scale (VAS) of pain at rest. VAS was higher in N-10 group at 3, 6, 9, 12 and 18 hr compare to placebo and higher at 3 and 6 hr compare to N-5 group
† Significantly different between N-10 and placebo
§ Significantly different between N-10 and N-5

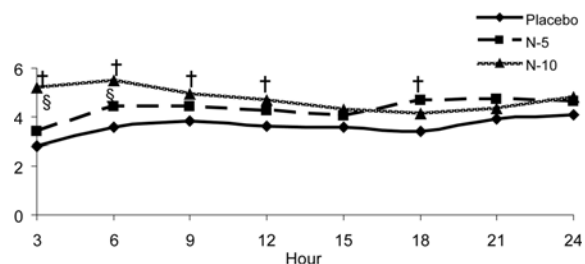


Fig. 4 Visual analog scale(VAS) of pain on movement. VAS was higher in N-10 group at 3, 6, 9, 12 and 18 hr compare to placebo and higher at 3 and 6 hr compare to N-5 group
† Significantly different between N-10 and placebo
§ Significantly different between N-10 and N-5

Wittles et al found that epidural nalbuphine 10 mg reduced the incidence of pruritus from 48% to 20% for 6 h⁽⁷⁾. In the present study, the incidence of pruritus

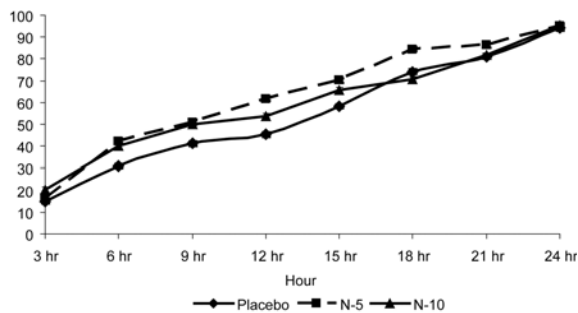


Fig. 5 Pethidine consumption

did not reduce in parturients receiving epidural nalbuphine 5 mg or 10 mg but severity of pruritus decreased in epidural nalbuphine groups. The VAS of severity of pruritus in control group in the present study was 0.8-2.77, with the peak at 12 hr. Epidural nalbuphine 5 mg can reduce severity of pruritus for 12 h compared to 6 h for nalbuphine 10 mg. The longer duration for reducing the severity of pruritus in N-5 group leads to the recommendation that it could be used for this purpose. The VAS pain score in the present study was low because the authors provided pethidine PCA for breakthrough pain in every patient. Pain scores at rest and in movement were higher in N-10 group for 18 h compared to placebo and higher than N-5 group for 6 h. There was no difference in pain score between the N-5 and placebo group. Epidural nalbuphine 10 mg reverse analgesic effect of epidural morphine but nalbuphine 5 mg did not show the anti-analgesic effect. This can be explained that epidural nalbuphine reverses the analgesic effect of morphine in dose related manner. In the present study, most of the parturients were satisfied with the method of pain relief and the treatment they received without significant difference between the groups. The severity of pruritus was quite low (VAS 0.25-2.77) in every group with statistically significant difference, whereas the clinical appearance may not be significantly different. This can explain the high percentage of patient's satisfaction and the similarity in asking for the treatment of pruritus which were not different between the groups. No patient in the present study had respiratory depression or agitation that may limit the use of combination between epidural morphine and nalbuphine.

In summary, epidural nalbuphine 5 mg reduced severity of morphine induced pruritus for 12 h with statistically significant difference advantages over epidural nalbuphine 10 mg without anti-analgesic effect. However, the overall severity of pruritus was

quite low in the present study which might not show in clinical appearance.

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การใช้ nalbuphine ทางช่องเหนือไขสันหลังสำหรับป้องกันอาการคันหลังได้รับ morphine ในผู้ป่วย ที่มารับการผ่าตัดคลอดบุตรทางหน้าท้อง

อรวรรณ พงศ์วิวรรณ, อุบลรัตน์ สันตวัตร, เลิศลักษณ์ วีรสาร, สุดสยาม มนวงษ์, อรณี สวัสดิ์-ชูโต

วัตถุประสงค์: การรักษาอาการปวดหลังผ่าตัดโดยการให้ morphine ฉีดเข้าทางช่องเหนือไขสันหลังสำหรับลดอาการปวดแผลหลังผ่าตัดคลอดบุตรทางหน้าท้อง เป็นวิธีการระงับปวดที่ดีและเป็นที่ยอมรับอย่างกว้างขวางเนื่องจากให้ผลการระงับปวดได้ดี ออกฤทธิ์ได้นานถึง 18-24 ชั่วโมง แต่ภาวะแทรกซ้อนของวิธีระงับปวดแบบนี้ ได้แก่ อาการคัน คลื่นไส้ อาเจียน อาจมีมากจนลดความพึงพอใจของผู้ป่วยได้ มีรายงานการใช้ nalbuphine ซึ่งเป็นยาที่ออกฤทธิ์ต้านฤทธิ์ของ morphine ในบริเวณ receptor ที่ทำให้เกิดอาการคันโดยการฉีดเข้าหลอดเลือดดำพบว่าให้ผลดีในการรักษาและป้องกันอาการคันที่เกิดขึ้น แต่ผลในการป้องกันและรักษาอยู่สั้นกว่าผลของ morphine ที่ทำให้เกิดอาการคัน การใช้ nalbuphine 10 มก. ฉีดเข้าทางช่องเหนือไขสันหลังสามารถป้องกันอาการคันได้นานถึง 6 ชั่วโมง แต่ผู้ป่วยบางส่วนอาจมีอาการระสับกระส่ายจากการมีฤทธิ์แก้อฤทธิ์ระงับปวดของ morphine การศึกษานี้ต้องการดูผลของการใช้ nalbuphine 5 มก. ฉีดเข้าทางช่องเหนือไขสันหลังว่าสามารถป้องกันอาการคันจากการได้รับ morphine ฉีดเข้าทางช่องเหนือไขสันหลังหรือไม่

วัสดุและวิธีการ: ศึกษาในผู้ป่วยที่มารับการผ่าตัดคลอดบุตรทางหน้าท้องชนิดไม่เร่งด่วน ที่ได้รับ morphine ฉีดเข้าทางช่องเหนือไขสันหลังสำหรับลดอาการปวดแผลหลังผ่าตัด โดยการสุ่มแบ่งผู้ป่วยออกเป็น 3 กลุ่ม ได้แก่ กลุ่ม placebo ได้รับ morphine 4 มก. ในน้ำเกลือ 4 มล. กลุ่ม N-5 ได้รับ morphine 4 มก. ร่วมกับ nalbuphine 5 มก. ในน้ำเกลือ 4 มล. และกลุ่ม N-10 ได้รับ morphine 4 มก. ร่วมกับ nalbuphine 10 มก. ในน้ำเกลือ 4 มล. หลังผ่าตัด ผู้ป่วยจะได้รับการบันทึก และติดตามดูแลอาการปวด อาการคัน อาการคลื่นไส้อาเจียน และได้รับการดูแลรักษาภาวะแทรกซ้อนที่อาจเกิดขึ้นเป็นเวลา 24 ชั่วโมง

ผลการศึกษา: ผู้ป่วย 182 คน ได้ถูกแบ่งออกเป็น กลุ่ม placebo 60 คน กลุ่ม N-5 61 คน และกลุ่ม N-10 61 คน พบว่ามีอุบัติการณ์ของอาการคันไม่แตกต่างกัน แต่ความรุนแรงของอาการคันในชั่วโมงที่ 3, 6, 9 และ 12 ลดลงอย่างมีนัยสำคัญในกลุ่มที่ได้รับ nalbuphine 5 มก. เมื่อเทียบกับกลุ่ม placebo และความรุนแรงของอาการคันในชั่วโมงที่ 3 และ 6 ลดลงอย่างมีนัยสำคัญในกลุ่มที่ได้รับ nalbuphine 10 มก. เมื่อเทียบกับกลุ่ม placebo ผู้ป่วยในกลุ่ม N-10 มีอาการปวดในชั่วโมงที่ 3, 6, 9, 12 และ 18 มากกว่ากลุ่ม placebo และมากกว่ากลุ่ม N-5 ในชั่วโมงที่ 3 และ 6 ผู้ป่วยในกลุ่ม N-5 มีอาการปวดไม่แตกต่างจากกลุ่ม placebo

สรุป: การใช้ nalbuphine 5 มก. และ 10 มก. สามารถลดความรุนแรงของอาการคันหลังได้รับ morphine ฉีดเข้าทางช่องเหนือไขสันหลังได้ แต่ nalbuphine 5 มก. ไม่มีฤทธิ์ต้านฤทธิ์ของ morphine ในการระงับปวด อย่างไรก็ตามคะแนนความคันโดยรวมในการศึกษานี้ถือว่าค่อนข้างต่ำจึงอาจไม่มีความแตกต่างในทางปฏิบัติ
