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

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 postoperative pain control(3,4). Mixed agonist-antagonist opioid effects of nalbuphine have been reported for prevention of pruritus after epidural morphine(5-7).

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(8). Epidural nalbuphine 10 mg reduce incidence of pruritus for 6 h(9) with increasing incidence of agitation(9). 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 (NCT 00707824).

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 $\geq 35$ kg/m$^2$. 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 $\geq 2$) or respiratory depression (RR $\leq 8$ 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 $\mu$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 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 Bonferroni 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 and 6 hr 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>
<thead>
<tr>
<th>Variables</th>
<th>Placebo (n = 60)</th>
<th>N-5 (n = 60)</th>
<th>N-10 (n = 60)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>29.72±4.68</td>
<td>31.07±5.17</td>
<td>31.26±5.00</td>
<td>0.179</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.27±7.12</td>
<td>68.51±8.52</td>
<td>68.21±8.71</td>
<td>0.766</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.00±4.95</td>
<td>154.91±5.6</td>
<td>155.67±4.86</td>
<td>0.496</td>
</tr>
<tr>
<td>ASA I</td>
<td>27 (45%)</td>
<td>27 (44.3%)</td>
<td>26 (42.6%)</td>
<td>0.964</td>
</tr>
<tr>
<td>ASA II</td>
<td>33 (55%)</td>
<td>34 (55.7%)</td>
<td>35 (57.4%)</td>
<td>0.964</td>
</tr>
<tr>
<td>Operative time</td>
<td>51.90±14.82</td>
<td>55.25±11.01</td>
<td>59.87±13.33</td>
<td>0.004</td>
</tr>
<tr>
<td>Patient’s satisfaction VAS score (0-10)</td>
<td>9.08±1.45</td>
<td>9.35±1.15</td>
<td>9.20±1.41</td>
<td>0.607</td>
</tr>
<tr>
<td>Chlorpheniramine treatment</td>
<td>15%</td>
<td>8.2%</td>
<td>3.3%</td>
<td>0.073</td>
</tr>
</tbody>
</table>
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.

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

References
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การใช้ nalbuphine ทางช่องเหนือไขสันหลังสำหรับป้องกันอาการคันหลังได้รับ morphine ในผู้ป่วยที่มีการรักษาติดต่อด้วยบูตูรัททางหน้าท้อง

การใช้นาลบูฟีน (nalbuphine) ทางช่องเหนือไขสันหลังสำหรับป้องกันอาการคันหลังในผู้ป่วยที่ได้รับมอร์ฟีน (morphine) ในการรักษาปวดหลังจากการผ่าตัดคลอดบุตรทางหน้าท้อง ได้นำไปสู่การศึกษาในผู้ป่วยที่มารับการผ่าตัดคลอดบุตรทางหน้าท้องที่รับยา bazepine อย่างละ 18 คน กลุ่ม bazepine ได้รับยา bazepine 10 mg. ผู้ป่วยที่ไม่ได้รับ bazepine อย่างละ 18 คน กลุ่ม bazepine ได้รับยา bazepine 10 mg. ผู้ป่วยที่ไม่ได้รับ bazepine อย่างละ 18 คน กลุ่ม bazepine ได้รับยา bazepine 10 mg.

ผลการศึกษา: ผู้ป่วยที่ได้รับยา bazepine 10 mg. ได้รับยา bazepine 10 mg. ผู้ป่วยที่ไม่ได้รับ bazepine อย่างละ 18 คน กลุ่ม bazepine ได้รับยา bazepine 10 mg. ผู้ป่วยที่ไม่ได้รับ bazepine อย่างละ 18 คน กลุ่ม bazepine ได้รับยา bazepine 10 mg. ผู้ป่วยที่ไม่ได้รับ bazepine อย่างละ 18 คน กลุ่ม bazepine ได้รับยา bazepine 10 mg.

สรุป: การใช้ nalbuphine 5 mg. และ 10 mg. สามารถป้องกันอาการคันหลังได้รับ morphine ซึ่งเข้าทางของเหนือไขสันหลังได้ แต่ nalbuphine 5 mg. ไม่มีฤทธิ์ต้านฤทธิ์ของ morphine ในการรักษาปวดหลัง อย่างไรก็ตาม คะแนนความคันโดยรวมในการศึกษาไม่มีข้อต้องสงสัยอย่างมากไม่มีความแตกต่างทางปฏิบัติ