Efficacy of Intramuscular Nalbuphine versus Diphenhydramine for the Prevention of Epidural Morphine-induced Pruritus after Cesarean Delivery

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Background: Pruritus is the most common side effect of epidural morphine analgesia. Diphenhydramine is a widely used agent for the treatment of urticarial pruritus. Nalbuphine is a mixed opioid agonist–antagonist and has been reported to be effective in treating opioid-induced pruritus. We compared the effectiveness of intramuscular diphenhydramine and nalbuphine for the prevention of epidural morphine-induced pruritus after cesarean section.

Methods: One hundred and fifty, American Society of Anesthesiologists physical status I or II, women undergoing cesarean section with epidural anesthesia were randomly assigned to three groups. Group S, group D, and group N received intramuscular normal saline (1 ml; n = 50), diphenhydramine (30 mg/1 ml; n = 50), and nalbuphine (10 mg/1 ml; n = 50), respectively, after delivery of the baby. The occurrence and the severity of pruritus were assessed at 1, 4, 12, and 24 hours after surgery.

Results: The overall incidence of pruritus during the 24 hr follow-up period was 72%, 68%, and 44% for group S, group D, and group N, respectively. Pruritus occurred less frequently in group N than group D ($p = 0.027$). At 4 and 12 hrs postoperatively, the pruritus severity was significantly different ($p = 0.003$ and $p = 0.002$) and was significantly less in group N than group D in the intergroup comparison ($p = 0.013$ and $p = 0.012$).

Conclusion: Nalbuphine proved better than diphenhydramine for prevention of epidural morphine-induced pruritus in patients who underwent cesarean section. Prophylactic intramuscular nalbuphine (10 mg) is effective in decreasing the incidence and severity of pruritus and does not affect analgesia.

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Key words: epidural morphine, nalbuphine, diphenhydramine, pruritus

Epidural morphine provides effective postoperative analgesia after cesarean delivery. However, it is associated with numerous side effects, including pruritus, nausea, vomiting, urinary retention, and res-

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piratory depression.[1-3] Pruritus is the most common side effect with a reported incidence of 58–85%.[2,4,5] It is an unpleasant experience and its prevention remains a challenge for anesthesiologists. Many different drugs have been used to prevent or to treat this side effect, including antihistamines, 5-HT3 (serotonin) receptor antagonists, opioid antagonists, opioid agonist-antagonists, propofol, and nonsteroidal anti-inflammatory drugs.[5-9]

Diphenhydramine is widely used for the treatment of urticarial pruritus and decreased histamine release. Previous studies have pointed out that morphine is known to cause histamine release and increase plasma histamine.[10] However, when morphine is used neuraxially, pruritus does not seem to depend on histamine release. Antihistamines such as promethazine have been reported effective for pruritus in parturients.[11] Even so, antihistamines for prevention of epidural morphine- induced pruritus are still contradictory. Nalbuphine is an opioid agonist–antagonist and its analgesic and possible antipruritic effects are mediated via actions on the μ- and κ-receptors.[12] Many studies have noted the efficacy of intravenous nalbuphine in treating opioid-induced pruritus without reversal of analgesia or other significant side effects.[13]

Although diphenhydramine and nalbuphine have both been used for the treatment of epidural morphine-induced pruritus, no study has directly compared the use of these two drugs via the intramuscular route in preventing pruritus induced by epidural morphine after ceserean delivery. Therefore, we conducted a randomized, prospective, double-blind study to compare the prophylactic effectiveness of intramuscular diphenhydramine and nalbuphine on epidural morphine-induced pruritus in patients scheduled to deliver by cesarean section.

METHODS

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital and written informed consent was obtained from all patients. One hundred and fifty patients (American Society of Anesthesiologists physical status: I-II; ages: 20~40) scheduled to undergo cesarean section were enrolled in this randomized, double-blind study. Patients with contraindications for regional anesthesia, any cutaneous pathology with pruritus, known allergies to any medications used in this study, inability to answer questions clearly or recent use of opioids or sedatives were excluded.

A computer-generated table of random numbers was used to assign patients to one of three groups, group S, group D, or group N. When patients arrived in the operating room, intravenous lactated Ringer's solution (500~1000 mL) was administered. Standard monitoring included electrocardiography, pulse oximetry, and noninvasive arterial blood pressure monitoring. All patients received epidural anesthesia at the L2–3 or L3–4 interspace with an 18-gauge Tuohy needle through the midline using 2% lidocaine (400 mg) and 1~2 mL of fentanyl with epinephrine (1:200000). No other systemic or neuraxial opiates were used before or during surgery. When a satisfactory sensory block was verified by loss of sensation to cold or pinprick, a standard cesarean delivery was performed. After completion, all patients received morphine 1.5 mg diluted to 5 mL in normal saline via epidural catheter for postoperative analgesia and the same dosage was injected every 12 hours postoperatively. Individuals were entered into the study in a double-blind manner and randomly received either normal saline (group S; 1 mL; n = 50), diphenhydramine (group D; 30 mg/1 mL; n = 50), or nalbuphine (group N; 10 mg/1 mL; n = 50) through the vastus lateralis muscle by an anesthesiologist.

At 1, 4, 12, and 24 hours after surgery, another anesthesiologist assessed pruritus, wound pain and the sedation level. The degree of pruritus was classified as: 1 = no pruritus; 2 = mild pruritus (restricted to one area, such as the face or arms, usually reported only after prompting); 3 = moderate pruritus (affecting a larger area, such as the face and arms or face and anterior thorax); 4 = severe pruritus (extensive, often disturbing the patient).[14] Postoperative wound pain was assessed at the same intervals using a verbal rating scale (VRS: 0~10, 0 = none, 10 = worst imaginable). The sedation level was evaluated using the Ramsay Sedation Scale.[15]

The Statistical Package for the Social Sciences (SPSS 15.0 for Windows; SPSS Inc., Chicago, IL, U.S.A.) 15.0 was used for statistical analysis. Based on previous pilot studies, the sample size was determined to be 49 patients per group to detect a decrease in the incidence of pruritus from 70% to 40% with a type II error of 0.2 and a type I error of

0.05. Continuous data is reported as mean ± standard deviation and was analyzed using one-way ANOVA or repeated- measures ANOVA as appropriate. Categorical data is reported as numbers and percentages and was analyzed using the chi-square test with the Yates correction, if appropriate. Ordinal data is reported as numbers and percentages and was analyzed using the Kruskal-Wallis test. *Post hoc* analysis was done using the Mann–Whitney U test for pairwise comparisons.

RESULTS

One hundred and fifty patients were enrolled in the study. No patient was withdrawn from the study. Characteristics and surgical data are listed in Table 1. There were no significant differences between the three groups in age, height, weight, gestational age, primigravida rate, and duration of surgery. The overall incidence of pruritus during the 24 hr follow-up period was 72%, 68%, and 44% for group S, group D, and group N, respectively. Pairwise comparisons show that pruritus was less frequent in group N than group D ($p = 0.027$). Pruritus severity for all three groups is shown in Table 2. At 4 and 12 hrs postoperatively, the severity of pruritus was significantly different ($p = 0.003$ and $p = 0.002$) and was significantly less in group N than group D in the intergroup comparison ($p = 0.013$ and $p = 0.012$). However, the pruritus severity was not significantly different between any of the groups at 1 and 24 hrs after surgery. Postoperative wound pain (VRS scores) is reported in Table 3. Pain scores were less than 5 for all patients. No significant differences were found in pain scores between the three groups at the four time intervals. The sedation level (Ramsay Sedation Scale) is noted in Table 4. No patients were oversedated (Ramsay score ≧ 5) and all scores were in the 2-4 range. Sedation scores were not significantly different between groups at the four time intervals. The pruritus incidence at the different time intervals is shown in the Fig. 1. The incidence of pruritus after epidural morphine injection peaked at 4–12 hrs and decreased at 24 hrs after surgery in groups S and D.

Table 1. Patient Characteristics and Surgical Data

	Group S (n = 50)	Group D (n = 50)	Group N (n = 50)
Age (yr)	32.4 ± 3.7	32.6 ± 4.6	33.1 ± 3.7
Height (cm)	158.4 ± 4.1	158.1 ± 5.3	159.2 ± 5.6
Weight (kg)	70.3 ± 9.6	68.3 ± 12.5	70.2 ± 10.1
Gestational age (wk)	36.9 ± 2.4	37.2 ± 2.0	37.0 ± 2.0
Primigravida	22 (44%)	22 (44%)	21 (42%)
Duration of surgery (min)	60.8 ± 11.5	63.6 ± 13.1	64.1 ± 13.0
Incidence of pruritus	36 (72%)	34 (68%)	22 (44%)*†

Values are means ± SD or numbers (%).

*: $p = 0.008$ when compared with group S; †: $p = 0.027$ when compared with group D.

DISCUSSION

Neuraxial opioids provide excellent postoperative analgesia after caesarean delivery. However, pruritus is the most frequent undesirable problem

Table 2. Pruritus Scores Assessed at 1, 4, 12, and 24 Hrs after Surgery

	1 h	4 h*	12 h*	24 h
Group S				
no pruritus	46 (92%)	18 (36%)	17 (34%)	24 (48%)
mild pruritus	4 (8%)	12 (24%)	17 (34%)	21 (42%)
moderate pruritus	0	19 (38%)	16 (32%)	5 (10%)
severe pruritus	0	1 (2%)	0	0
Group D				
no pruritus	49 (98%)	22 (44%)	21 (42%)	25 (50%)
mild pruritus	1 (2%)	13 (26%)	15 (30%)	23 (46%)
moderate pruritus	0	14 (28%)	13 (26%)	2 (4%)
severe pruritus	0	1 (2%)	1 (2%)	0
Group N†‡				
no pruritus	48 (96%)	31 (62%)	32 (64%)	30 (60%)
mild pruritus	2 (4%)	15 (30%)	16 (32%)	18 (36%)
moderate pruritus	0	3 (6%)	2 (4%)	2 (4%)
severe pruritus	0	1 (2%)	0	0

Values are numbers (%)

*: $p < 0.005$ when compared with Kruskal-Wallis test between three groups; †: $p < 0.001$ when compared with group S at 4 and 12 hrs; ‡: $p < 0.05$ when compared with group D at 4 and 12 hrs after surgery.

Table 3. Postoperative Wound Pain Assessed at 1, 4, 12, and 24 hrs after Surgery (VRS scores)

	1	4	12	24
Group S	0.24 ± 0.74	1.60 ± 1.01	1.46 ± 0.79	1.30 ± 0.76
Group D	0.14 ± 0.57	1.58 ± 0.90	1.58 ± 0.57	1.38 ± 0.53
Group N	0.14 ± 0.50	1.58 ± 0.97	1.72 ± 0.61	1.58 ± 0.57

Values are means ± SD. Abbreviation: VRS: verbal rating scale.

No significant differences were found in pain scores between groups at the four time intervals.

Table 4. Ramsay Sedation Scores Assessed at 1, 4, 12, and 24 hrs after Surgery

	1	4	12	24
Group S	2.28 ± 0.54	2.22 ± 0.42	2.10 ± 0.30	2.20 ± 0.40
Group D	2.34 ± 0.56	2.16 ± 0.37	2.06 ± 0.24	2.22 ± 0.42
Group N	2.30 ± 0.54	2.08 ± 0.44	2.14 ± 0.35	2.19 ± 0.40

Values are means ± SD.

No significant differences were found in sedation scores between groups at the four time intervals.

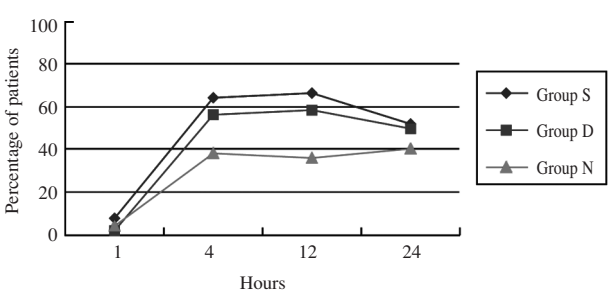

Fig. 1 Incidence of pruritus at different time intervals.

associated with neuraxial opioids. The incidence of pruritus after intrathecal morphine ranges from 62 to 85%; after epidural morphine, it ranges from 65 to 70%.[5] Parturients appear to be the most susceptible to pruritus. This increased incidence may be due to an interaction between estrogen and opioid receptors.[16-18] The increased cephalic spread of neuraxially administered drugs in a pregnant woman may also play a role.[19] In our study, the overall pruritus incidence after epidural morphine injection for parturients who underwent cesarean section was 72% during the 24-hr follow-up period, which is consistent with other reports in the literature.[2,4,5]

The mechanism for pruritus after neuraxial opioid administration is complex. Although itch-specific neuronal pathways are distinct from pain pathways, there are close interactions between them. Continuing activity in the pain processing system suppresses activity in spinal itch-processing neurons. Clinically, if pain-processing neurons are inhibited by application of μ-opioid agonists, suppression of the itch neurons may become insufficient and activation of the itch pathway causes pruritus.[20] Neuraxia opioids activate the μ receptors in the substantia gelatinosa of the dorsal horn and trigeminal nucleus in the medulla.[21,22] They are responsible for pain modulation and some side effects, especially pruritus. Additionally, many studies also showed that κ-receptor agonists inhibit neuraxial opioid-induced pruritus.[12,23] Nalbuphine is a mixed opioid κ- agonist and μ-antagonist. This would explain its antipruritic effect via action on the μ- and κ-receptors. In a previous study, intravenous nalbuphine (2 to 3 mg) was proven optimal in the treatment of intrathecal morphine-induced pruritus after cesarean section without increased pain scores or other side effects.[24,25] In our results, intramuscular nalbuphine (10 mg) decreased the incidence of epidural morphine-induced pruritus by 28% ($p = 0.008$) compared with that in the placebo (saline) group. The severity of pruritus decreased for group N when compared with group S at 4 and 12 hrs postoperatively. Postoperative wound pain was not different in any group during the study period.

Histamine is a key itching mediator produced by opioids administered systemically. Opioid receptors evoke histamine release from mast cells and induce itching.[26,27] However, in neuraxial opioid-induced pruritus, histamine is not released and does not appear to be causative.[28] Although one previous study reported that antihistamines were effective,[11] our results show that prophylactic diphenhydramine does not reduce the incidence or severity of pruritus when compared with that in the placebo group. Many studies have reported that patients often deny the presence of pruritus, even though they are observed to be scratching.[29] The sedative properties of antihistamines may be helpful for parturients because they temporarily cause much needed sleep even if they do not relieve the pruritus sensation.[30]

In our data, more patients in group D than group S had no pruritus at 4 and 12 hrs postoperatively (44% vs. 36%, 42% vs. 34%), which might seem to be a good result; this could be explained by the sedative effects of diphenhydramine. However, the sedation level was not significantly different between the three groups during the first 24 postoperative hours and the pruritus severity was not significantly different between group D and S. If we consider an effective prophylaxis for pruritus, the incidence of moderate and severe pruritus should be reduced.

After intrathecal administration, opioids reach peak concentrations in the cerebrospinal fluid almost immediately. After epidural morphine administration, there is a delay in the rise to peak concentration of 1 to 4 hours.[31] Epidural morphine also has a longer duration of action (12–24 hrs) than other opioids. According to pharmacokinetic study, intramuscular administration of nalbuphine results in a longer elimination half-life than intravenous administration.[32] We chose an intramuscular rather than intravenous injection of nalbuphine and diphenhydramine because of the longer expected duration of the antipruritus effect. In our study, pruritus onset was at 4 hrs after surgery for all three groups and it peaked at 4–12 hrs after epidural morphine injection. The incidence of pruritus after epidural morphine administration was lower in group N at 4 and 12 hrs postoperatively than in groups S and D. However, there were no obvious differences in the incidence of pruritus at 24 hrs postoperatively. Intramuscular nalbuphine (10 mg) proved more successful in preventing epidural morphine-induced pruritus for at least the first 12 hrs postoperatively than 30 mg of diphenhydramine. Intramuscular dose responsiveness for nalbuphine and the optimal dosages required need to be assessed in further studies.

In conclusion, nalbuphine proved better than diphenhydramine for prevention of epidural morphine-induced pruritus in patients who underwent caesarean section. Prophylactic intramuscular nalbuphine (10 mg) is effective in decreasing the incidence and severity of pruritus and does not affect analgesia.

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比較預防性肌肉注射 nalbuphine 和 diphenhydramine 對剖腹生產術後硬膜外嗎啡止痛引起之皮膚搔癢的效果

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背 景： 剖腹生產後硬膜外嗎啡止痛所引起之副作用最常見爲皮膚搔癢。diphenhydramine (鹽酸二苯胺明) 爲臨床上常用來治療蕁麻疹引起之皮膚搔癢的藥物，而 nalbuphine (芯奔) 也有報告對於治療硬膜外嗎啡止痛所引起之皮膚搔癢的效果，本實驗目的在比較預防性肌肉注射 diphenhydramine 和 nalbuphine 對剖腹生產術後硬膜外嗎啡止痛引起之皮膚搔癢的效果。

方 法： 選擇 150 位 ASA I 或 II 接受剖腹生產的病人，採隨機方法將病人分成三組。在胎兒產出後 group S 給予病人肌肉注射 1 ml 的 normal saline (n = 50)，group D 給予 30 mg/1 ml 的 diphenhydramine (n = 50)，group N 給予 10 mg/1 ml 的 nalbuphine (n = 50)。術後 1, 4, 12, 24 hrs 分別評估病人皮膚搔癢的發生率及嚴重程度。

結 果： 病人術後 24 h 期間皮膚搔癢發生率分別爲 group S: 72%，group D: 68%，group N: 44%，group N 病人發生比率明顯較 group D 爲低 (p = 0.027)。在術後 4 hrs 及 12 hrs，group N 的病人皮膚搔癢的嚴重程度明顯比 group D 的病人輕微 (p = 0.013 and p = 0.012)。

結 論： Nalbuphine 對於預防剖腹生產病人接受硬膜外嗎啡止痛引起之皮膚搔癢的效果優於 diphenhydramine，預防性肌肉注射 10 mg 的 nalbuphine 可以有效減低皮膚搔癢的發生率及嚴重程度。

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關鍵詞： 硬膜外嗎啡，芯奔，鹽酸二苯胺明，皮膚搔癢

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