Combination of Low-dose Nalbuphine and Morphine in Patient-controlled Analgesia Decreases Incidence of Opioid-related Side Effects

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Background/Purpose: The addition of ultra-low-dose naloxone to patient-controlled analgesia (PCA) with morphine reduces opioid-related side effects. Nalbuphine, a mixed opioid agonist–antagonist, may be able to attenuate opioid-related side effects. The goal of the present study was to investigate the effect of combined low-dose nalbuphine and morphine in PCA for postoperative pain control after gynecological surgery.

Methods: This randomized, double-blind, controlled study enrolled 174 female patients who were undergoing total abdominal hysterectomy, myomectomy, or ovarian tumor excision. In the control group, the PCA formula was 1 mg/mL pure morphine. In the study group, the PCA formula was 1 mg/mL morphine and 10 μg/mL nalbuphine (1:100). Numerical rating score, PCA requirement, nausea, vomiting, use of antiemetics, pruritus, use of antipruritics, and opioid-related adverse events were investigated at 1, 2, 4, and 24 hours postoperatively.

Results: One hundred and sixty-nine patients completed the study: 86 in the control group and 83 in the study group. The incidence of nausea was lower in the study group (41%) than in the control group (65%). The incidence of vomiting, use of antiemetics, pruritus, and use of antipruritics did not differ between the two groups. The numerical rating pain score and PCA requirements were not significantly different between the two groups.

Conclusion: Combination of low-dose nalbuphine and morphine in PCA decreases the incidence of opioid-related nausea, without affecting the analgesia and PCA requirement. This novel combination can improve the quality of PCA used for postoperative pain control after gynecological surgery. [J Formos Med Assoc 2009;108(7):548–553]

Key Words: adverse effects, morphine, nalbuphine, opioids, patient-controlled analgesia

Nalbuphine is known as a mixed opioid agonist–antagonist.1–3 Nalbuphine derives its analgesic and sedative effects through kappa-opioid receptors, and it may attenuate mu-opioid-receptor-related side effects.4 Morphine is the popular opioid used in patient-controlled analgesia (PCA). However, morphine causes many side effects including pruritus, nausea, vomiting, constipation, urinary retention, respiratory depression, and sedation. Since morphine binds most readily to

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the mu-opioid receptor, and less well to the kappa-receptor, this implies that the undesirable side effects of morphine are likely related to the mu-opioid receptor.4

The addition of ultra-low-dose naloxone to postoperative morphine PCA can reduce opioid-related side effects.5,6 Moreover, several studies have tried to compare the effect of naloxone and nalbuphine on opioid-related side effects.7–9 However, no previous study has evaluated the effect of combining low-dose nalbuphine and morphine in intravenous PCA. The goal of this study was to investigate the effect of combined low-lose nalbuphine and morphine in intravenous PCA for postoperative pain control after gynecological surgery.

Materials and Methods

Patients
This randomized, double-blind, controlled study enrolled 174 female patients aged 18–65 years old with an American Society of Anesthesiologists (ASA) physical status of I, II, or III. They had undergone one of the following gynecological operations: total abdominal hysterectomy, myomectomy, or ovarian tumor excision. The protocol was approved by the National Taiwan University Hospital Research Ethics Committee, and informed consent was obtained. Patients who had a history of drug abuse, chronic pain, or psychiatric disorders were excluded. The patients were also excluded if they took sedatives, antiemetics, or antipruritics within 24 hours before surgery.

Randomization and grouping
The PCA solutions were prepared by a nurse anesthetist. After reviewing the literature, the potency difference between naloxone and nalbuphine was judged to be about 25–50:1.7–10 After considering the characteristic of PCA use and longer half-life of nalbuphine, we decided to use a concentration of 10 μg/mL in the study group. Compared with the ultra-low-dose naloxone study,5 the potency difference between naloxone and nalbuphine was assumed as 16.7:1 in the present study. Patients were randomly allocated into two groups using a computer-generated randomized number table. In the control group, 100 mg preservative-free morphine was added to normal saline to make a total volume of 100 mL. In the study group, 100 mg preservative-free morphine and 1 mg nalbuphine were added to normal saline to make a total volume of 100 mL. Before surgery, patients were instructed in the 0–10 numerical rating score (NRS) for pain and the use of PCA. A score of 0 represented no pain and 10 represented the worst pain imaginable. The goal of PCA analgesia was to maintain NRS at rest ≤4 between 4 and 24 hours postoperatively.

Anesthesia, postoperative analgesia and PCA
No patients received any drug for premedication. Anesthesia was induced with thiopental (3–5 mg/kg) and fentanyl (1.5–3 mg/kg), and maintained with sevoflurane 1.2–1.5% in oxygen. Rocuronium (0.8 mg/kg) was given to facilitate endotracheal intubation and maintained at 0.2 mg/kg every 30 minutes. At the end of surgery, atropine (0.015 mg/kg) and neostigmine (0.05 mg/kg) were administered for reversal of neuromuscular block. After the trachea was extubated, patients were transported to the postanesthesia care unit. During the 1-hour stay there, vital signs were monitored every 5 minutes and oxygen saturation was monitored continuously by pulse oximetry. The patients were attached to a PCA machine (Lifecare 5500 PCA; Abbott Laboratories, Abbott Park, IL, USA). Postoperative analgesia was commenced with an intravenous loading dose of 3 mL PCA solution, administered by a nurse. Incremental doses of 1 mL PCA solution were given as needed. After the patients were responsive, they were allowed to use the PCA machine by themselves. The setting for PCA was 1 mL bolus with a 5-minute lockout. There was no background continuous infusion throughout the postoperative period.

Postoperative evaluation
After transferring back to the general ward, all patients were observed for 24 hours after surgery.
The cumulative PCA requirements were recorded in PCA machines, and the data were transferred to a computer for interpretation. Pain intensity was evaluated with a 0–10 NRS at rest. The incidence of opioid-related side effects (nausea, vomiting, and pruritus) was evaluated. A vomiting episode was defined as vomiting that occurred in a rapid sequence (< 1 minute between events), and retching (same as vomiting but without expulsion of gastric contents). If vomiting events were separated by longer than 1 minute, they were considered as separate episodes. The total number of vomiting episodes was recorded. Vomiting that occurred more than four times within 24 hours was considered as severe vomiting. Rescue antiemesis (intravenous prochlorperazine mesylate 10 mg) was given at the patient’s request. All data were collected at 1, 2, 4 and 24 hours postoperatively by direct questioning from investigators.

Definition of treatment failure and adverse events

Treatment failures included insufficient analgesia, intolerable nausea and vomiting, and pruritus. Insufficient analgesia was defined as NRS > 4 at rest during 4–24 hours postoperatively.5 Adjunctive analgesia with 50 mg meperidine or 30 mg ketorolac was administered intravenously for insufficient analgesia. Intolerable nausea and vomiting were defined as persistent nausea or vomiting episodes that required more than three administrations of antiemetics (prochlorperazine mesylate). In this situation, the patient could decide to use PCA continuously or receive nonsteroidal anti-inflammatory drugs (NSAIDs; ketorolac) for postoperative pain management. Intolerable pruritus was defined as persistent pruritus that required more than three administrations of antipruritics (diphenhydramine). In this situation, the patient could decide to use PCA continuously or receive NSAIDs (ketorolac) for postoperative pain management.

PCA-related hypotension, allergic reaction, bronchospasm, unconsciousness, and respiratory depression were considered as adverse events. Hypotension was defined as systolic blood pressure < 90 mmHg at any investigated time. Respiratory depression was defined as respiratory rate < 8 per minute or hypoxemia (SpO2 < 90%). If adverse events occurred, the use of PCA was stopped immediately and the patient was observed closely. Naloxone and oxygen supplementation were administered for respiratory depression.

Statistical analysis

In our previous study, the incidence of nausea in morphine intravenous PCA was 67.6%.12 A sample size of 85 in each group was able to detect an absolute 20% reduction of incidence of nausea with an \( \alpha \) level of 0.05 (one-sided) and a \( \beta \) level of 0.2. Student’s t tests were conducted to examine differences with respect to parametric variables, such as patient characteristics, duration of surgery, fentanyl use during operation, and PCA requirement. The Mann–Whitney U test was used to determine differences with respect to nonparametric variables, such as numerical rating score of pain at rest. The incidence of nausea, vomiting, pruritus, use of antiemetics, and use of antipruritics were analyzed by the \( \chi^2 \) test. A value of \( p < 0.05 \) was considered to be statistically significant.

Results

One hundred and sixty-nine patients completed this study: 86 in the control group, and 83 in the study group. Five patients discontinued the investigation for the following reasons: three used < 5 mL PCA solution (1 in the control group and 2 in the study group); one patient in the control group used 84 mL PCA solution; and one patient in the control group suffered from renal colic caused by a renal stone (Figure). There was no significant difference in demographic characteristics, ASA classification, duration of surgery, or intraoperative consumption of fentanyl between the two groups (Table 1).

Pain intensity and PCA requirements

The NRS did not differ significantly between the two groups throughout the observation period.
The cumulative dose for PCA did not differ significantly between the two groups (Table 2). Three patients experienced insufficient analgesia and received adjunctive analgesics: one in the control group and two in the study group.

**Opioid-related side effects**

The incidence of nausea was lower in the study group (41%) than the control group (65%; Table 3). The incidence of vomiting seemed lower in the study group than the control group, but the difference was not significant. The incidence of severe vomiting and the requirement for antiemetics did not differ significantly between the two groups. The incidence of pruritus and use of antipruritics did not differ significantly between the two groups. No adverse events occurred in this study. The combination of low-dose nalbuphine and morphine in PCA decreased the incidence of opioid-related nausea by 37%. The absolute reduction in the incidence of nausea was 24%, and the number needed to treat was 4.2. As a result of the sample size, the 11% absolute reduction in the incidence of vomiting between the two groups was not statistically significant. We suggest further studies to investigate whether vomiting is significantly reduced with nalbuphine and morphine PCA.

**Discussion**

This study found that a combination of low-dose nalbuphine and morphine in PCA did not affect the analgesic effect or the PCA requirement. We suggest that this combination can improve the quality of PCA use.

The reduction in the incidence of opioid-related nausea might result from blocking the excitatory effects of opioids.13 Nalbuphine is a mixed opioid agonist–antagonist. Low-dose nalbuphine may act like ultra-low-dose naloxone—this can decrease the opioid-related side effects, with unchanged analgesic and opioid requirements.5 Two studies have reported that ultra-low doses of opioid antagonists enhance opioid analgesia.14,15 However, in our study and another using ultra-low-dose naloxone, the analgesia and opioid requirement was unchanged. We suggest that the combination ratio between opioid antagonist and agonist is important for enhancing opioid analgesia. In a previous using ultra-low-dose naloxone,5 the incidence of pruritus was lower after addition of naloxone to morphine PCA. Moreover, several studies have reported that nalbuphine infusion can reduce epidural

**Figure.** Consort-type diagram of the study.
In the present study, the incidence of pruritus did not differ significantly between the two groups. Compared with the previous studies in which the total consumption of nalbuphine for 24 hours was 1200–60,000 μg, the mean consumption of nalbuphine for 24 hours in our study was 247–257 μg. We suggest that a higher dose of nalbuphine was needed to reduce the incidence of opioid-related pruritus. We suggest that the potency for each opioid-related side effect might be different between naloxone and nalbuphine.

The results of this study were based on a population of women after gynecological surgery, and the effect in a group of men might not be the same. Several studies have revealed that nalbuphine has different effects in women and men. Gear et al. found an unexpected anti-analgesic effect in men receiving nalbuphine alone after bone-impacted third molar extraction, compared with women with a dose-dependent analgesic response. They also reported that kappa-opioids produce significantly greater analgesia in women than in men. Therefore, we suggest that further studies are needed to investigate whether the influence of nalbuphine on opioid-related side effects differs between women and men.

In conclusion, the combination of low-dose nalbuphine and morphine in PCA decreases the incidence of opioid-related nausea. It does not affect analgesia and PCA requirements. This novel combination can improve the quality of PCA for postoperative pain control after gynecological surgery.

**References**


