Different Doses of Nalbuphine Combined with Dexmedetomidine in Laparoscopic Oophorocystectomy

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Background: The goal of this study was to investigate different doses of nalbuphine combined with dexmedetomidine in the postoperative treatment of laparoscopic oophorocystectomy.

Material/Methods: This prospective single-blinded randomized controlled study included 219 patients with benign ovarian cysts who received laparoscopic oophorocystectomy from March 2017 to October 2019. Patients were randomized into 4 groups: low (0.5 mg/kg), middle (1.0 mg/kg), and high (1.5 mg/kg) doses of nalbuphine combined with dexmedetomidine (4 μg/kg) (LND, MND, and HND groups, respectively) and a control group with sufentanil (2.5 μg/kg), with different patient-controlled intravenous analgesia pump (PCIA) strategies. Rest and active visual analog scale (VAS) scores measured postoperative pain, and Ramsay scores were used to measure sedation.

Results: The HND group showed the lowest rest and cough VAS scores at 2 h, 8 h, 12 h, and 24 h after surgery, the lowest PCIA pressing time within 48 h after surgery, and the highest Ramsay scores at 2 h, 8 h, 24 h and 48 h after surgery. Rest and cough VAS scores decreased with higher nalbuphine doses in a dose-dependent manner. One day after surgery, IL-1β and IL-6 levels increased in all groups, with the lowest levels of IL-1β and IL-6 in the HND group. Hospitalization time was significantly shorter in the HND group compared with the LND and MND groups. There were no significant differences in complications among groups.

Conclusions: Combined nalbuphine and dexmedetomidine improved postoperative pain and sedative conditions, reduced inflammation in a nalbuphine dose-dependent manner, and might facilitate patient recovery.

Keywords: Abdominal Pain • Dexmedetomidine • Nalbuphine

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/930197
Background

The ovarian cyst is a common gynecological disease, which approximately 1 in 25 women will have in their lifetime [1]. Most ovarian cysts are benign, and surgical treatment is usually recommended when the cyst diameter is $>5\text{ cm}$ [2,3]. With the development of surgical methods, minimally invasive techniques such as laparoscopic oophorocystectomy, which is now the main treatment strategy for benign ovarian cysts, have gradually taken the place of open surgery [4,5].

It has been found that laparoscopic oophorocystectomy can achieve shorter surgery time, hospital stay, and postoperative recovery time than traditional open surgery [6]. It was further reported that combined abdominal laparoscopic procedures of gynecologic and general surgeries are safe for female patients and provide a choice with less pain, shorter hospital stays, and earlier recovery [7]. Also, neuromuscular blockade following a single-bolus dose of rocuronium can prolong the time from injection of rocuronium to spontaneous recovery [8]. However, postoperative treatment, such as pain management, is still a clinical problem in improving patients’ surgical recovery.

Nalbuphine is a newly developed opioid receptor agonist-antagonist [9]. Currently, many studies are reporting on the use of nalbuphine in postoperative treatment, mainly for pain relief, including in pediatric anesthesia [10]. Naaez et al reported that doses of 0.8 mg and 1.6 mg nalbuphine can reduce postoperative pain after lower-limb orthopedic surgery. In a randomized controlled trial, Deng et al compared the efficacy of nalbuphine and sufentanil for colonoscopy and demonstrated that respiratory depression was significantly more common in sufentanil-treated patients than in patients receiving 0.1 mg/kg or 0.15 mg/kg of nalbuphine, while the incidence of nausea was higher in nalbuphine groups [11]. In addition to nalbuphine, dexmedetomidine, a type of $\alpha_2$-adrenergic receptor agonist, has been reported in postoperative analgesia and sedation, including gynecological surgeries. It was found that the use of dexmedetomidine during general anesthesia could decrease the perioperative serum levels of TNF-$\alpha$ and IL-6 and reduce postoperative pain in patients undergoing radical resection of ovarian cancer [12]. However, most gynecological surgery uses a single dose of nalbuphine, and few studies reported the application of nalbuphine or its dose in postoperative treatment in laparoscopic oophorocystectomy.

Here, we conducted a single-blinded randomized controlled study to investigate the effects of different doses of nalbuphine combined with dexmedetomidine in laparoscopic oophorocystectomy. The study mainly focused on effects of nalbuphine on postoperative pain and inflammatory factors, the latter of which are rarely reported in gynecological surgeries. This research will provide more clinical evidence for the combination of nalbuphine and dexmedetomidine in postoperative treatment.

Material and Methods

Patients

The present prospective single-blinded randomized controlled study included a total of 219 patients with benign ovarian cysts who received laparoscopic oophorocystectomy in our hospital from March 2017 to October 2019. All patients were diagnosed with benign ovarian cyst by imaging methods, including computed tomography scan and magnetic resonance imaging, as well as with histological evidence. The inclusion criteria were as follows: (1) patients with benign ovarian cysts with a diameter $\geq 5\text{ cm}$; (2) patients with American Society of Anesthesiologists stages of I-II; (3) patients with no contraindications to laparoscopic surgery; (4) patients aged 20 to 45 years who agreed to participate. The exclusion criteria were as follows: (1) patients with bilateral salpingectomy or contraception; (2) patients with cancers such as endometrial carcinoma or ovarian cancer; (3) patients with severe liver, renal, or cardiovascular diseases. All patients gave their written informed consent. The study was approved by the Ethics Committee of the Second Hospital of Anhui Medical University.

Grouping and Anesthesia Strategy

The study sample size was calculated with the formula:

$$\frac{\left(\sqrt{T} + t_b\right)^2}{\delta}$$

The visual analog scale (VAS) score was used as the main clinical outcome, and VAS score reduction by at least 1 at 24 h after surgery was considered effective. The mean VAS score was about 6.0±2.0 at 24 h after surgery, according to clinical experience. Thus, $a=1$, $b=2$ $a_2=0.05$, and $b=0.10$. The minimum sample size was 42 for each group.

All patients were instructed to fast and avoid drinking water before surgery. The peripheral venous access of the upper limb was opened. After local infiltration anesthesia with a 1% lidocaine injection, radial artery catheterization was performed. The anesthesia induction was performed with midazolam 0.04 mg/kg to 0.1 mg/kg, sufentanil 0.3 $\mu$g/kg, cisatracurium besylate 0.1 mg/kg to 0.2 mg/kg, propofol 2 mg/kg, and atropine 0.5 mg/kg. After endotracheal intubation and mechanical ventilation, the maintenance of anesthesia was achieved by propofol 4 mg/kg/h to 10 mg/kg/h, remifentanil 5 $\mu$g/kg/h to 10 $\mu$g/kg/h by intravenous pumping, and continuously inhaled sevoflurane (1-2%). Patients’ vital signs were monitored and the doses for anesthesia maintenance were adjusted.
according to the depth of anesthesia via monitoring conditions. The bispectral index was maintained between 40 and 60. Atropine could be injected intravenously when the heart rate was <50 beats/min, and sufentanil 0.3 μg/kg was added when preparing to close the incision. Propofol, remifentanil, and sevoflurane were stopped after the incision was sutured. After the surgery, the prepared analgesia pump was immediately connected to a peripheral vein.

All groups of patients used a patient-controlled intravenous analgesia pump (PCIA) (automatic electronic drug injection pump ZB- II type, Jiangsu Al Peng Medical Equipment Co., Ltd., China) for postoperative analgesia. Patients were randomized into 4 groups using a list generated by SPSS software, according to different PCIA strategies: (1) low dose of nalbuphine (0.5 mg/kg) combined with dexmedetomidine (4 μg/kg) (LND group); (2) middle dose of nalbuphine (1.0 mg/kg) combined with dexmedetomidine (4 μg/kg) (MND group); (3) high dose of nalbuphine (1.5 mg/kg) combined with dexmedetomidine (4 μg/kg) (HND group); and (4) sufentanil 2.5 μg/kg group (control). Tropisetron (5 mg) was added in PCIA in all groups of patients. For PCIA, the background infusion dose was 2 mL/h, patient-controlled analgesia dose was 2 mL, and the locking time was 15 min. The surgeries were all conducted by the same team and according to the same protocol.

Data Collection and Measurement

Basic patient characteristics including age and body mass index (BMI) and pathological type and the diameter of the benign ovarian cysts were collected. Mean operative time and blood loss were recorded. The rest and active VAS scores were tested for postoperative pain at 2 h, 8 h, 12 h, 24 h, and 48 h after surgery. The PCIA pressing times within 48 h after each time-point were collected. The Ramsay scores at 1 h, 6 h, 24 h, and 48 h after surgery were used to measure sedation. Patients’ venous blood on the non-infusion side was collected before surgery and 1 day after surgery, and the serum levels of interleukin (IL)-1β and IL-6 were tested using the enzyme-linked immunosorbent assay method. The length of hospitalization and patient complications and adverse effects within 7 days after surgery were recorded.

Statistical Analysis

All analyses were conducted using SPSS version 18.0. The measurement data were expressed by mean±standard deviation. Comparisons among the 3 groups were evaluated using one-way analysis of variance (ANOVA), followed by the Tukey post hoc test. The rates were compared using chi-squared test. P<0.05 was considered a statistically significant difference.

Results

Characteristics of All Patients and Intro-Operative Indices

The present study enrolled a total of 230 patients with benign ovarian cysts who underwent laparoscopic oophorocystectomy. Briefly, 6 patients dropped out of the study, 3 patients were transferred to open surgery, and 2 patients were transferred to the intensive care unit after surgery. Finally, 219 patients who met the inclusion criteria were included in the analyses. The mean cyst diameter was 6.03±0.57 cm. A total of 61 (27.85%) patients had a serous cyst, while other pathological types were 55 (25.11%) patients with a mucinous cyst, 51 (23.29%) patients with an endometrioma, and 52 (23.74%) patients with a teratoma. The mean operative time was 46.71±9.85 min, with mean blood loss of 44.32±5.76 mL. No significant differences were found in all basic characteristics among the different groups of patients (Table 1).

VAS Scores, Ramsay Scores, and PCIA Pressing Times Within 48 H After Surgery

Next, we measured the VAS and Ramsay scores after surgery in the different groups. We found that both the rest and cough VAS scores were highest in the control group and lowest in the HND group at 2 h, 8 h, 12 h, and 24 h after surgery, and the difference between the groups was significant (P<0.05; Table 2). Also, at 2 h, 8 h, 12 h, and 24 h after surgery, the rest and cough VAS scores decreased with increased nalbuphine doses in a dose-dependent manner. Also, the PCIA pressing time was markedly higher in the control group and was lowest in the HND group within 48 h after surgery, compared with the other groups (P<0.05). Similarly, the Ramsay scores were highest in the HND group at 2 h, 8 h, 24 h, and 48 h after surgery, and the difference was significant (P<0.05; Table 3). The Ramsay scores at 2 h, 8 h, 24 h, and 48 h after surgery increased with the increase in nalbuphine dose in a dose-dependent manner. All these results suggested that the high-dose nalbuphine (1.5 mg/kg) combined with dexmedetomidine (4 μg/kg) had the best effects on pain and sedation control.

Serum Levels of IL-1β and IL-6 Before and After Surgery

Serum levels of IL-1β and IL-6 were measured before and after surgery to measure patient inflammation response. As shown in Table 4, there were no significant differences in IL-1β and IL-6 levels among the groups. However, at 1 day after surgery, IL-1β and IL-6 levels increased in all groups, with the lowest levels of IL-1β and IL-6 found in the HND group and the highest levels of IL-1β and IL-6 found in the control group; the differences in IL-1β and IL-6 levels between the HND and control groups were significant (P<0.05). The levels of IL-1β and IL-6 also decreased with the increased doses of nalbuphine.
in a dose-dependent manner, indicating the application of nalbuphine combined with dexmedetomidine improved patients’ inflammation response after laparoscopic oophorocystectomy surgery.

**Hospitalization and Complications**

We recorded the length of hospitalization and complications of all patients. We found that the hospitalization time was remarkably shorter in the LND, MND, and HND groups compared with that of the control group (P<0.05; Table 5). However, a significant difference in hospitalization time was found only in the comparison of the HND group with the LND and MND groups. No significant difference in hospitalization time was found between the LND and MND groups. There were no significant differences in complications among the groups. These results implied that the high-dose nalbuphine (1.5 mg/kg) combined with dexmedetomidine (4 μg/kg) can facilitate patient recovery.

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**Table 1. Characteristics of all patients.**

| Variables            | Total, n=219 | LND, n=55 | MND, n=54 | HND, n=55 | Control, n=55 | P value |
|----------------------|--------------|-----------|-----------|-----------|---------------|---------|
| Age, years           | 36.34±8.20   | 37.34±8.15| 36.61±8.35| 35.72±7.46| 35.69±8.86    | 0.677   |
| BMI, kg/m²           | 21.27±2.15   | 21.29±2.14| 21.15±2.23| 21.69±2.14| 20.95±2.07    | 0.329   |
| Cyst diameter, cm    | 6.03±0.57    | 6.10±0.50 | 6.06±0.55 | 5.95±0.62 | 6.00±0.61     | 0.543   |
| Pathological types, n (%) |             |           |           |           |               | 0.841   |
| Serous cyst          | 61 (27.85)   | 17 (30.91)| 14 (25.93)| 15 (27.27)| 15 (27.27)    |         |
| Mucinous cyst        | 55 (25.11)   | 13 (23.64)| 16 (29.63)| 12 (21.82)| 14 (25.45)    |         |
| Endometrioma         | 51 (23.29)   | 15 (27.27)| 11 (20.37)| 13 (23.64)| 12 (21.82)    |         |
| Teratoma             | 52 (23.74)   | 10 (18.18)| 13 (24.07)| 15 (27.27)| 14 (25.45)    |         |
| Operative time, min  | 46.71±9.85   | 48.43±9.36| 45.86±10.29| 44.67±9.57| 47.84±9.97     | 0.114   |
| Blood loss, mL       | 44.32±5.76   | 43.67±5.62| 44.77±5.46| 43.19±6.04| 45.64±5.73     | 0.112   |

BMI – body mass index; LND – low-dose nalbuphine and dexmedetomidine; MDN – middle-dose nalbuphine and dexmedetomidine; HND – high-dose nalbuphine and dexmedetomidine.

**Table 2. VAS scores and PCIA pressing times within 48 h after surgery in all patients.**

| Variables | LND, n=55 | MND n=54 | HND, n=55 | Control, n=55 | P value |
|-----------|-----------|----------|-----------|---------------|---------|
| VAS at 2 h| 3.24±0.89 | 3.03±0.59 | 2.61±0.49 | 4.24±0.93     | <0.001  |
| Rest VAS at 8 h | 3.00±0.60 | 2.49±0.31 | 2.14±0.32 | 3.80±0.78     | <0.001  |
| VAS at 12 h| 2.07±0.52 | 1.93±0.36 | 1.50±0.33 | 2.96±0.71     | <0.001  |
| VAS at 24 h| 1.51±0.28 | 1.24±0.47 | 1.05±0.33 | 2.28±0.45     | <0.001  |
| VAS at 48 h| 1.10±0.32 | 1.08±0.33 | 1.05±0.31 | 1.05±0.32     | 0.849   |
| Cough VAS at 2 h | 4.44±0.83 | 3.87±0.64 | 3.20±0.57 | 5.14±1.16     | <0.001  |
| VAS at 8 h | 4.12±0.62 | 3.37±0.74 | 2.74±0.72 | 4.53±0.94     | <0.001  |
| VAS at 12 h| 2.93±0.64 | 2.57±0.61 | 2.18±0.50 | 3.55±0.85     | <0.001  |
| VAS at 24 h| 2.02±0.54 | 1.43±0.51 | 1.29±0.52 | 2.84±0.52     | <0.001  |
| VAS at 48 h| 1.45±0.35 | 1.44±0.34 | 1.46±0.37 | 1.51±0.38     | 0.799   |
| PCIA        | 2.18±1.09 | 2.16±0.90 | 1.57±0.49 | 3.16±1.31     | <0.001  |

a P<0.05 vs LND group; b P<0.05 vs MND group; c P<0.05 vs HND group; d P<0.05 vs Control group. LND – low-dose nalbuphine and dexmedetomidine; MDN – middle-dose nalbuphine and dexmedetomidine; HND – high-dose nalbuphine and dexmedetomidine; PCIA – patient-controlled intravenous analgesia pump.
Laparoscopic oophorocystectomy is currently the main treatment strategy for benign ovarian cysts, and its postoperative pain management and recovery are important to patient healing [13,14]. Nalbuphine is a newly developed opioid receptor agonist-antagonist used mainly for postoperative pain. However, most studies used a single dose of nalbuphine in gynecological surgery, and few studies reported the dose effects of nalbuphine on patients after laparoscopic oophorocystectomy. In the present research, we conducted a randomized controlled study to investigate whether the application of nalbuphine combined with dexmedetomidine could reduce patient postoperative pain and provide sedative effects as well as improve patient inflammation response in a dose-dependent manner. We further evaluated whether high-dose nalbuphine (1.5 mg/kg) combined with dexmedetomidine (4 μg/kg) could facilitate patient recovery.

The application of nalbuphine has been reported in postoperative treatment in many surgeries. In a recent study, Wen et al demonstrated that the preoperative intramuscular injection of nalbuphine could reduce postoperative pain and improve postoperative comfort of postherpetic neuralgia in patients after trigeminal ganglion pulse radiofrequency surgery [15]. In another study, Kim et al showed that nalbuphine could be used in postoperative treatment after robot-assisted minimally invasive pancreaticoduodenectomy [16]. In a meta-analysis,

### Discussion

| Table 3. Ramsay scores within 48 h after surgery in all patients. |
| --- |
| Variables | LND, n=55 | MND, n=54 | HND, n=55 | Control, n=55 | \( P \) value |
| Ramsay at 2 h | 1.89±0.49\(^a\) | 1.96±0.43\(^d\) | 2.20±0.45\(^abd\) | 1.74±0.51\(^c\) | <0.001 |
| Ramsay at 8 h | 1.80±0.48\(^b\) | 1.87±0.39 \(^c\) | 2.12±0.39\(^abd\) | 1.69±0.50\(^d\) | <0.001 |
| Ramsay at 24 h | 1.78±0.45\(^a\) | 1.87±0.39 \(^d\) | 2.11±0.37\(^abd\) | 1.67±0.47\(^c\) | <0.001 |
| Ramsay at 48 h | 1.75±0.42\(^d\) | 1.85±0.35 | 2.00±0.19\(^abd\) | 1.67±0.47\(^d\) | <0.001 |

\( a \) P<0.05 vs LND group; \( b \) P<0.05 vs MND group; \( c \) P<0.05 vs HND group; \( d \) P<0.05 vs Control group. LND – low-dose nalbuphine and dexmedetomidine; MDN – middle-dose nalbuphine and dexmedetomidine; HND – high-dose nalbuphine and dexmedetomidine.

| Table 4. Serum levels of IL-1\(\beta\) and IL-6 before and after surgery in different groups of patients (pg/mL). |
| --- |
| Variables | LND, n=55 | MND, n=54 | HND, n=55 | Control, n=55 | \( P \) value |
| IL-1\(\beta\), before | 5.38±2.53 | 5.81±2.87 | 5.23±2.85 | 5.87±2.51 | 0.526 |
| IL-1\(\beta\), after | 31.13±9.00\(^c\) | 26.72±6.53\(^d\) | 20.22±5.71\(^abd\) | 40.19±12.47\(^abc\) | <0.001 |
| IL-6, before | 5.24±2.44 | 5.83±2.46 | 5.71±2.74 | 5.50±2.53 | 0.637 |
| IL-6, after | 34.80±12.44\(^c\) | 30.87±9.02\(^d\) | 21.91±6.99\(^abd\) | 43.77±12.96\(^abc\) | <0.001 |

\( a \) P<0.05 vs LND group; \( b \) P<0.05 vs MND group; \( c \) P<0.05 vs HND group; \( d \) P<0.05 vs Control group. IL-1\(\beta\) – interleukin-1\(\beta\); IL-6 – interleukin-6; LND – low-dose nalbuphine and dexmedetomidine; MDN – middle-dose nalbuphine and dexmedetomidine; HND – high-dose nalbuphine and dexmedetomidine.

| Table 5. Hospitalization time and complications in all patients. |
| --- |
| Variables | LND, n=55 | MND, n=54 | HND, n=55 | Control, n=55 | \( P \) value |
| Hospitalization, days | 6.20±1.41\(^c\) | 6.05±1.54\(^d\) | 4.33±1.14\(^abd\) | 6.94±1.40\(^abc\) | <0.001 |
| Complications, n (%) |  |  |  |  | 0.650 |
| Nausea and vomiting | 3 (5.45) | 2 (3.70) | 2 (3.70) | 3 (5.45) |  |
| Dizziness and headache | 1 (1.82) | 1 (1.82) | 1 (1.82) | 2 (3.70) |  |
| Fidgety | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) |  |
| Skin itch | 1 (1.82) | 0 (0.00) | 1 (1.82) | 0 (0.00) |  |

\( a \) P<0.05 vs LND group; \( b \) P<0.05 vs MND group; \( c \) P<0.05 vs HND group; \( d \) P<0.05 vs Control group. LND – low-dose nalbuphine and dexmedetomidine; MDN – middle-dose nalbuphine and dexmedetomidine; HND – high-dose nalbuphine and dexmedetomidine.

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Zeng et al showed that nalbuphine has similar effects to morphine; however, nalbuphine is safer than morphine and has fewer adverse effects, especially for pruritus and respiratory depression [17]. It was also reported that nalbuphine could be used in an epidural block in orthopedic surgery [18]. However, the application of nalbuphine in laparoscopic oophorocystectomy has been rarely reported. In the present research, we found that the use of nalbuphine could improve patient pain and sedative conditions after laparoscopic oophorocystectomy.

The combination of nalbuphine and dexmedetomidine, a kind of α2-adrenergic receptor agonist, as well as the comparison between nalbuphine and dexmedetomidine has been reported in several studies. Jiang et al found that nalbuphine showed better adjuvant effects in a supravclavicular brachial plexus block than did dexmedetomidine [19]. Lakshmi et al demonstrated that both dexmedetomidine and nalbuphine were effective in postoperative treatment of lower-limb orthopedic surgeries and found that dexmedetomidine was better in onset and sedation and postoperative analgesia control [20]. In a recent study, Kamar et al demonstrated that the combination of nalbuphine and dexmedetomidine could enhance the efficacy of the analgesic and sedative functions of nalbuphine as well as reduce its consumption in laparoscopic cholecystectomy [21]. In another study, it was found that the combination of nalbuphine and dexmedetomidine showed similar effects to the combination of butorphanol and dexmedetomidine in postoperative treatment [22]. Several studies also reported that nalbuphine or dexmedetomidine improved the inflammatory response. It was found that dexmedetomidine decreased the levels of IL-1β and TNF-α in patients with senility [23].

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Nalbuphine was also found to reduce the levels of inflammatory cytokines (IL-6, TNF-α, IL-1, and hs-CRP) after fracture surgery [24]. However, the effects of nalbuphine on inflammatory factors in gynecological surgeries have been rarely reported. In the present study, we found that patients receiving nalbuphine and dexmedetomidine showed better pain and sedative management as well as reduced levels of inflammatory factors. We also found that nalbuphine (1.5 mg/kg) combined with dexmedetomidine (4 μg/kg) can facilitate patient recovery.

Conclusions

The present study showed that the combination of nalbuphine and dexmedetomidine improved postoperative pain and sedative conditions, reduced inflammation in a nalbuphine dose-dependent manner, and may have facilitated patient recovery, but did not reduce the rate of postoperative complications. This research might provide an additional clinical basis for the combination of nalbuphine and dexmedetomidine in postoperative treatment after laparoscopic oophorocystectomy.

Ethics Statement

The research protocol was reviewed and approved by the Ethics Committee and Institutional Review Board of the Second Hospital of Anhui Medical University.

Conflicts of Interest

None.

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