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Research article

Sufentanil combined with nalmefene reduce the adverse events in recovery period of patients undergoing uvulopalatopharyngoplasty – A randomized controlled trial

Jin Wang [a,1], Kang Zheng [b,1], Quan Wen [a], Jie Sun [a,*]

[a] Department of Anesthesiology, Zhongda Hospital, Southeast University, Nanjing 210009, China
[b] Department of Anesthesiology, Nanjing Pukou District Hospital of Chinese Medicine, Nanjing 210000, China

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ABSTRACT

Background: The opioid receptors related to analgesia are mainly μ recipient, the μ receptor has a two-way mode of action: manifested by opioid analgesics and μ1 Receptor binding produces the desired analgesic effect, and μ2 Receptor binding may cause respiratory depression, nausea and vomiting and other adverse reactions. Nalmefene is an opioid receptor antagonist. Low dose Nalmefene has priority over μ2 Receptor binding makes opioid analgesics turn more to μ1 receptor binding, which is reversed μ2 Receptor mediated nausea, vomiting, respiratory depression and other adverse reactions, but does not reverse the analgesic effect. We assume that sufentanil combined with nalmefene could reduce respiratory adverse events in the patients who underwent uvulopalatopharyngoplasty during recovery.

Methods: Patients with UPPP under general anesthesia were selected, and divided into control group (group C) and nalmefene group (group N) randomly. Patients in group N received sufentanil 0.1 μg/kg and nalmefene hydrochloride 0.25μg/kg at the end of the operation. Additionally, patients in group C received sufentanil 0.1 μg/kg at the end of the operation. The heart rate (HR) and mean arterial pressure (MAP) were observed and recorded before operation, immediately after extubation, and 5 min after extubation. The breathing recovery time, tracheal extubation time, consciousness score (Ramsay score、sedation-agitation scale (SAS)) and visual analog score (VAS) were carefully recorded at 5 min after extubation, and the various adverse reactions were monitored during the recovery period.

Results: Ninety-six patients were finished our study finally. The breathing recovery and extubation time of group N was significantly shorter than those of group C ($P < 0.05$). The Ramsay score after extubation in group N was significantly lower as compared to that in group C ($P < 0.05$). The sedation-agitation scale of group N was observed to be significantly higher than that of group C ($P < 0.05$). Moreover, the incidences of respiratory depression, nausea and vomiting during the recovery period was significantly less than those in group C ($P < 0.05$).

Conclusion: Nalmefene combined with sufentanil can significantly reduce adverse reactions in the cases of patients after UPPP, which may be beneficial to improve the quality and safety of emergence after general anesthesia.

* Corresponding author.
E-mail address: dgsunjie@hotmail.com (J. Sun).
[1] Denotes the authors make equal contributions to the study

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1. Introduction

Uvulopalatopharyngoplasty (UPPP) remains the main clinical treatment for obstructive sleep apnea syndrome (OSAS). The anatomical structure of OSAS patients has been reported to be special and characterized by pharyngeal stenosis, short neck, mandibular retraction, giant tongue etc. [1]. During the recovery period, the administration of analgesic drugs could lead to tongue fallback, cause respiratory depression, and resulting in hypoxia [2]. However, insufficient analgesics may lead to significant pain and agitation during the recovery period, thereby causing bleeding, hemodynamic instability, stress responses during this stage, and thus promoting upper respiratory tract obstruction or aspiration. Therefore, for OSAS patients in recovery period, it is difficult for anesthesiologists to give enough analgesics to avoid pain and agitation, so as to reduce the risk of surgical field bleeding, upper respiratory tract obstruction and aspiration. At the same time, it is also necessary to avoid respiratory depression caused by relatively excessive analgesics. Nalmefene is a highly selective and specific opioid receptor antagonist that has been used clinically in many years [3, 4].

Some researches have reported that low-dose nalmefene can reduce the adverse effects of opioids without significantly affecting opioid analgesic effects [5, 6]. In this study, low-dose nalmefene combined with sufentanil was used at the end of surgery prior to patients emergence to observe their potential analgesic and sedative effects as well as various opioids adverse reactions. The findings could provide a basis for a clinical rational for the combination use of these drugs.

2. Material and methods

2.1. Participants

Male patients, ASA grade I-II and 18–65 years old, undergoing UPPP in the Zhongda Hospital Affiliated to Southeast University from April 2021 to October 2021 were enrolled in this study. The signed informed consent before surgery was obtained from all the subjects and the study was approved by the Ethics committee of Zhongda Hospital affiliated to Southeast University (2021ZDSYLL057-P01). The exclusion criteria were as follows: ① History of opioid usage or allergy or abuse; ② Patients with abnormal liver and kidney function (alanine aminotransferase >100 u/L, aspartate aminotransferase >100 u/L, creatinine >100 μmol/L); ③ Patients with hematological diseases or other hemorrhagic diseases; ④ Patients with a history of chronic obstructive pulmonary disease or severe asthma (need daily drug control or attack in the last month); ⑤ Patients with myasthenia gravis or other neuromuscular diseases; ⑥ Patients who cannot express postoperative pain and cannot understand visual analog score (VAS). The 120 patients were enrolled in this study.

2.2. Randomization and preparation of trial medication

A computer-generated randomization list was used to randomize consented study participants on a 1:1 ratio to two groups:

(1) Group C (control): Patients received sufentanil 0.1 μg/kg at the end of the operation.
(2) Group N: Patients received sufentanil 0.1 μg/kg and nalmefene hydrochloride 0.25 μg/kg at the end of the operation.

The study medication were prepared by a nurse who did not know the purpose of the study. Both groups of drugs were prepared into 5 ml colorless liquid at half an hour before the end of the operation. The patients, surgeons, and research staff who enrolled participants and collected study data were blinded to the group assignments.

2.3. Anesthesia and recovery

The patients were informed about the possible significance of VAS score at the preoperative visit. After the patient was transferred to the operation room, the peripheral vein was established and received monitoring of non-invasive blood pressure, ECG, and SpO2. Aneshesia induction was performed as follows: Midazolam 0.04–0.06 mg/kg, sufentanil 0.4–0.6 μg/kg, propofol 2–3 mg/kg and atracurium cisbesilate 0.15–0.2 mg/kg. After muscle relaxation, tracheal intubation was performed through the nose, and mechanical ventilation was connected to an anesthesia machine. Tidal volume was set 6–8 ml/kg according ideal body weight and the respiratory rate was set to maintain partial pressure of end tidal carbon dioxide (PETCO2) at 35–45mmHg. Thereafter, propofol, remifentanil, and atracurium cissylate were infused continuously to maintain anesthesia depth (bispect ral index (BIS) at 40–60). Moreover, about 30 min before the end of the operation, the muscle relaxant administration was discontinued. At the end of the operation, all the intravenous anesthetics were stopped and neostigmine 1 mg and atropine 0.5 mg were given intravenously to antagonize the effect of residual muscle relaxation. At the end of the operation, Patients in group N received sufentanil 0.1 μg/kg and nalmefene hydrochloride 0.25 μg/kg. Patients in group C received sufentanil at a dose of 0.1 μg/kg at the end of the operation. After transferring the patients to the post anesthesia care unit (PACU), ventilator was connected with 40% oxygen in synchronized intermittent mandatory ventilation (SIMV) mode until spontaneous breathing resumed, with satisfactory tidal volume, TOFr(train of four stimulation)≥90%, clear consciousness, and exhaustive passage of airway and oral secretions. In addition, any incidence of active bleeding in the patient's oral cavity was carefully observed before extubation, and after confirming that the airway was completely unobstructed, the patient was extubated with a head-up trachea. Thereafter patients were observed for 1 h after extubation and then returned to the ward. The observation, treatment and recording in PACU were in charged of another doctor who is blind to the study protocol.

2.4. Observation data

The patient's breathing recovery time (from the end of surgery to spontaneous breathing), extubation time (from the end of surgery to extraction), HR and MAP before surgery (T0), immediately after extubation (T1), and 5 min after extubation (T2) were carefully recorded. The incidence of adverse reactions including respiratory depression, nausea, vomiting, and restlessness during emergence period were recorded till 1 h after extubation. The VAS score was observed and recorded with (0 is no pain, and 10 is severe pain) along with Ramsay score and sedation-agitation scale (SAS) at 5 min (T2) after extubation. The scoring criteria for Ramsay score was as follows: 1 point indicates irritability; 2 points indicates awake, quiet, and cooperative; 3 points indicates lethargy, quick response to commands; 4 points indicates light sleep, awakening; 5 points indicates falling asleep, slow response to calls; 6 points means deep sleep, and no response to calls. The scoring criteria for SAS was as follows: 1 point indicates unable to wake up, no or only slight response to malignant stimulation, unable to communicate and obey instructions; 2 points indicates very sedative. Respond to physical stimulation, unable to communicate and obey instructions, have autonomous movement; 3 points indicates sedative drowsiness, verbal stimulation or gentle shaking can wake up and obey simple instructions, but fall asleep quickly; 4 points indicates quiet cooperation, quiet, easy to wake up, obey instructions; 5 points indicates restlessness, anxiety or physical restlessness can be quiet after verbal prompt and persuasion; 6 points means very restless, need protective restraint and repeated language prompts to dissuade, bite endotracheal intubation; 7 points means dangerous agitation, trying to pull out various catheters, climbing over the bed fence, attacking medical staff, tossing and struggling in bed. Additionally, no oxygen was administered after extubation and percutaneous arterial oxygen saturation (SPO2) $< 92\%$ was considered as respiratory depression.

2.5. Statistical analysis

Statistical analysis was performed using SPSS26.0 statistical software. The various data measured such as respiratory recovery time, extubation time, HR, MAP, the ramsay score, SAS, VAS scores were expressed as mean $\pm$ standard deviation, and normality test was performed before data analysis. An independent sample *t*-test was used for distribution analysis. The adverse reaction rate of the respiratory depression was examined by continuous correction chi-square test, and the adverse reaction rate of nausea and vomiting was determined by Pearson chi-square test. P value < 0.05 indicates that the difference was statistically significant.

Sample size calculation: In a previous study [7], the incidence of the adverse events on the recovery period of patients with OSAS after operation was more than 30%. We expected a greater than 15% point decrease in postoperative pulmonary complications in nalmefene group. To obtain a two-sided alpha error of 5% and beta error of 80% power, the minimal size in each group was 55,110 patients were required for this research to compensate for 20% withdrawals and dropouts, and to obtain additional safety data [8].

3. Results

One hundred twenty patients were assessed for eligibility, and 110 patients were enrolled into the study after exclusion. 14 patients

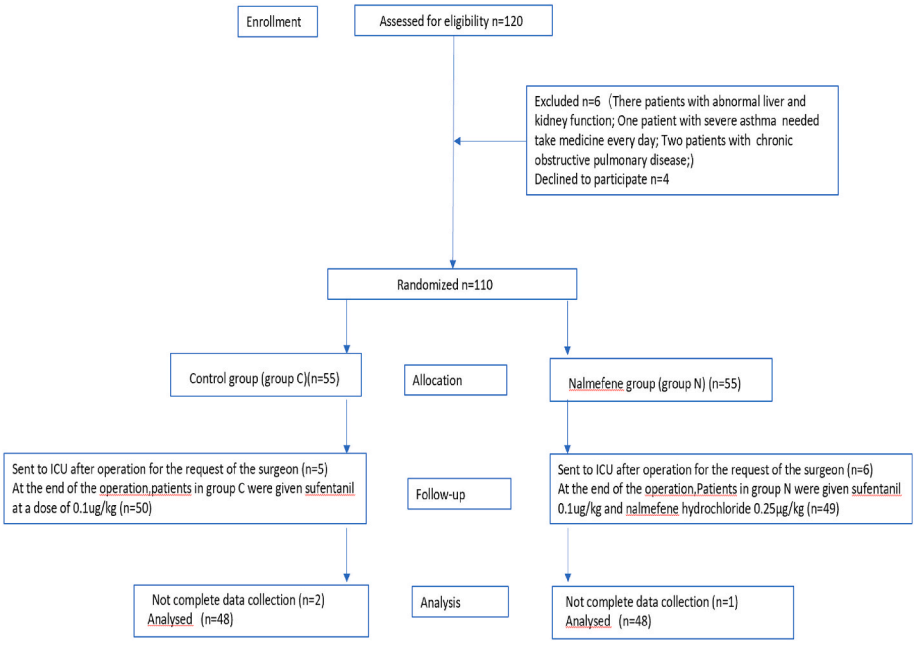

Fig. 1. Patient enrollment and inclusion and exclusion process. One hundred twenty patients were assessed for eligibility, and 110 patients were enrolled into the study after exclusion. 14 patients withdrew from the study.

withdrew from the study. The reasons for withdrawal were as follows: in group C, 5 cases were sent to ICU with endotracheal tube to the surgeon's request, and 2 cases were excluded due to incomplete records; In group N, 6 patients were sent to ICU with endotracheal tube after surgery, and 1 case was excluded due to incomplete records (Fig. 1). There were no significant differences in age, ASA (American Society of Anesthesiologists), body weight, BMI(body mass index),comorbidities including hypertension, diabetes melitus and operation time between the two different groups of patients, and they were observed to be comparable ($P > 0.05$) (Table 1).

There was no significant difference in MAP and HR between the two different groups of patients before surgery, immediately after extubation, and 5 min after extubation period ($P > 0.05$) (Table 2).

The breathing recovery time and extubation time of patients in group N was found to be significantly shorter than those in group C ($P < 0.05$), (Table 3).

The Ramsay score of group N was observed to be significantly lower than that of group C ($P < 0.05$). The sedation-agitation scale of group N was observed to be significantly higher than that of group C ($P < 0.05$). There was no significant differences in VAS scores between the two groups ($P > 0.05$). The symptoms of respiratory depression, nausea and vomiting in group N were significantly lower than those in group C ($P < 0.05$). There were no significant differences in the agitation rate between the two groups analyzed ($P > 0.05$), (Table 4).

4. Discussion

The UPPP surgical site is largely sensitive, therefore the patients can suffer from postoperative abnormal foreign body sensation, which can cause dysphagia and respiratory discomfort. It can also potentially lead to the release of significant amount of inflammatory mediators and algogenic substances, which can substantially increase the sensitivity of nonciceptive receptors, thus decreasing the pain threshold, and hence generating severe postoperative pain [9]. Postoperative pain and agitation can cause surgical field bleed, and lead to the development of upper respiratory tract edema and even upper respiratory tract obstructions or aspirations, which may promote serious cardiopulmonary complications [10]. Therefore, OASA patients often need timely and adequate analgesia after UPPP. Opioids are commonly used drugs for postoperative analgesia and for the prevention of extubation agitation. Sufentanil is a synthetic and potent opioid analgesic, which has affinity for μ receptors up to 6–10 times greater that of fentanyl [11]. A number of clinical studies have found that sufentanil can display a significant analgesic effects and high safety profile, but there are also common adverse reactions associated with the administration of opioids such as nausea, vomiting and respiratory depression [12, 13]. Opioids can directly inhibit the respiratory center, and therefore can interfere with the respiratory rate, increase the apnea threshold, and substantially inhibit the muscular activity of the upper respiratory tract. In general, OSAS patients have been found to be very sensitive to analgesics, and are often also display other medical conditions such as obesity, short neck, narrow pharyngeal cavity, and tongue hypertrophy. During the recovery period, they are also prone to fall back and experience apnea due to the prolonged use of analgesics [14]. In addition, OSAS patients can also have long-term hypoxia and hypercapnia, their central nervous system may be less sensitive to carbon dioxide, and a significantly higher incidences of respiratory depression have been observed in these patients during the recovery period [15].

Nalmefene is a long-acting opioid receptor antagonist, which can produce receptor antagonism after 2 min of intravenous injection, and can block 80% of brain opioid receptors within 5 min. The elimination half-life of this drug has been reported to be 8.2–8.9 h. Nalmefene has gradually replaced the traditional drug naloxone as it can display high bioavailability, longer duration of action, better efficiency and low toxicity. It has also been widely used clinically such as during anesthesia, anti-shock, and in treating alcoholism, brain damage, spinal cord injuries, gastrointestinal dysfunctions, etc. [16]. A number of studies have indicated that [17] The opioid receptors related to analgesia are mainly μ recipient, μ The receptor has a two-way mode of action: manifested as opioid analgesics and μ 1 receptor binding, through inhibitory G protein (Gi/Go), to produce the required analgesic effect; Opioid analgesics and μ2 Receptor binding leads to respiratory depression, nausea, vomiting and other adverse reactions through excitatory G proteins (Gs). Namefene is an opioid receptor antagonist. The priority of low-dose nalmefene is μ2 Receptor binding causes more diversion of opioid analgesics μ 1 receptor binding, which can be reversed μ2 Receptor mediated nausea, vomiting, respiratory depression and other adverse reactions, but could not reverse the analgesic effect. For instance, small doses of opioid receptor blockers can specifically block the various adverse reactions associated with opioids mediated by Gs protein without significantly affecting the analgesic effects mediated by Gi/Go protein. For instance, Class et al. highlighted that when the intravenous dosage of nalmefene is 0.1–1μg/kg was used, it was

Table 1
General information of the two groups of patients.

Groups	Group C n = 48	Group N = 48	P
Age (year)	45.1 ± 7.0	44.2 ± 8.3	0.576
ASA score (I/II)	18/30	16/32	0.831
Weight (kg)	93.0 ± 9.7	95.0 ± 8.1	0.286
BMI(kg/m^2)	31 ± 3.5	31.9 ± 3.1	0.459
Operation time (min)	121.4 ± 8.6	124.2 ± 7.0	0.084
Comorbidities			
Hypertension	24 (50%)	26 (54.2%)	0.838
Diabetes melitus	18 (37.5%)	17 (35.4%)	1.0

Data were expressed as mean ± SD and n (%). There were no significant differences between groups. ASA indicates American Society of Anesthesiologists; BMI indicates body mass index.

Table 2
MAP, HR at each time point of the two different groups of patients.

Groups		Group C n = 48	Group N = 48	P
T0	MAP (mmHg)	100.0 ± 9.5	98.9 ± 13.0	0.630
	HR (Times/min)	67.8 ± 7.2	70.2 ± 10.2	0.185
T	MAP (mmHg)	111.7 ± 9.7	114.2 ± 8.6	0.180
	HR (Times/min)	91.8 ± 8.7	95.0 ± 9.0	0.073
T2	MAP (mmHg)	97.6 ± 11.2	98.5 ± 10.7	0.696
	HR (Times/min)	75.4 ± 11.2	72.3 ± 10.6	0.161

Data are expressed as the mean ± SD for numbers. There were no significant differences between groups.MAP:Mean artery pressure.HR:Heart rate.

Table 3
Respiratory recovery time and extubation time of the two groups of patients.

Groups	Group C n = 48	Group N = 48	P
Respiration recovery time (s)	10.9 ± 2.6	6.2 ± 1.5*	<0.001
Extubation time (s)	23.2 ± 6.4	15.4 ± 3.9*	<0.001

Data are expressed as the mean ± SD for numbers. *p < 0.05 compared to the control group.

Table 4
Comparison of Ramsay score, SAS, VAS score and adverse reactions between the two groups of patients.

Groups	Group C n = 48	Group N = 48	P
Respiratory depression	8 (16.7%)	1 (2.1%)*	0.036
sick and vomit	14 (29.2%)	5 (10.4%)*	0.039
Restlessness	0 (0%)	2 (4.2%)	0.475
SAS	3.1 ± 0.3	4 ± 0.4*	<0.001
Ramsay score	3.2 ± 0.7	2.3 ± 0.7*	<0.001
VAS	2.4 ± 1.0	2.7 ± 0.9	0.129

Data were expressed as mean ± SD and n (%).*p < 0.05 compared to the control group. VAS indicates visual analog score; SAS indicates sedation-agitation scale.

found to effectively reverse the respiratory depression and other adverse effects caused by opioid analgesics after surgery. It can also effectively antagonize respiratory depression up to 8 h or longer without compromising their potential analgesic effects [18].

The results of our study showed that after patients received nalmefene, the spontaneous breathing recovery time and extubation time were reduced significantly compared with the control group. The incidence of postoperative respiratory depression as well as nausea and vomiting in the experimental group were significantly lower when compared with the control group, and there were no significant differences in agitation, VAS scores, SAS, blood pressure, and heart rate during the recovery period. The above results showed that this dose of nalmefene (0.25 μg/kg) can be beneficial for anesthesia recovery, and can significantly reduce the adverse reactions of sufentanil without affecting its potential analgesic effects and hemodynamic effects. In the control group, deep sedation (Ramsay score 3.2 ± 0.7 and sedation-agitation scale 3.1 ± 0.3) after extubation resulted in a significant inhibitory effect on the respiratory rate and depth. The Ramsay sedation score after was significantly lower in nalmefene group than that of the control group, and the respiratory depression was also observed to be significantly reduced. It has been suggested that nalmefene can reduce the respiratory depression caused by sufentanil, which is possibly related to its anti-sedative effect. A number of previous studies have also shown [19] that nalmefene can safely and effectively antagonize opioid-induced sedation and significantly improve the state of consciousness score. For OSAS patients, enough sedation and analgesia without respiratory depression is extremely important during the emergence period [20].

This clinical trial also has two major shortcomings. First, only a single dose of nalmefene was used, and other alternative doses were not tested. Second, only the recovery period of patients was observed, but the clinical effect period of nalmefene was considerably longer, and the possible adverse reactions associated with the use of nalmefene could not be neglected and should be studied in the future research.

5. Conclusion

In summary, the potential application of nalmefene hydrochloride combined with sufentanil after UPPP in OSAS patients can significantly shorten the extubation and recovery time and the recovery process was found to be more stable. The respiratory depression was significantly reduced with fewer adverse effects. Moreover, it can effectively improve the quality of anesthesia recovery and thus may be useful for widespread clinical applications.

Declaration

Ethics approval and consent to participate

This research was approved by Ethics committee of Zhongda Hospital affiliated to Southeast University (2021ZDSYLL057-P01). This research was conducted in accordance with the Declaration of Helsinki. Each subject signed an informed consent form.

Declaration of interests

The authors declared that they had no competing financial interests or personal relationships that would influence the work reported in this paper.

Authors' Contributions

Jin Wang: conceived and designed the experiments; performed the experiments; analyzed and interpreted the data; wrote the paper. Kang Zheng: performed the experiments. Quan Wen:analyzed and interpreted the data. Jie Sun: contributed reagents, materials, analysis tools or data; conceived and designed the experiments.

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