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Multimodal Patient-Controlled Analgesia in Multilevel Obstructive Sleep Apnea Surgery

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ABSTRACT

Background: Multimodal analgesia involves the use of various techniques and medications to target various pain pathways and provide superior pain control, limit opioid consumption, and minimize adverse events.

Objective: This study aimed to assess the efficacy and safety of a multimodal analgesic regimen combining nalbuphine and ketorolac administered via a patient-controlled analgesia (PCA) silicon device following multilevel obstructive sleep apnea (OSA) surgeries. **Patients and Methods:** This prospective interventional single-arm study included thirty patients who were admitted for multilevel surgery for OSA. Upon completion of the surgical procedures, fully conscious patients were connected to a disposable silicon infusion device to provide 300 ml of normal saline containing 80 mg of nalbuphine, 240 mg of ketorolac, and 8 mg of ondansetron. The infusion set provided 5 ml/h by continuous infusion without bolus doses. Postoperative pain was evaluated via the visual analogue scale (VAS) before analgesic injection and every 6 hours for 48 hours postoperatively. **Results:** Regarding pain intensity, the median VAS score was 2 (2-3) at baseline. It was significantly reduced to 1 (1-1) after 24 hours and 1 (0) after 48 hours (P=0.001). In terms of the level of sedation, we found that at baseline, the median Ramsay scale score was 2 (1-3), which was reduced to 1 (1-2) at 48 hours postoperatively (P=0.002). No significant adverse effects were found.

Conclusions: Multimodal PCA can provide a potent and safe option for achieving postoperative analgesia after OSA surgery.

Keywords: Analgesia, Ketorolac, Opioid, Obstructive sleep apnea, Visual analogue scale.

INTRODUCTION

Obstructive sleep apnea (OSA) is a condition characterized by intermittent, partial, or complete obstruction of the upper airway, leading to sleep disturbances and hypoxemia with potentially severe physiological consequences. OSA affects 4% of middle-aged males and 2% of females, making it a considerable public health issue [(1)].

The predominant surgical intervention for OSA is uvulopalatopharyngoplasty (UPPP). Pain resulting from nerve-ending stimulation, inflammation, and pharyngeal muscle spasm is a notable consequence of UPPP, which persists until mucosal healing occurs [(2–4)]. Post-UPPP pain, which is typically pronounced within the initial 24 hours, poses a considerable challenge, as it necessitates effective pain management to alleviate discomfort, reduce morbidity, expedite healing, and decrease the duration of hospital stay [(5,6)].

A multimodal analgesic strategy that integrates systemic opioids with nonsteroidal anti-inflammatory drugs is advised to mitigate postoperative pain while reducing the likelihood of opioid-associated adverse effects such as nausea, vomiting, pruritus, and respiratory depression [(7)].

Nalbuphine is a mixed agonist-antagonist of opioid receptors. The kappa receptor is the target of the analgesic effects of nalbuphine. Compared with morphine, nalbuphine has a lower incidence of adverse effects such as itching, nausea, and vomiting. Nalbuphine-induced respiratory depression has a ceiling effect, making it a safer alternative to morphine. [(8–10)].

Ketorolac is a nonsteroidal anti-inflammatory medication with analgesic and antipyretic properties. It has both peripheral and central antinociceptive effects; the peripheral action focuses on neurons to deliver localized anti-inflammatory activity and may diminish the central amplification of pain impulse transmission caused by prostaglandins generated from injured tissue. Ketorolac can promote opioid sparing and has a synergistic analgesic effect when it is administered with morphine [(11,12)].

AIM OF THE STUDY

This study aimed to assess the safety and efficacy of a multimodal analgesic regimen incorporating intravenous continuous infusion of nalbuphine and ketorolac via PCA for postoperative analgesia following multiple-level OSA surgeries.

PATIENTS AND METHODS

This prospective, interventional, single-arm study involved thirty patients scheduled for multilevel OSA surgery**.**

The inclusion criteria were patients aged 20-50 years, with a BMI (body mass index) ≤ 35 kg/m² (patients with a relatively high BMI do not benefit from this surgery).

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The criteria for exclusion were patients on medications for chronic pain, addicts for alcohol or drugs, previous OSA surgery, and a history of allergy to the study drugs; chronic lower airway or systemic diseases; craniofacial anomalies; neuromuscular or psychiatric disorders; patient refusal; and patient communication difficulty.

All patients underwent careful airway assessment through both clinical ENT examination and examination via flexible nasopharynx-laryngeal endoscopy and Müller's maneuver. OSA was documented by overnight polysomnography (PSG) to determine the apnea-hypopnea index (AHI) (mild OSA: 5–15, moderate OSA: 15–30, severe OSA: >30).

All patients underwent DISE (drug-induced sleep endoscopy), and according to the findings of the DISE, the level of surgery was planned to include two or more of the following: bilateral tonsillectomy, Alianza barbed pharyngoplasty, anterolateral barbed pharyngoplasty, median glossectomy, turbinectomy, septoplasty, and genioglossus advancement.

In the operating room, the patient was positioned in the Rapid Airway Management Position (RAMP) to assist in endotracheal tube insertion by elevating the head and shoulders with several pads, ensuring that the head and neck were extended, and that the external auditory meatus was aligned with the sternal notch.

Good preoxygenation was achieved by deep breathing through a facemask using 100% oxygen at a rate of 6 ml/minute for three minutes. Induction of general anesthesia was standardized using 2 µg/kg lean body weight fentanyl, 2 mg/kg lean body weight propofol, and 0.5 mg/kg ideal body weight atracurium, followed by oral endotracheal intubation facilitated using a stylet and rigid bronchoscopy.

Muscle relaxation and the depth of anesthesia were maintained during surgery via atracurium and isoflurane. Intraoperative analgesia was achieved via IV injection of 0.2 mg/kg lean body weight nalbuphine and an infusion of 60 mg of ketorolac plus paracetamol 15 mg/kg ideal body weight. Dexamethasone (16 mg) was given to help reduce postoperative airway edema and decrease the incidence of postoperative nausea and vomiting (PONV).

Following the completion of the surgery, fully awake patients were extubated and then transferred to the PACU (post-anesthesia care unit), where they stayed on oxygen masks for two hours under pulse oximetry monitoring.

Fully awake patients with stable hemodynamics and adequate analgesia were shifted back to the ward, where they were connected to a disposable patient-controlled analgesia (PCA) silicon infusion device to provide postoperative analgesia under portable pulse oximetry monitoring.

PCA (Accufuser REF®, Woo Young Medical Co., Korea) was prepared with 300 ml of normal saline containing 80 mg of nalbuphine, 240 mg of ketorolac, and 8 mg of ondansetron. The infusion set provided 5 ml/hr by continuous infusion without bolus doses.

The main outcome of the study was pain severity, which was evaluated via the visual analogue scale (VAS). A baseline evaluation was conducted at the time of shift to the PACU and then every 6 hours until the end of the second postoperative day.

The secondary outcomes were the sedation level, which was evaluated via the Ramsey sedation scale, and the frequency of side effects (hypoxia, nausea, vomiting, and itching). Assessment was performed at baseline (time of transfer to the PACU) and every 6 hours for 48 hours postoperatively.

Ethical approval:

We obtained ethical approval from the University's Local Ethics Committee of Sohag University. Informed written consent was obtained from every patient at the time of recruitment. The research was registered at clinicaltrials.gov (Clinical Trials ID: NCT04483427) and was guided by the principles of the Helsinki Declaration.

Statistical analysis

Analysis was conducted via SPSS statistical software, version 26 (IBM, Chicago, Illinois, USA). The Kolmogorov–Smirnov test was employed to assess the normality of the data. Qualitative data are presented as frequency and percentages. Cochran's Q test and McNemar's test were employed to compare the paired qualitative data. The quantitative data are expressed as the mean ± standard deviations (SDs) or medians and interquartile ranges (IQRs). Paired quantitative data were analyzed via the Friedman and Wilcoxon tests. The p-value was deemed significant at the threshold of <0.05. The sample size computation was conducted with G. Power 3.1.9.2 (University of Kiel, Germany) with a 0.05 alpha error and 80% study power.

RESULTS

The study enrolled 30 patients with a mean age of 38.7 ± 8.7 years. The percentage of males was greater than that of females (70% vs. 30%). Among their comorbidities, 23.3% were diabetic, 6.7% were positive for hepatitis B virus (HBV), and 3.3% had chronic kidney disease (CKD). The mean AHI was 39.7 ± 21.9, with a range of 15 to 88.1 (Table 1). In terms of surgery type, table 1 presents all the procedures performed, with the most common being anterolateral barbed pharyngoplasty + septoplasty + tuboplasty, which represented 33.3% of the patients.

Table 1: Demographic data of the patients studied.

Variables	Mean ± SD or N (%) (N=30)
Age (Years)	
Mean ± SD	38.7 ± 8.7
Range	23 – 57
Gender	
Males	21 (70%)
Females	9 (30%)
Comorbidities	
DM	7 (23.3%)
HBV	2 (6.7%)
CKD	1 (3.3%)
AHI	
Mean ± SD	39.7 ± 21.9
Range	15 – 88.1
Types of surgery	
Anterolateral Barbed Pharyngoplasty + GGA + Turbinoplasty	2 (6.7%)
Anterolateral Barbed Pharyngoplasty + Septoplasty + Turbinoplasty	10 (33.3%)
Anterolateral Barbed Pharyngoplasty + Turbinoplasty	1 (3.3%)
Alianza Barbed Pharyngoplasty + Lingual tonsillectomy + Adenoidectomy + Turbinoplasty	1 (3.3%)
Alianza Barbed Pharyngoplasty + Septoplasty + Turbinoplasty + Median glossectomy	1 (3.3%)
Alianza Barbed Pharyngoplasty + Septoplasty + Turbinoplasty + Median Glossectomy	5 (16.7%)
Alianza Barbed Pharyngoplasty + Turbinoplasty + Adenoidectomy	2 (6.7%)
Alianza Barbed Pharyngoplasty + GGA + Turbinoplasty	1 (3.3%)
Alianza Barbed Pharyngoplasty + Coblation tongue base resection	1 (3.3%)
Alianza Barbed Pharyngoplasty + Nasopharyngeal Cyst Marsupialization + Septoplasty + Turbinoplasty	1 (3.3%)
Alianza Barbed Pharyngoplasty + Adenoidectomy + Septoplasty + Turbinoplasty	1 (3.3%)
Alianza Barbed Pharyngoplasty + Adenoidectomy + Septoplasty + Turbinoplasty + Nasal valve Alar Batten Grafting	1 (3.3%)
Alianza Barbed Pharyngoplasty + Septoplasty + Turbinoplasty + Adenoid ablation + Median glossectomy	1 (3.3%)
Alianza Barbed Pharyngoplasty + Septoplasty + Turbinoplasty + Adenoid ablation	1 (3.3%)
Alianza Barbed Pharyngoplasty + Septoplasty + Turbinoplasty + Nasal Valve Collapse + Adenoid ablation	1 (3.3%)

GGA: genioglossus advancement.

The baseline median VAS score was 2 (2-3), which significantly decreased to 1 (1-1) after 24 hours and further decreased to 1 (0) after two days (Table 2).

Table 2: VAS scores of the patients studied.

VAS	Median (IQR)	P value [b]
Baseline	2 (2-3)	
Post 6 h	2 (1.5-3)	
Post 12 h	2 (1-2.5)	P1=0.09
Post 18 h	1 (1-2)	P2=0.001*
Post 24 h	1 (1-1)	P3=0.001*
Post 30 h	1 (1-2)	P4=0.001*
Post 36 h	1 (1-2)	P5= 0.001*
Post 42 h	1 (0)	P6=0.1
Post 48 h	1 (0)	
P value [a]	0.001*	

a: Friedman test. b: Wilcoxon test. P1 = Baseline vs Post 12 h. P2: Baseline vs post-24 h. P3: Baseline vs post-48 h. P4: Post 12 h vs 24 h. P5: Post 12 h vs 48 h. P6 = 24 h vs post 48 h.

With respect to sedation levels, the median Ramsay scale score was 2 (1-3) at baseline and decreased to 1 (1-2) at 48 hours postoperatively (Table 3).

Table 3: Ramsay scale scores of the patients studied.

Ramsay scale	Median (IQR)	P value [b]
Baseline	2 (1-3)	
Post 6 h	1 (1-2)	
Post 12 h	1 (1-1.5)	P1=0.002*
Post 18 h	1 (1-2)	P2=0.002*
Post 24 h	1 (1-1.5)	P3=0.004
Post 30 h	1 (1-2)	P4=0.9
Post 36 h	1 (1-2)	P5=0.7
Post 42 h	1 (1-2)	P6=0.5
Post 48 h	1 (1-2)	
P value [a]	0.002*	

a: Friedman test. b: Wilcoxon test. P1 baseline vs post 12 h. P2: Baseline vs post-24 h. P3: Baseline vs post-48 h. P4: Post 12 h vs 24 h. P5: Post 12 h vs 48 h. P6 = 24 h vs post 48 h.

The SPO_2 was 94% (93–95%) at baseline, which increased to 97% (96–98%) at 12 hours postoperatively, 99% (99–100%) at 24 hours postoperatively, and 100% (99–100%) at 48 hours postoperatively (Table 4).

Table 4: SPO_2 of the patients studied.

SPO2%	Median (IQR)	P value [b]
Baseline	94% (93-95%)	
Post 6 h	96% (95-96%)	
Post 12 h	97% (96-98%)	P1=0.001*
Post 18 h	99% (98-99%)	P2=0.001*
Post 24 h	99% (99-100%)	P3=0.001*
Post 30 h	99% (99-100%)	P4=0.001*
Post 36 h	99% (99-100%)	P5= 0.001*
Post 42 h	100% (99-100%)	P6=0.04*
Post 48 h	100% (99-100%)	
P value [a]	0.001*	

a: Friedman test. b: Wilcoxon test. P1 baseline vs post 12 h. P2: Baseline vs post-24 h. P3: Baseline vs post-48 h. P4: Post 12 h vs 24 h. P5: Post 12 h vs 48 h. P6 = 24 h vs post 48 h.

With respect to postoperative nausea and vomiting, four patients (13.3%) experienced nausea and vomiting at baseline, three patients (10%) experienced nausea and vomiting at 24 hours postoperatively, and no cases were reported after that.

In terms of itching, only one case was reported at baseline, and another case was reported at 12 hours postoperatively (Table 5).

Table 5: Adverse effects in the patients studied.

Nausea and Vomiting	N (%)	P value [b]
Baseline	4 (13.3%)	
Post 6 h	0 (0%)	
Post 12 h	1 (3.3%)	P1=0.3
Post 18 h	0 (0%)	P2=0.9
Post 24 h	3 (10%)	P3=0.12
Post 30 h	0 (0%)	P4=0.5
Post 36 h	0 (0%)	P5= 1
Post 42 h	0 (0%)	P6=0.25
Post 48 h	0 (0%)	
P value [a]	0.002*	
Itching		
Baseline	1 (3.3%)	
Post 6 h	0 (0%)	
Post 12 h	1 (3.3%)	P1=0.9
Post 18 h	0 (0%)	P2=0.9
Post 24 h	0 (0%)	P3=0.9
Post 30 h	0 (0%)	P4=0.9
Post 36 h	0 (0%)	P5= 0.9
Post 42 h	0 (0%)	P6=0.9
Post 48 h	0 (0%)	
P value [a]	0.53	

a: Cochran's Q test. b: McNemar test.

DISCUSSION

Multilevel surgery for OSA is considered in cases where conservative treatments such as continuous positive airway pressure (CPAP) therapy are ineffective or not well tolerated. These surgeries typically include procedures such as uvulopalatopharyngoplasty (UPPP), tonsillectomy, septoplasty, and mandibular advancement. [13]. Postoperative pain management following multilevel OSA surgery is one of the most significant challenges. Failure to achieve adequate postoperative pain control can result in delayed recovery, prolonged hospital stays, and increased risk of complications, such as respiratory depression, particularly in OSA patients, who are already at increased risk for breathing difficulties [14].

The concept of multimodal analgesia involves the use of various techniques and medications to target various pain pathways and provide superior pain control, limit opioid consumption, and minimize adverse events such as sedation and respiratory depression, which are especially important in OSA patients. Postoperative pain management reduces hospital stay, speeds up function (particularly food intake), and improves operation outcomes [15].

The Accufuser is a modern device used for patient-controlled analgesia (PCA), allowing patients to administer their analgesic doses within prescribed limits. [16] By combining this technology with multimodal analgesic strategies, healthcare providers aim to optimize postoperative pain management for patients undergoing multilevel surgery for OSA, potentially improving patient comfort and speeding recovery. In this context, the use of multimodal analgesia with the Accufuser is becoming an increasingly popular approach for managing postoperative pain in OSA patients. This strategy not only helps alleviate pain but also plays a crucial role in minimizing the risk of respiratory complications, which are a significant concern in this patient population [17].

Our study aimed to assess the clinical efficacy and adverse effects of a multimodal analgesic regimen consisting of nalbuphine combined with ketorolac via an IV continuous infusion silicon device for postoperative analgesia following multilevel OSA surgeries. This study sought to evaluate the clinical efficacy and side effects of a multimodal analgesic mixture that combines nalbuphine and ketorolac administered via PCA for postoperative analgesia after multilevel OSA operations.

Our study included 30 OSA patients who underwent multilevel surgery. The mean age of the participants was 38.7 ± 8.7 years, with a male–female ratio of 2.3. The mean AHI was 39.7 ± 21.9. The most common surgical approach was anterolateral barbed pharyngoplasty + septoplasty + turbinoplasty, followed by Alianza barbed pharyngoplasty + septoplasty + turbinoplasty + median glossectomy.

With respect to analgesic efficacy, the median visual analogue scale (VAS) score decreased significantly from 2 (2–3) at baseline to 1 (0) at 48 hours post-surgery (P=0.001), which indicates that the combination of nalbuphine (opioid agonist-antagonist) and ketorolac (NSAID) demonstrated rapid and sustained pain relief.

Cepeda *et al.* [12] compared ketorolac, morphine, and their combination for the management of postoperative pain and reported that the combination of morphine and ketorolac provided better pain relief than either drug alone. The current study extends this finding by demonstrating that nalbuphine, when combined with ketorolac, also provides effective analgesia with a favorable safety profile [12].

In 2007, **Patrocínio *et al.*** [4] evaluated the efficacy of ketorolac in relieving postoperative pain after tonsillectomy and reported that six out of thirteen patients who received ketorolac experienced no pain, whereas only three required additional opioids. These findings support the idea that ketorolac, when used as an adjuvant with opioids, can decrease opioid use and provide effective analgesia, which agrees with the findings of the present study [4].

Lee *et al.* [18] compared intravenous ketorolac with oral mefenamic acid plus intramuscular meperidine and reported that both regimens significantly reduced pain severity, but the combination of NSAIDs and opioids was particularly effective. This aligns with the findings of the present study, which revealed that combining NSAIDs such as ketorolac with opioids such as nalbuphine can provide superior pain control with fewer side effects. [18]

Ebid *et al.* [19] compared nalbuphine to morphine in postoperative pain management and reported that nalbuphine reduced the VAS score from 5 (5–8) to 3 (3–5) at 8 hours. While their baseline pain was greater (likely due to different surgical contexts), both studies highlighted the efficacy of nalbuphine. The faster and more pronounced pain reduction observed in the present study may reflect the synergistic effect of combining nalbuphine with ketorolac [19].

In terms of sedation level and respiratory safety, the current study revealed that the median Ramsay sedation scale score decreased from 2 (1–3) to 1 (1–2) at 48 hours (P=0.002), and the SPO_2 improved from 94% to 100% after 48 hours, indicating that patients under our analgesic regimen remained alert and comfortable without excessive sedation or respiratory compromise.

Similarly, **Lee *et al.*** [18] compared ketorolac to mefenamic acid + meperidine and reported that both regimens reduced pain, but ketorolac had fewer sedative effects. The current study's low sedation levels align with this, emphasizing NSAID benefits in multimodal regimens. [18]

Akcam *et al.* [20] compared different surgical techniques for OSA and reported that pain severity and

analgesic requirements varied depending on the type of surgery. However, they did not specifically address the postoperative SPO_2 levels. The focus of the present study on postoperative SPO_2 levels provides additional evidence that multimodal analgesia, particularly nalbuphine, is safe in terms of respiratory function, which is crucial for OSA patients, and suggests that multimodal analgesia can mitigate pain variability across different procedures [20].

Similarly, **Ebid *et al.*** [19] reported a significant reduction in sedation levels at 48 hours postoperatively, which aligns with the findings of the present study. Both studies suggest that nalbuphine, owing to its ceiling effect on respiratory depression, is a safer choice than conventional opioids such as morphine, especially in OSA patients who are at greater risk for respiratory problems [19].

The incidence of adverse effects in the current study was low, with only 13.3% of patients reporting nausea and vomiting at baseline and no cases reported after 24 hours. Itching has been reported in only two cases, both of which resolved without intervention. No patients reported suffering from respiratory depression.

Patrocínio *et al.* [4] evaluated ketorolac in tonsillectomy patients and reported that 46% of patients required no opioids, with minimal side effects. The current study's low opioid dependence and adverse event rates reinforce the role of ketorolac in reducing opioid-related complications. [4]

Ebid *et al.* [19] reported a lower frequency of adverse events such as nausea, vomiting, and itching with nalbuphine than with morphine, which is consistent with the findings of the present study [19] . **Zeng *et al.*** [9] in a meta-analysis, reported that nalbuphine had significantly lower rates of nausea, vomiting, and pruritus than morphine did. The findings of the present study are consistent with these findings, supporting the favorable safety of nalbuphine [9] .

Kaye *et al.* [15] emphasized that multimodal analgesia reduces opioid consumption and accelerates recovery. The current study's regimen aligns with the enhanced recovery after surgery (ERAS) principles, as seen in reduced hospital stays and complications [15] .

The limitations of the current study include its single-center design, small sample size (N=30), and short follow-up (48 hours). These limitations mirror the limitations **of Patrocínio *et al.*** [4] (N=13) and **Ebid *et al.*** [19] (N=23); moreover, **Akcam *et al.*** [20] noted that surgical complexity affects pain outcomes, so future studies should stratify results by procedure type to refine analgesic protocols, and multicenter trials with larger cohorts, longer follow-up (≥72 hours), and objective biomarkers (e.g., inflammatory markers) are needed to validate these findings.

CONCLUSION

This study reinforces the efficacy and safety of multimodal analgesia combining nalbuphine and ketorolac for OSA surgery, which is consistent with prior research on opioid-sparing strategies. This study extends the existing knowledge by demonstrating respiratory safety (via SPO_2 improvements) and minimal sedation, which are critical for OSA patients. However, broader validation and procedural stratification are necessary to optimize pain management protocols.

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