BMC Oral Health

RESEARCH

Open Access

The effect of esketamine combined with sufentanil based patient-controlled intravenous analgesia for postoperative pain in patients undergoing third molar surgery and maxillofacial trauma: a randomized clinical trial

Xue Li[1], Xin He[1], Mengya Li[2], Xiao Gu[2], Ping Wang[3], Yong Wu[3] and Ying Chen[3*]

Abstract

Purpose This study aims to investigate the effects of combining esketamine with sufentanil for postoperative patient-controlled intravenous analgesia (PCIA) in patients undergoing elective impacted tooth surgery or open reduction and internal fixation.

Methods In this single-center, prospective, double-blinded, randomized, parallel-controlled trial, 91 patients were randomly divided into two groups. The experimental group (group ES, $n=46$) received a combination of sufentanil 1.5 μg/kg and esketamine 1.0 mg/kg, while the control group (group S, $n=45$) received sufentanil 2 μg/kg alone for PCIA after surgery. Primary outcome was assessed using the Visual Analogue Scale (VAS) for patients at rest and during mouth opening at 6 h, 12 h, 24 h, and 48 h post-surgery. Secondary outcomes included the Ramsay Sedation Scale (RSS) scores, the Quality of Recovery-15 (QoR-15) scores, patient satisfaction with analgesia, and the occurrence of adverse events within 48 h post-surgery. The frequency of PCIA button presses and the number of patients requiring rescue analgesia were also recorded.

Results The resting VAS scores and the mouth-opening VAS scores at 6 h, 12 h, 24 h, and 48 h post-surgery were significantly lower in Group ES than in Group S ($P<0.05$). Additionally, the RSS scores were significantly higher at 6 h ($P=0.032$) and 12 h ($P=0.021$) post-surgery in Group ES. The frequency of PCIA postoperative use within 48 h post-surgery decreased ($P=0.021$) in Group ES, while satisfaction with analgesia and QoR-15 scores increased ($P=0.001$ and $P<0.001$, respectively). The incidences of postoperative dizziness and nausea/vomiting reduced ($P=0.045$ and $P=0.036$, respectively) in Group ES, but one adverse event of nightmare was observed. There was no significant difference in rescue analgesia between the two groups.

*Correspondence:
Ying Chen
yingchen20825@163.com
Full list of author information is available at the end of the article

Conclusion The use of esketamine combined with sufentanil in patients undergoing third molar surgery and maxillofacial trauma can alleviate short-term postoperative pain, and improve the quality of postoperative recovery. Esketamine is worth promoting in the clinical application of oral and maxillofacial surgery.

Trial registration The study was retrospectively registered in chictr.org.cn with the identifier: ChiCTR2400086662 on 08/07/2024.

Keywords Esketamine, Sufentanil, Third molar surgery and maxillofacial trauma, Postoperative Pain, Patient-Controlled Intravenous Analgesia

Introduction

Studies have shown that approximately 80% of patients reported moderate to severe pain after oral and maxillofacial surgeries [1], which can lead to more hospital stay, higher medical costs, and delayed rehabilitation [2]. There is evidence that up to 21% of oral surgery patients still experience pain a year after surgery [3]. Therefore, postoperative analgesia for oral and maxillofacial surgeries is particularly important. Patient-controlled intravenous analgesia (PCIA) is now routinely used for postoperative pain in developed countries. According to a survey conducted in China in 2017, the proportion of hospitals using PCIA is 43.8% [4], and the number of patients using PCIA after surgery has shown an increasing trend in recent years [5]. Currently, opioid drugs are the primary choice for postoperative pain control in surgical patients. Despite their efficacy in alleviating pain, opioids are associated with a high incidence of adverse reactions [6, 7], which limits their clinical application.

One effective approach is to combine different types of analgesics using multiple strategies to achieve synergistic analgesia while minimizing the usage of individual drug, thereby reducing the side effects [8]. The N-methyl-D-aspartate (NMDA) receptor antagonists have emerged as promising agents for enhancing postoperative analgesia [9]. Kido et al. [10] reported that postoperative acute opioid tolerance induced by high-dose intraoperative remifentanil could be prevented by infusion of ketamine in patients undergoing orthognathic surgery. In particular, esketamine, which is the S (+) isomer of ketamine, has demonstrated a stronger affinity for NMDA receptors and opioid μ receptors than ketamine, allowing for the use of different doses to achieve comparable anesthetic and analgesic effects with fewer side effects [11–14]. Eriksson et al. [15] found the pre-emptive single use of esketamine could give a global significant reduction of pain during the first 24 h post-surgery in third molar surgery. There is no doubt that the repeated or continuous administration of esketamine may be better for optimizing the analgesic effect.

The purpose of this study was to explore effective postoperative analgesia methods in patients undergoing elective impacted tooth surgery or open reduction and internal fixation. The combination of esketamine and sufentanil for PCIA was compared with sufentanil alone. By exploring this analgesic combination, we hope to contribute to the development of safer and more effective pain management strategies that can improve patient outcomes and enhance the overall quality of postoperative care.

Methods

Study design

A prospective, randomized, controlled trial following the CONSORT statement was conducted on patients undergoing elective impacted tooth extraction or open reduction and internal fixation surgery at the Lianyungang Hospital affiliated with Xuzhou Medical University from November 2023 to April 2024.

The study followed the relevant provisions of the Helsinki Declaration of the World Medical Congress and was approved by the Ethics Committee of the Affiliated Lianyungang Hospital of Xuzhou Medical University on November 16, 2023 (KY-20231013001–01). The trial was retrospectively registered at the Chinese Clinical Trial Registry (ChiCTR2400086662; date of registration: July 8, 2024). The reporting of the study was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [16]. All patients provided written informed consent before enrolment in the study.

Participants

Initially, 93 patients were recruited for third molar surgery and maxillofacial trauma at the Lianyungang Hospital affiliated with Xuzhou Medical University between November 2023 and April 2024. The inclusion criteria included patients aged between 18 and 75 years old; patients scheduled for elective impacted tooth surgery (surgery for the removal of four or more impacted teeth) or open reduction and internal fixation; Body Mass Index (BMI) between 18 and 30 kg/m^2; the American Society of Anesthesiologists (ASA) physical status classification I to III; clearly understand and voluntarily participate in this study, and have signed an informed consent form. The exclusion criteria were as follows: allergic to the drugs in

trial; unstable ischemic heart disease; severe pulmonary arterial hypertension; poorly controlled or untreated hypertension (systolic/diastolic blood pressure exceeding 180/100 mmHg); those at high risk of increased intracranial or intraocular pressure; history of untreated or inadequately treated hyperthyroidism or epilepsy; long-term use of non-steroidal anti-inflammatory drugs, opioids, sedatives; any history or treatment of neurological or psychiatric diseases, including drug abuse, anxiety (Hamilton Anxiety Scale score more than 15 [17]), or depression (Montgomery-Asberg Depression Rating Scale score more than 26 [18]); significant dysfunction of vital organs, liver dysfunction (alanine aminotransferase or aspartate aminotransferase levels ≥ twice the normal upper limit or total bilirubin > 1.5 times the normal upper limit), kidney dysfunction (serum creatinine ≥ 2 mg/dL); those who do not agree to or are unable to use the PCIA pump.

Before beginning this study, we conducted a pilot study to determine the sample size. The average resting VAS score at 6 h post-surgery in Group ES was 2.93 with a standard deviation of 0.59. Meanwhile, the average resting VAS score at 6 h post-surgery was 3.29 with a standard deviation of 0.45 in Group S. A total of 74 patients were required for two-sided alpha of 5% and 80% statistical power (t-test). Expecting a dropout rate of 20% and a 1:1 ratio, the total required number was at least 90 cases in the study.

A random allocation sequence was generated using the computer by a third party. The patients were randomly divided into the experimental group (Group ES) or the control group (Group S). The opaque sealed envelopes were prepared for the grouping information. Until the patients entered the operating room, the envelope was randomly selected by the investigator, and the intervention for patients was based on a computer-generated code. Patients, anesthesiologists, surgeons, and data recorders were unaware of the allocation. Patients did not receive any preoperative medication. A standardized anesthesia method was used for all patients. After entering the operating room, an invasive arterial puncture was performed, followed by continuous monitoring of electrocardiogram (ECG), pulse oxygen saturation (SpO_2), invasive arterial blood pressure (IBP), and bispectral index (BIS). Adequate pre-oxygenation was conducted, and intravenous injection of dexamethasone 10 mg was administered before anesthesia induction. Anesthesia induction was performed with intravenous injection of propofol at 2–2.5 mg/kg, sufentanil at 0.3–0.5 μg/kg, and cisatracurium at 0.15–0.2 mg/kg, and then endotracheal intubation was performed when intubation conditions were met. An endotracheal tube with 6.5 mm or 7.0 mm for females and 7.0 mm or 7.5 mm for males was selected. Oral endotracheal intubation was the primary choice. All surgeries were performed by the same group of experienced doctors using a unified standard procedure and technique.

During the surgery, all patients continuously inhaled a 60% air-oxygen mixture and were mechanically ventilated using the pressure-controlled ventilation-volume guaranteed (PCV-VG) mode with a tidal volume set at 6–8 mL/kg. Respiratory parameters were adjusted to keep End-tidal carbon dioxide pressure ($PETCO_2$) between 35–45 mmHg. Anesthesia was maintained with continuous infusion of propofol at 4–10 mg/kg/h and remifentanil at 6–12 μg/kg/h via pump, and the BIS was kept between 40–60. Cisatracurium at 0.03 mg/kg was additionally administered as needed to preserve muscle relaxation. Palonosetron 0.5 mg was given during surgery. Fifteen minutes before the end of the surgery, a loading dose of sufentanil 0.1 μg/kg was given intravenously. After the surgery, the patient was awake and the endotracheal tube was removed. The patient was connected to the PCIA pump. PCIA was set as follows: sufentanil 2 μg/kg, palonosetron 0.5 mg and 0.9% NaCl injection solution in 100 mL in Group S; sufentanil 1.5 μg/kg, esketamine 1 mg/kg, palonosetron 0.5 mg and 0.9% NaCl injection solution in 100 mL in Group ES. The total amount of PCIA was 100 mL and programmed with an hourly limit of 6.5 mL. The initial loading dose was 2 mL, the background dose was 2 mL/h, the single dose was 1.5 mL each time, and locking time was 15 min in both groups. Patients were returned to the ward after being scored at least 9 as per the Aldrete's scoring system in the Post-Anaesthetic Care Unit (PACU) in both groups. The pain can be alleviated by increasing the frequency of PCIA use. Rescue analgesia was administered by intravenous injection of flurbiprofen axetil 50 mg when the Visual Analogue Scale (VAS) score was still ≥ 4 at rest according to the plan.

Assessment of outcomes

The general information and surgical conditions of the two groups of patients were recorded. The primary outcome was assessed using the VAS score for patients at rest and during mouth opening at 6 h, 12 h, 24 h and 48 h post-surgery. The secondary outcomes were also assessed, including the Ramsay Sedation Scale (RSS) scores was recorded at 6 h, 12 h, 24 h, and 48 h post-surgery, the Quality of Recovery-15 (QoR-15) scores at 24 h and 48 h post-surgery, patient satisfaction with analgesia, and the occurrence of adverse events within 48 h post-surgery including dizziness, nausea, vomiting, skin itching, neuropsychiatric symptoms (nightmare or hallucination), postoperative somnolence, respiratory depression, respiratory distress, tachycardia, bradycardia, and

increased secretions. The frequency of PCIA use and the number of patients requiring rescue analgesia within 48 h post-surgery were equally observed.

For pain intensity, the VAS score is anchored with a '0' at one end representing 'no pain' and '10' at the other end representing 'the worst pain imaginable' [19]. The VAS score with mouth opening was evaluated by asking patients to open their mouths as wide as comfortably possible without inducing additional pain. The RSS for sedation levels is straightforward to complete and provides three levels of 'awake' states (score 1–3) and three levels of 'asleep' states (score 4–6) [20]. The Chinese version of the QoR-15 was used to evaluate overall recovery. The QoR-15 is a 15-item questionnaire intended to measure QoR after anesthesia and surgery. It comprises five subscales: pain ($n=2$), physical comfort ($n=5$), physical independence ($n=2$), psychological support ($n=2$), and emotional state ($n=4$). Each item is scored from 0 to 10, and the possible total score ranges from 0 to 150 [21]. A higher total score means better patient QoR.

Statistical analysis

Data were analyzed using SPSS 25.0 statistical software. The Shapiro–Wilk test was used to verify the normality of the data. Normally distributed quantitative data were represented as mean ± standard deviation and compared using the independent samples t-test between groups. Repeated measures data were analyzed by the two-way repeated measures ANOVA and post hoc tests with Bonferroni correction. Cohen's d was employed to indicate the effect size (0.2 small; 0.5 medium; 0.8 large). Categorical data were expressed as number of cases (n) and percentage (%) and compared using the chi-square test or Fisher' s exact test between groups. Phi (ϕ) was used to indicate the effect size (0.1 small; 0.3 medium; 0.5 large). A difference was considered statistically significant at $P<0.05$.

Results

A total of 93 patients were evaluated, and 2 patients were excluded due to not meeting the inclusion criteria or refusing to participate. 91 patients who entered the study were randomly assigned to two groups. There were 1 patient in Group ES and 1 patient in Group S who failed to complete the study. Ultimately, 46 patients in Group ES and 45 patients in Group S were included in the analysis (Fig. 1).

There were no significant differences in age, gender, BMI, heart rate, mean arterial pressure, surgical site, anesthesia duration, surgery duration, infusion volume,

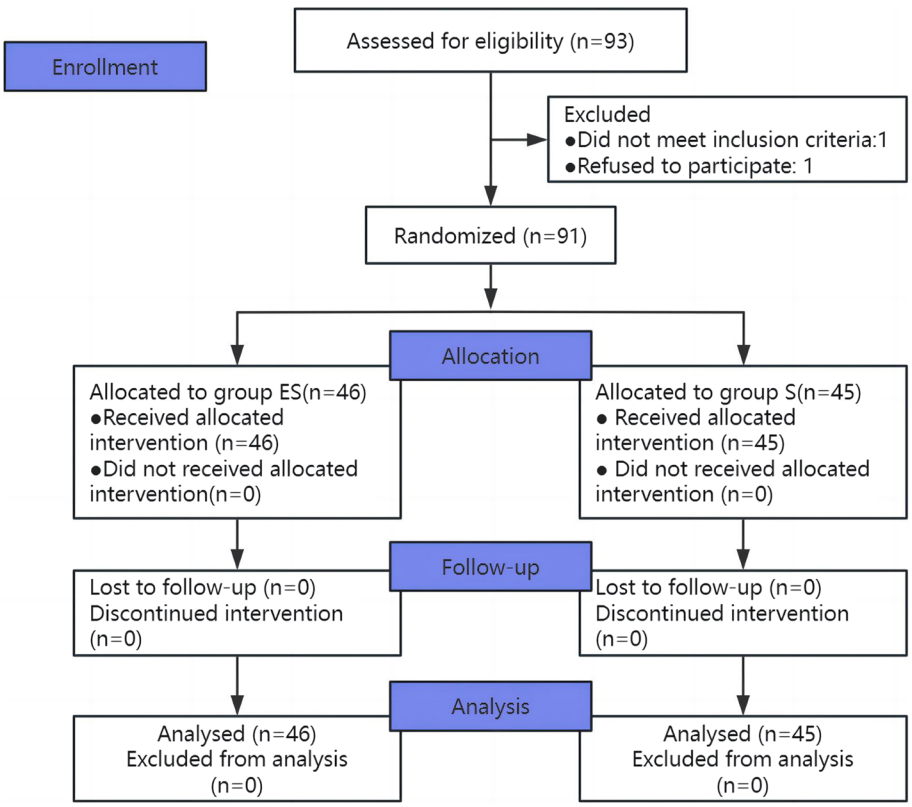

Fig. 1 CONSORT flow diagram for the study

PACU time and length of hospital stay between the two groups (Table 1).

Repeated measures analysis of variance showed there was a significant group-by-time interaction effect for the mouth-opening VAS ($F_{group\times time}=4.718$, $P=0.003$), but not the resting VAS scores ($F_{group\times time}=0.783$, $P=0.504$) and the RSS scores ($F_{group\times time}=1.540$, $P=0.204$). The results indicated a significantly better improvement for the mouth-opening VAS scores over time in Group ES than in Group S. The between-group main effects for the resting VAS scores ($F_{group}=13.973$, $P<0.001$), the mouth-opening VAS scores ($F_{group}=28.198$, $P<0.001$), and the RSS scores ($F_{group}=8.405$, $P=0.005$) were statistically significant. While the time main effects for the resting VAS scores ($F_{time}=304.454$, $P<0.001$), the mouth-opening VAS scores ($F_{time}=334.501$, $P<0.001$), and the RSS scores ($F_{time}=12.436$, $P<0.001$) were also statistically significant.

The results of multiple comparison tests showed the resting VAS scores and the mouth-opening VAS scores were significantly lower at 6 h ($P=0.001$, $P=0.004$), 12 h ($P=0.015$, $P=0.002$), 24 h ($P=0.047$, $P<0.001$), and 48 h ($P<0.001$, $P<0.001$) post-surgery in Group ES than in Group S, respectively. The mouth-opening VAS scores between groups had medium to large effect sizes (Cohen's d range = 0.604 to 1.544), indicating a clinically significant reduction, while the resting VAS scores between groups had small to medium effect sizes (Cohen's d range = 0.424 to 0.793). Compared to Group S, the RSS scores in Group ES were significantly higher at 6 h ($P=0.032$) and 12 h ($P=0.021$) post-surgery. The effect sizes were small to medium (Cohen's d = 0.461, Cohen's d = 0.509) (Table 2, Table 3).

The frequency of PCIA use within 48 h post-surgery in Group ES was significantly decreased compared to Group S ($P=0.021$) and the effect size was medium (Cohen's d = 0.503). There were 2 patients required rescue analgesia within 48 h post-surgery in Group S, and no significant difference was found between the two groups ($P>0.05$) (Table 4).

The total QoR-15 scores were significantly higher at 24 h and 48 h post-surgery in Group ES than in Group S. ($P<0.001$, $P<0.001$). The effect sizes were large (Cohen's d = 1.372, Cohen's d = 1.764), indicating significant clinical changes. The satisfaction with analgesia was also significantly increased within 48 h post-surgery in Group ES compared to Group S ($P=0.001$), and the effect size was medium (Cohen's d = 0.711) (Table 5).

In Group ES, the incidences of postoperative dizziness and nausea/vomiting were significantly reduced ($P=0.045$ and $P=0.036$, respectively) compared to Group S. The effect sizes were small ($\phi=0.220$ and $\phi=0.211$, respectively). The incidences of other adverse reactions were not significantly different between the two groups ($P>0.05$), but there was one adverse event of nightmares in Group ES (Table 6).

Table 1 Patient general information and surgical conditions

Index	Group S ($n=45$)	Group ES ($n=46$)	*P*
Age (years)	34.40 ± 14.78	34.37 ± 12.10	0.541*
Gender (M/F)	23/22	24/22	0.919#
HR (beats/min)	71.24 ± 7.23	70.59 ± 7.89	0.680*
MAP (mmHg)	90.73 ± 9.71	91.37 ± 8.02	0.559*
BMI (kg/m^2)	23.71 ± 3.04	23.97 ± 2.91	0.681*
Surgical Site			
Impacted Tooth	25	26	0.996#
Maxilla	14	14	
Mandible	6	6	
Anesthesia Duration (min)	52.78 ± 9.55	56.54 ± 8.33	0.248*
Surgery Duration (min)	35.22 ± 7.99	35.48 ± 6.90	0.808*
Infusion Volume (mL)	525.56 ± 96.31	545.65 ± 105.32	0.367*
PACU Time (min)	30.22 ± 3.63	31.67 ± 5.42	0.356*
Length of Hospital Stay (d)	8.40 ± 2.59	8.41 ± 3.14	0.983*

Data are present as mean ± standard deviation or number. *HR* Heart Rate, *MAP* Mean Arterial Pressure, *BMI* Body Mass Index, *PACU* Post-Anaesthetic Care Unit

* *P*-value for the independent samples t-test

P-value for the chi-square test

Discussion

The results of this study indicate that the combination of esketamine with sufentanil for PCIA not only reduces the intensity of pain within 48 h post-surgery but also increases sedation scores and the quality of postoperative recovery, while reducing the incidences of postoperative nausea, vomiting, and dizziness in patients undergoing third molar surgery and maxillofacial trauma.

At present, PCIA is widely used in clinical practice for pain relief after surgery, and the use of two or more types of analgesic drugs for PCIA can achieve good analgesic effects and reduce drug dose [22–24]. Some of the pathophysiological mechanisms of acute postoperative pain involve the activation of NMDA receptors by noxious stimuli, resulting in their excessive excitation [25, 26]. However, the role of NMDA receptor blockers in postoperative pain after oral and maxillofacial surgery is still controversial, with varying methods of administration leading to diverse outcomes. Some experiments have confirmed the exact postoperative analgesic effect, but Cheung et al. [27] reported no evidence that a preoperative sub-anesthetic dose of ketamine could reduce pain after third molar surgery or have any effects on non-opioid or opioid analgesic consumption.

Table 2 Resting and mouth-opening VAS scores within 48 h post-surgery

Index	Group S ($n=45$)	Group ES ($n=46$)	*P*	Effect Size
Resting VAS scores				
6 h	3.31 ± 0.47	2.96 ± 0.51	0.001#	0.714
12 h	3.44 ± 0.55	3.20 ± 0.40	0.015#	0.499
24 h	2.60 ± 0.50	2.39 ± 0.49	0.047#	0.424
48 h	2.09 ± 0.36	1.78 ± 0.42	0.000#	0.793
F_{group}	13.973		0.000*	
F_{time}	304.454		0.000*	
$F_{group×time}$	0.783		0.504*	
Mouth Opening VAS scores				
6 h	3.64 ± 0.48	3.35 ± 0.48	0.004#	0.604
12 h	3.87 ± 0.50	3.52 ± 0.51	0.002#	0.693
24 h	3.04 ± 0.47	2.61 ± 0.49	0.000#	0.896
48 h	2.69 ± 0.51	2.07 ± 0.25	0.000#	1.544
F_{group}	28.198		0.000*	
F_{time}	334.501		0.000*	
$F_{group×time}$	4.718		0.003*	

Effect Size is shown as Cohen's d

Data are present as mean ± standard deviation. *VAS* Visual Analogue Scale

* *P*-value for the two-way repeated measures ANOVA

P-value for post hoc tests with Bonferroni correction

Table 3 RSS scores within 48 h post-surgery

RSS scores	Group S ($n=45$)	Group ES ($n=46$)	*P*	Effect Size
6 h	2.02 ± 0.26	2.17 ± 0.38	0.032#	0.461
12 h	2.24 ± 0.43	2.48 ± 0.51	0.021#	0.509
24 h	2.11 ± 0.32	2.20 ± 0.40	0.268#	0.248
48 h	2.07 ± 0.25	2.09 ± 0.28	0.718#	0.075
F_{group}	8.405		0.005*	
F_{time}	12.436		0.000*	
$F_{group×time}$	1.540		0.204*	

Effect Size is shown as Cohen's d

Data are present as mean ± standard deviation. *RRS* Ramsay Sedation Scale

* *P*-value for the two-way repeated measures ANOVA

P-value for post hoc tests with Bonferroni correction

Esketamine exerts specific NMDA-blocking effects and regulates central sensitization, thereby producing an anti-hyperalgesic effect, which may play an essential role in the treatment of acute postoperative pain [28]. The meta-analysis of 32 randomized controlled trials showed that the use of esketamine combined with sufentanil for postoperative PCIA could improve postoperative pain in various types of surgeries [29], while oral and maxillofacial surgery is not included. The results of this study indicate that continuous infusion of esketamine can improve short-term pain scores after oral surgery within 48 h post-surgery, and enhance RSS scores at 12 h post-surgery. However, its effect on the sedation score was not obvious after 12 h post-surgery. The RSS score is one

Table 4 PCIA Press Counts and Rescue analgesics within 48 h post-surgery

Group	Group S ($n=45$)	Group ES ($n=46$)	*P*	Effect Size
PCIA Press Counts (times)	2.87 ± 1.46	2.17 ± 1.32	0.021*	0.503
Rescue analgesics (n)	2/43	0/46	0.242#	0.152

Effect Size is shown as Cohen's d or Phi (φ)

Data are present as mean ± standard deviation or number. *PCIA* Patient-Controlled Intravenous Analgesia

* *P*-value for the independent samples t-test

P-value for the chi-square test or Fisher's exact test

Table 5 The QoR-15 scores and pain satisfaction scores within 48 h post-surgery

Index	Group S ($n=45$)	Group ES ($n=46$)	*P*	Effect Size
24 h QoR15	124.11 ± 3.59	128.80 ± 2.24	0.000*	1.372
48 h QoR15	132.91 ± 2.75	137.85 ± 2.85	0.000*	1.764
Pain Satisfaction Scores	8.82 ± 0.61	9.24 ± 0.57	0.001*	0.711

Effect Size is shown as Cohen's d

Data are present as mean ± standard deviation. *QoR-15* Quality of Recovery-15

* *P*-value for the independent samples t-test

Table 6 The occurrence of adverse reactions within 48 h post-surgery

Adverse Reaction	Group S ($n=45$)	Group ES ($n=46$)	*P*	Effect Size
Nausea and Vomiting	19 (42.2%)	10 (21.7%)	0.036*	0.220
Itching	0	0	NS	NS
Dizziness	23 (51.1%)	14 (30.4%)	0.045*	0.211
Nightmares	0	1 (2.2%)	1.000*	0.104
Hallucinations	0	0	NS	NS
Increased Secretions	0	0	NS	NS
Laryngospasm	0	0	NS	NS
Blurred Vision	0	0	NS	NS

Effect Size is shown as Phi (φ)

Data are expressed as number of cases (n) and percentage (%)

* *P*-value for the chi-square test or Fisher's exact test

of the earliest scoring systems used to assess the sedation status of patients, effectively reflecting the sedative effect after the administration of anesthesia [30]. Esketamine regulates the central nervous system, not only providing effective analgesic effects but also enhancing the sedation level of patients after surgery by controlling the release and function of neurotransmitters. This leads to a calmer state in patients, which is conducive to postoperative recovery. Over time, the pain levels of both groups of patients decreased at 24 h and 48 h postoperatively, and the reduction in postoperative pain levels also improved the sedation scores of patients, thus the sedative effects of the two groups tend to be consistent later. Our findings suggest that the combination of esketamine with sufentanil may offer potential benefits in postoperative pain management. Although our study was not designed as a superiority trial to definitively establish the superiority of this combination over sufentanil alone, the trends in the data indicate that this regimen could lead to improved pain control and patient satisfaction.

The QoR-15 scale, as an assessment tool for recovery quality, is characterized by strong validity, high reliability, and sensitive response, and is easily accepted by both patients and clinicians [11, 31]. The study results showed that the QoR-15 scores and pain satisfaction of patients using esketamine combined with sufentanil were significantly improved. The improvement in postoperative pain scores and physical comfort of patients is beneficial for their early recovery. Several factors may explain the beneficial impact of esketamine on early postoperative quality of recovery. Esketamine interacts with NMDA receptors, cholinergic receptors, opioid receptors, and monoamine receptors, leading to opioid drug sensitization, thereby enhancing the activity of the endogenous anti-nociceptive system, reducing the use of opioid drugs, and exerting analgesic and sedative effects [32–35]. The intraoperative or postoperative application of esketamine is a potentially effective treatment for perioperative depression, which may alleviate postoperative mental stress and improve the emotional state [36–38]. Esketamine also stabilizes hemodynamic responses, ameliorates both stress and inflammatory reactions from surgery, and accelerates anesthesia recovery [39, 40].

In this study, the incidences of postoperative dizziness, nausea, and vomiting in Group ES were significantly lower than that in Group S. This reduction may be attributed to the addition of esketamine in PCIA, which potentially reduced the requirement for opioid analgesic medication, thereby decreasing the opioid-related incidence of nausea and vomiting. In addition, esketamine itself has a potential improvement effect. Qi et al. [41] reported esketamine could maintain hemodynamic stability, which is also beneficial to reduce nausea and vomiting caused by stimulation of histamine and

5-hydroxytryptamine receptors in the chemoreceptor region. Various studies have also suggested that the effect may be related to different doses and routes of administration of esketamine.

Previous studies have shown that the combination of 1.2 mg/kg or 1.5 mg/kg esketamine with sufentanil for postoperative PCIA did not cause postoperative respiratory depression, laryngospasm, or cognitive dysfunction after surgeries [42–44]. Therefore, it is safe to choose 1 mg/kg esketamine for postoperative analgesia with PCIA. Liu et al. reported the combination of 1 mg/kg esketamine with sufentanil could enhance postoperative pain management in patients undergoing gastrointestinal surgery by using similar subgroups and dosage of drugs in the experiment [45]. During this study, one case of psychiatric symptoms, specifically nightmare, was observed in the Group ES. Currently, it is not possible to definitively establish a correlation between this adverse reaction and the use of esketamine. Further investigation is necessary to clarify any potential connections.

There are some limitations in our study. First, although sequentially numbered, sealed envelopes and computer randomization were adopted, but the group allocation was not completely free from bias. Second, we well reported criteria/condition, but there might be other interference factors that influenced the results. Third, the types of surgery were limited and this study was only a single-center trial with a small sample size. It is necessary to conduct more further large-sample, multi-center studies to establish the optimal dosing regimens and to assess the potential for esketamine to reduce opioid-related side effects in a broader patient population. Our study adds to the existing body of research, further studies are warranted to corroborate our findings and explore the long-term effects of esketamine combined with sufentanil for PCIA in third molar surgery and maxillofacial trauma.

Conclusion

The combination of esketamine with sufentanil for PCIA presents a promising strategy for improving postoperative pain control and recovery outcomes in third molar surgery and maxillofacial trauma. This approach not only offers better analgesia but also reduces the risk of opioid-related side effects, making it a valuable addition to the clinical armamentarium for postoperative pain management. It is worth promoting in clinical applications.

Abbreviations

PCIA	Patient-Controlled Intravenous Analgesia
VAS	Visual Analogue Scale
RSS	Ramsay Sedation Scale
QoR-15	Quality of Recovery-15
NMDA	N-methyl-D-aspartate
HR	Heart Rate
MAP	Mean Arterial Pressure
BMI	Body Mass Index
ASA	American Society of Anesthesiologists
ECG	Electrocardiogram
SpO_2	Pulse oxygen saturation
IBP	Invasive Arterial Blood Pressure
BIS	Bispectral Index
PCV-VG	Pressure Control Ventilation-Volume Guaranteed
$PETCO_2$	End-tidal carbon dioxide pressure
PACU	Post-Anaesthetic Care Unit
M	Median
IQR	Interquartile Range
PONV	Postoperative Nausea and Vomiting

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-024-05273-8.

Supplemenentary Material 1.

Acknowledgements

Not applicable.

Authors' contributions

Ying Chen and Xue Li conceived the study, Yong Wu and Xue Li developed the methodology; Xin He and Xue Li collected and collated the data; Xiao Gu and Mengya Li analyzed data; Xue Li wrote the manuscript; Ying Chen and Ping Wang critically revised the manuscript for important intellectual content; Ying Chen and Yong Wu administered the project; Ying Chen and Yong Wu acquired funding. All authors read and approved the final manuscript.

Funding

The research did not receive any fund from public, commercial or not-for profit sectors.

Data availability

The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Approval for this study was obtained from the ethics committee of the Affiliated Lianyungang Hospital of Xuzhou Medical University on November 16, 2023 (KY-20231013001–01). The trial was retrospectively registered at the Chinese Clinical Trial Registry (ChiCTR2400086662; date of registration:8 July 2024). All patients provided written informed consent before enrolment in the study.

Consent for publication

Not applicable.

Conflicts of interests

The authors declare no competing interests.

Author details

[1]Department of Anesthesiology, Graduate Training Base of Lianyungang First People's Hospital of Xuzhou Medical University, Jiangsu, Lianyungang, People's Republic of China. [2]Department of Anesthesiology, Graduate Training Base of Lianyungang First People's Hospital of Nanjing Medical University, Jiangsu, Lianyungang, People's Republic of China. [3]Department of Anesthesiology, The First People's Hospital of Lianyungang, No. 6 East Zhenhua Road, Jiangsu, Lianyungang, People's Republic of China.

Received: 23 August 2024 Accepted: 28 November 2024
Published online: 02 December 2024

References

1. Evans SW, McCahon RA. Management of postoperative pain in maxillofacial surgery. Br J Oral Maxillofac Surg. 2019;57(1):4–11.
2. Kuang SJ, He YQ, Zheng YH, Zhang ZG. Open reduction and internal fixation of mandibular condylar fractures: A national inpatient sample analysis, 2005–2014. Medicine (Baltimore). 2019;98(37): e16814.
3. Luo Y, Svensson P, Jensen JD, Jensen T, Neuman B, Arendt-Nielsen L, et al. Quantitative sensory testing in patients with or without ongoing pain one year after orthognathic surgery. J Oral Facial Pain Headache. 2014;28(4):306–16.
4. Chang FS, Burrows SA, Gebauer DP. Patient-Controlled Analgesia and Length of Hospital Stay in Orthognathic Surgery: A Randomized Controlled Trial. J Oral Maxillofac Surg. 2019;77(4):818–27.
5. Sun J, Li N, Liu B, Duan G, Zheng H, Cao X, et al. Efficacy and safety of patient-controlled intravenous analgesia after APS team standardized postoperative pain management: A 6-year experience of an acute pain service in 107802 Chinese patients. Heliyon. 2024;10(2):e24387.
6. Moussa N, Ogle OE. Acute Pain Management. Oral Maxillofac Surg Clin North Am. 2022;34(1):35–47.
7. Mendonça FT, Pellizzaro D, Grossi BJ, Calvano LA, de Carvalho LSF, Sposito AC. Synergistic effect of the association between lidocaine and magnesium sulfate on peri-operative pain after mastectomy: A randomised, double-blind trial. Eur J Anaesthesiol. 2020;37(3):224–34.
8. Elmore B, Nguyen V, Blank R, Yount K, Lau C. Pain Management Following Thoracic Surgery. Thorac Surg Clin. 2015;25(4):393–409.
9. Schwenk ES, Viscusi ER, Buvanendran A, Hurley RW, Wasan AD, Narouze S, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43(5):456–66.
10. Kido K, Toda S, Shindo Y, Miyashita H, Sugino S, Masaki E. Effects of low-dose ketamine infusion on remifentanil-induced acute opioid tolerance and the inflammatory response in patients undergoing orthognathic surgery. J Pain Res. 2019;12:377–85.
11. Zhu M, Xu S, Ju X, Wang S, Yu X. Effects of the Different Doses of Esketamine on Postoperative Quality of Recovery in Patients Undergoing Modified Radical Mastectomy: A Randomized, Double-Blind. Controlled Trial Drug Des Devel Ther. 2022;16:4291–9.
12. Schatzberg AF. Mechanisms of Action of Ketamine and Esketamine. Am J Psychiatry. 2021;178(12):1130.
13. Wang J, Huang J, Yang S, Cui C, Ye L, Wang SY, et al. Pharmacokinetics and Safety of Esketamine in Chinese Patients Undergoing Painless Gastroscopy in Comparison with Ketamine: A Randomized, Open-Label Clinical Study. Drug Des Devel Ther. 2019;13:4135–44.
14. Jonkman K, van Rijnsoever E, Olofsen E, Aarts L, Sarton E, van Velzen M, et al. Esketamine counters opioid-induced respiratory depression. Br J Anaesth. 2018;120(5):1117–27.
15. Eriksson LB, Gordh T, Karlsten R, LoMartire R, Thor A, Tegelberg Å. Intravenous S-ketamine's analgesic efficacy in third molar surgery. A randomized placebo-controlled double-blind clinical trial. Br J Pain. 2024;18(2):197–208.
16. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. J Pharmacol Pharmacother. 2010;1(2):100–7.
17. Wang J, Zhu E, Ai P, Liu J, Chen Z, Wang F, et al. The potency of psychiatric questionnaires to distinguish major mental disorders in Chinese outpatients. Front Psychiatry. 2022;13:1091798.
18. Liu J, Xiang YT, Lei H, Wang Q, Wang G, Ungvari GS, et al. Guidance on the conversion of the Chinese versions of the Quick Inventory of Depressive Symptomatology-Self-Report (C-QIDS-SR) and the Montgomery-Asberg Scale (C-MADRS) in Chinese patients with major depression. J Affect Disord. 2014;152–154:530–3.
19. Grondin F, Hall T. Changes in cervical movement impairment and pain following orofacial treatment in patients with chronic arthralgic temporomandibular disorder with pain: A prospective case series. Physiother Theory Pract. 2017;33(1):52–61.
20. van Dishoeck AM, van der Hooft T, Simoons ML, van der Ent M, Reimer WJ. Reliable assessment of sedation level in routine clinical practice by adding an instruction to the Ramsay Scale. Eur J Cardiovasc Nurs. 2009;8(2):125–8.
21. Bu XS, Zhang J, Zuo YX. Validation of the Chinese Version of the Quality of Recovery-15 Score and Its Comparison with the Post-Operative Quality Recovery Scale. Patient. 2016;9(3):251–9.
22. Peng K, Zhang J, Meng XW, Liu HY, Ji FH. Optimization of Postoperative Intravenous Patient-Controlled Analgesia with Opioid-Dexmedetomidine Combinations: An Updated Meta-Analysis with Trial Sequential Analysis of Randomized Controlled Trials. Pain Physician. 2017;20(7):569–96.
23. Song JW, Shim JK, Song Y, Yang SY, Park SJ, Kwak YL. Effect of ketamine as an adjunct to intravenous patient-controlled analgesia, in patients at high risk of postoperative nausea and vomiting undergoing lumbar spinal surgery. Br J Anaesth. 2013;111(4):630–5.
24. De Kock MF, Lavand'homme PM. The clinical role of NMDA receptor antagonists for the treatment of postoperative pain. Best Pract Res Clin Anaesthesiol. 2007;21(1):85–98.
25. Edinoff AN, Askins D, Bobo E, White KL, Eswani Z, Jackson ED, et al. The Emerging Role of Ketamine in Acute Postoperative Pain Management. Curr Pain Headache Rep. 2023;27(9):387–97.
26. Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: A systematic review and meta-analysis. J Clin Anesth. 2021;68: 110071.
27. Cheung J, Alashi A, Koto P, Brady J, Davis B. Does Sub-Anesthetic Ketamine Provide Postoperative Analgesia for Third Molar Surgery? J Oral Maxillofac Surg. 2019;77(12):2452–64.
28. Jing Z, Han Y, Li Y, Zeng R, Wu J, Wang Y, et al. Effect of subanesthetic dose of esketamine on postoperative pain in elderly patients undergoing laparoscopic gastrointestinal tumor Surgery: A prospective, double-blind, randomized controlled trial. Heliyon. 2024;10(5): e27593.
29. Yao M, Fang B, Yang J, Chen P, Chen F. Esketamine combined with sufentanil versus sufentanil in patient-controlled intravenous analgesia: a meta-analysis. Front Pharmacol. 2024;15:1247646.
30. Rekatsina M, Theodosopoulou P, Staikou C. Perioperative Dexmedetomidine or Lidocaine Infusion for the Prevention of Chronic Postoperative and Neuropathic Pain After Gynecological Surgery: A Randomized, Placebo-Controlled. Double-Blind Study Pain Ther. 2022;11(2):529–43.
31. Myles PS, Shulman MA, Reilly J, Kasza J, Romero L. Measurement of quality of recovery after surgery using the 15-item quality of recovery scale: a systematic review and meta-analysis. Br J Anaesth. 2022;128(6):1029–39.
32. Mohammad Shehata I, Masood W, Nemr N, Anderson A, Bhusal K, Edinoff AN, et al. The Possible Application of Ketamine in the Treatment of Depression in Alzheimer's Disease. Neurol Int. 2022;14(2):310–21.
33. Subramanian S, Haroutounian S, Palanca BJA, Lenze EJ. Ketamine as a therapeutic agent for depression and pain: mechanisms and evidence. J Neurol Sci. 2022;434:120152.
34. Verkhratsky A, Kirchhoff F. NMDA Receptors in glia. Neuroscientist. 2007;13(1):28–37.
35. Raghunatha P, Vosoughi A, Kauppinen TM, Jackson MF. Microglial NMDA receptors drive pro-inflammatory responses via PARP-1/TRMP2 signaling. Glia. 2020;68(7):1421–34.
36. Wen W, Wenjing Z, Xia X, Duan X, Zhang L, Duomao L, et al. Efficacy of ketamine versus esketamine in the treatment of perioperative depression: A review. Pharmacol Biochem Behav. 2024;242: 173773.
37. Lou XJ, Qiu D, Ren ZY, Hashimoto K, Zhang GF, Yang JJ. Efficacy and safety of esketamine for perioperative depression in patients undergoing elective surgery: A meta-analysis of randomized controlled trials. Asian J Psychiatr. 2024;95: 103997.
38. Hung KC, Kao CL, Ho CN, Hsing CH, Chang YJ, Wang LK, et al. The impact of perioperative ketamine or esketamine on the subjective quality of recovery after surgery: a meta-analysis of randomised controlled trials. Br J Anaesth. 2024;132(6):1293–303.
39. Zhao L, Li Z, Jin B, Hou N, Yang H. Safety and efficacy of low-dose esketamine in laparoscopic cholecystectomy: a prospective, double-blind randomized controlled trial. BMC Anesthesiol. 2024;24(1):47.
40. Liu C, Zhang T, Cao L, Lin W. Comparison of esketamine versus dexmedetomidine for attenuation of cardiovascular stress response to double-lumen tracheal tube intubation: a randomized controlled trial. Front Cardiovasc Med. 2023;10:1289841.
41. Qi Y, Zhou M, Zheng W, Dong Y, Li W, Wang L, et al. Effect of S-Ketamine on Postoperative Nausea and Vomiting in Patients Undergoing Video-Assisted Thoracic Surgery: A Randomized Controlled Trial. Drug Des Devel Ther. 2024;18:1189–98.

42. Eberl S, Koers L, van Hooft J, de Jong E, Hermanides J, Hollmann MW, et al. The effectiveness of a low-dose esketamine versus an alfentanil adjunct to propofol sedation during endoscopic retrograde cholangiopancreatography: A randomised controlled multicentre trial. Eur J Anaesthesiol. 2020;37(5):394–401.
43. Massoth C, Schwellenbach J, Saadat-Gilani K, Weiss R, Pöpping D, Küllmar M, et al. Impact of opioid-free anaesthesia on postoperative nausea, vomiting and pain after gynaecological laparoscopy - A randomised controlled trial. J Clin Anesth. 2021;75: 110437.
44. Cata JP, Owusu-Agyemang P, Koyyalagunta D, Corrales G, Feng L, Fournier K. Impact of Ketamine on Opioid Use and Persistent Pain After Cytoreductive Surgery with Hyperthermic Chemotherapy. J Pain Res. 2021;14:2433–9.
45. Liu J, Wang T, Song J, Cao L. Effect of esketamine on postoperative analgesia and postoperative delirium in elderly patients undergoing gastrointestinal surgery. BMC Anesthesiol. 2024;24(1):46.

Publisher's Note