ORIGINAL RESEARCH

The Effectiveness of Low-dose Esmketamine Versus Remifentanil Adjunct to Propofol for Sedation in Patients Undergoing Radiofrequency Thermocoagulation for Trigeminal Neuralgia

An Xie, MM; Jia Han, MM; Feng Ju, MM; Yukai Zhou, MM; Dan Wu, MM; Xianjie Zhang, MD

ABSTRACT

Objectives • To access the effectiveness of propofol-esketamine versus propofol-remifentanyl in patients undergoing radiofrequency Thermocoagulation for Trigeminal Neuralgia of gasserian ganglion.

Methods • In this clinical trial, 80 patients were candidates for RFT were randomly divided into two groups (n= 40). These patients aged from 21 to 81 years old. Before the start of the procedure, both groups received propofol TCI with a target level of 1.5 $\mu g ml^{-1}$. The intervention group (group E) received esketamine 0.15 $mg kg^{-1}$, and the control group (group R) received remifentanyl 1.0 $\mu g kg^{-1}$. The patients, the anesthetists and the surgeons were unaware of the medication regimen. Sedation level (based on a MOAA/S), blood pressure, oxygen saturation, the dosage of propofol, recovery time (based on Aldrete scores), postoperation pain (based on NRS), surgeons and patient satisfaction, and Pittsburgh Sleep Quality Index (PQSI) were recorded.

Results • Data from 80 patients were analyzed. The sedative effects were equal in the two groups (P = .680) and the MOAA/s scores of both groups were basically maintained at or below 2 points, however, the dosage of propofol in group E was significantly less than that in group R [5.3$mg kg^{-1}h^{-1}$ (5.0 to 5.7) vs 5.8 $mg kg^{-1}h^{-1}$ (5.3 to 6.3), P = .000]. The group E had higher blood pressure levels during the procedure (P_{SBP} = .002, P_{DBP} = .023). Surgeons and patient satisfaction (P_s = .164, P_p = .580), recovery time (P = .228),The NRS values after 24hrs (P = .777)and PQSI showed no significant differences between the two groups (P = .133).

Conclusions • Low-dose esketamine reduces the total amount of propofol necessary for sedation and incidence of respiratory depression during RFT of gasserian ganglion in American Society of Anesthesiologists I to III patients without affecting recovery time, satisfaction of surgeons and patients, cardiovascular adverse events, when compared with remifentanil. (*Altern Ther Health Med.* 2024;30(12):324-329).

An Xie, MM; **Jia Han,** MM; **Feng Ju,** MM; **Yukai Zhou,** MM; **Dan Wu,** MM; **Xianjie Zhang,** MM, Department of Anesthesiology; People's Hospital of Deyang City; Deyang, Sichuan; China.

Corresponding author: Jia Han, MM
E-mail: Hanjia1122332023@163.com

INTRODUCTION

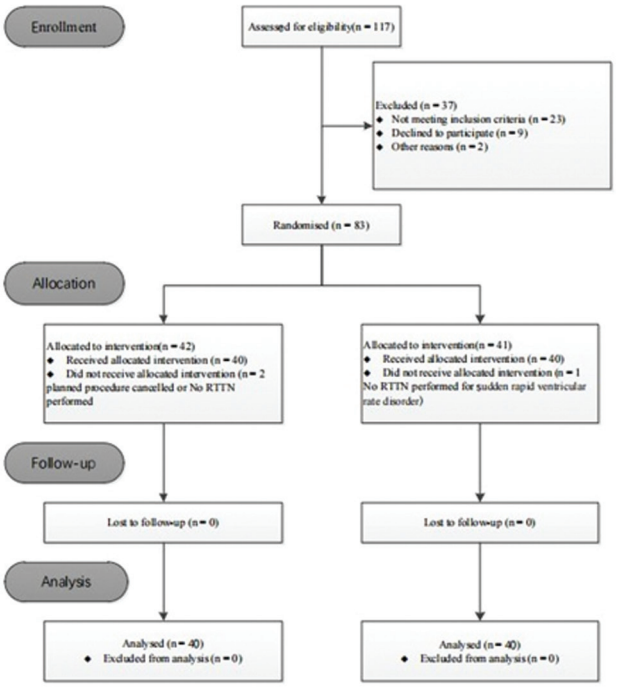
Idiopathic trigeminal neuralgia (ITN) is a paroxysmal electric shock-like pain innervated by one or more branches of the trigeminal nerve. It is characterized by no obvious organic or functional lesions, and its pathogenesis is still unclear.[1] However, Its occurrence is generally believed to have a certain relationship with the trigeminal nerve. The lifetime prevalence of ITN is about 3 to 5 per 100 000 people, with the highest incidence usually between the ages of 50 and 70 years.[2,3] At present, the treatment of primary trigeminal neuralgia is mainly Conservative medication, microvascular decompression, stereotactic radiation therapy and percutaneous radiofrequency thermocoagulation (RFT).[3-5] With the characteristics of minimally invasive, low cost and repeatable Operation, RFT has gradually become one of the conventional surgical methods for ITN.[4] With the development of imaging and nerve stimulation technology in recent years, the clinical effectiveness and safety of RFT of gasserian ganglion have been significantly improved, with an effective in relieving pain and prolonging the relapse interval rate of almost 80%.[6]

However, the severe pain associated with the insertion of the needle into the gasserian ganglion, adjusting the position of the needle tip in the gasserian ganglion, and radiofrequency heating often make patients unable to complete the Operation. In recent years, the bold attempts of intravenous anesthesia, especially remifentanil combined with propofol for RFT of Gasserian ganglion have promoted the promotion of this Operation to a certain extent and increased the satisfaction

Table 1. Modified Observer's Alertness/Sedation scale score

Score	Responsiveness
5	Responds readily to name spoken in a normal tone
4	Lethargic response to name spoken in a normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Figure 1. Consort flow diagram.



of patients.[7] However, the disadvantages of respiratory and circulatory inhibition caused by opioids and propofol have attracted much attention.[8-10] Therefore, a analgesic with less impact on respiratory and circulatory is needed to break this dilemma.

Esketamine, as a new type of intravenous general anesthetic, has the characteristics of rapid onset, complete recovery, slight respiratory and circulatory inhibition, as well as sedation, analgesia and amnesia,[11,12] so it is often used in patients undergoing gastrointestinal endoscopy[13] and mechanical ventilation in ICU.[14] However, when combined with propofol for sedation, esketamine can reduce the dose of propofol.[10,15,16] Based on this, this study aimed to evaluate the sedative and analgesic effects and clinical safety of low-dose esketamine combined with propofol for RFT of the Gasserian ganglion.

MATERIALS AND METHODS

Paticipants

A total of 80 adult patients who underwent conventional Radiofrequency thermocoagulation (RFT) of the gasserian ganglion in our hospital from November 2018 to Octotber 2021 were included in the study. None of them had general anesthesia contraindications. Exclusion criteria which based on that opioids or ketamine can worsen these conditions were a known a history of unregulated or malignant hypertension, allergic reaction to planned medication, diabetes, severe liver and kidney disease, significant ischaemic heart disease, pregnancy, chronic pain, coagulation disorders, psychiatric disease, increased intracranial pressure, substance abuse or use of drugs that affect the central nervous system. Ethical approval was obtained from the Clinical Trial Ethics Committee of Deyang People's Hospital (Approval Number: 2019-03-11-K01), and all the patients provided written informed consent. They were randomized to receive either propofol and esketamine (0.15 $mgkg^{-1}$, group E) or propofol and remifentanil (1.0 $ugkg^{-1}$, group R). Randomization was accomplished using computer-generated random numbers concealed in sequentially numbered sealed opaque envelopes. In group E, patients were aged 22 to 76 years, with BMIs of 15.62-30.85 kgm^{-1}. In group R, patients were aged 21 to 81 years, and the BMI was 17.48-29.75kgm^{-1}. All patients had ASA grades of I–III. Eighty patients completed the study, and no patients withdrew from it. The baseline demographic information is summarized in Table 1.

Study Design

This was a randomized, controlled single-center study based on a flowchart (Figure 1). The trial was ended after the completion of the follow-up of the last participant of the study. In our hospital, RFT guided by CT are expertly performed 50 times a year by three consultant pain management doctors. Specialised sedation practitioners performed sedational procedures and the data was recorded by two trained residents. 15 minutes before the start of sedation, the study drugs (The appearance is a colorless transparent 20ml diluted liquid in a 20ml syringe) was assigned to the practitioner. The syringe is labeled with a number (practitioner can get the get the details of the drug through the study drug allocation form or telephone inquiry), and cannot be disclosed to other personnel. Except for the sedation practitioner, all persons involved in the procedure (patient, surgeon, nurse and independent researcher) were blinded to the allocation of the study group and thus to which drugs were given to the patient.

Surgical procedure and monitoring. All patients fasted for at least 8 hours before RFT. After intravenous access was obtained, an infusion of 500 ml Sodium acetate Ringer's solution was started at a rate of 250 mlh^{-1}. Patients were asked to position themselves in the supine position after entering the operation room. The noninvasive blood pressure, ECG, heart rate and oxyhemoglobin saturation were conventionally monitored and Oxygen (2 $Lmin^{-1}$) was supplied using a nasal cannula. Three minutes before Operation, propofol TCI and either esketamine or remifentanil were administered intravenously. The sedation level [assessed by the Modified Observer's Alertness/Sedation scale (MOAA/S)] was measured at the beginning of the procedure followed by a puncture of the needle electrode under computed tomography (CT) guidance. The foramen ovale (FO) was visualized by manipulating the real-time CT, and electrical stimulation was conducted to

confirm the accurate therapeutic cite. Patients, meanwhile, were sedation appropriately so they could cooperate and answer during electrical stimulation. The vital signs and MOAA/S were measured at 5-minute intervals. The MOAA/S scale described by Susanne Eberl[16] is a modification to the OAAS scale to describe deeper sedation states and is scored from 5 to 0 (Table 1). We targeted a sedation level with a MOAA/S score of 2 at the beginning of RFT, with the patient responding only after prodding or shaking.

In the recovery room, standard monitoring was limited to HR, SpO2, respiratory rate, NIBP and MOAA/S. Recovery was assessed using the modified Aldrete Score at arrival in the recovery room and 15, 30, 45 and 60 min later. This score describes the patient's activity, respiration, SpO2, circulation (BP and HR), consciousness, nausea, vomiting and pain. The maximum score is 10. In accordance with the local protocols, post-procedural pain was treated with 50mg of tramadol intravenously when the Numerical Rating Scale (NRS) was reported to be more than 4 on a scale of 0 to 10. Routinely, 5mg of intravenous tropisetron was given to prevent postoperative nausea. Patients, who had to stay in the recovery room for at least 1 h, were permitted to discharge when they were awake and alert with normal vital signs, and the Aldrete Score was at least 9 or equal to the preprocedural score and without significant side effects such as nausea and dizziness.

Sedative intervention

Procedural sedation was performed by anesthetists trained in the standards of care for procedural sedation and analgesia according to the Chinese national guidelines.[17] An anesthetist was available for liaison, supervision and as a backup in case of emergencies. Before RFT, patients in both groups were sedated using a TCI of propofol (Propofol 1% MCT Fresenius Kabi Beijing China). We used the Willy's Ark (China, Shanghai) infusion pump preprogrammed for propofol TCI with a targeted plasma drug concentration (Cpt), which determined the pump infusion rate and a calculated effect concentration (Ce).[18] Propofol TCI was started prior to the administration of esketamine to limit the possible psychotomimetic effects of esketamine. When the Ce had reached the target level of 1.5 $\mu g ml^{-1}$, group E received esketamine (Ketanest S; Pfizer, Siegfried Hameln GmbH, Hameln, Germany) 0.15 $mg kg^{-1}$, group R received remifentanil (Ruifen; Nhwa, Jiangsu, China) 1.0 $\mu g kg^{-1}$. Two minutes after administering esketamine or remifentanil, the level of patient sedation was assessed using the MOAA/S scale; target level was a score of 2. If MOAA/S was above 2, the propofol TCI target (Cpt) was increased to 2.5$\mu g ml^{-1}$. If the sedation practitioner noticed a sudden decrease of the MOAA/S score to less than 1 or airway obstruction, TCI propofol was stopped. The Target Ce to the start of the procedure was 2.5 $mg ml^{-1}$; at this point MOAA/S was assessed again. When MOAA/S was 1, Cpt or less was decreased in steps of 0.5 $\mu g ml^{-1}$. If MOAA/S was above 2, for example, the patient was still too responsive to tolerate the procedure, additional sedation was provided with increments of 0.5 $\mu g ml^{-1}$ in plasma target level (Cpt) every 3min. For every 0.5$\mu g ml^{-1}$ step up of propofol TCI, esketamine 150$\mu g kg^{-1}$ or remifentanil 0.3$\mu g kg^{-1}$ was added. Maximum dose was 0.5$mg kg^{-1} h^{-1}$ esketamine or 2 $\mu g kg^{-1} h^{-1}$remifentanil.

Outcome assessment

The primary outcome was the total dose of propofol as a surrogate parameter of the effectiveness of the sedative adjunct, with a targeted MOAA/S of 2. The total amount of esketamine, remifentanil, atropine, ephedrine and aramine used to treat hypotension and/or bradycardia was recorded. The recovery time (MOAA/S>4) and time that the patient was fit for discharge. Quality Index (PSQI) were determined by the subsequent questionnaires. (Patients completed an evaluation directly during the procedure, every 15 min after the procedure in the recovery unit and 24h after discharge) The pain were assessed using a Numerical Rating Scale (NRS) ranging from 0 = no pain to 10 = worst insufferable pain.To evaluate possible psychotomimetic effects, delirium characterized by an acute onset or fluctuating course, inattention, and either disorganized thought (manifesting as memory, language, and orientation difficulties[19]) or altered level of consciousness was assessed 1h after the procedure and the next day. PSQI scale contains seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. There are 19 questions in this questionnaire, with a total score ranging from 0–21. A higher score indicated worse sleep quality.[20] Immediately after Operation, surgeons were asked to rate patients for pain (NRS score ranging from 0= no pain to 10= worst imaginable pain) and sedation (MOAA/S). The satisfaction levels of surgeons and patients was rated on a five-point Likert scale (ranging from 1= very dissatisfied to 10= very satisfied).

All adverse respiratory and cardiovascular events were registered and defined as per recommendations from the World SIVA International Sedation Task Force.[21] Respiratory events were defined as oxygen desaturation (SpO2 75 to 90% for <60 s), severe oxygen desaturation (SpO2<75% at any time or prolonged SpO2<90% for >60 s), and airway obstruction with a need for airway maneuver, such as chin lift, facemask ventilation, use of nasopharyngeal or oropharyngeal airway, or endotracheal intubation.[22] 2.Cardiovascular events were defined as bradycardia, tachycardia, hypotension or hypertension, which were defined as a change of more than 20% from baseline and/or a necessitating intervention.[21]

Sample size calculation

We hypothesized that sedation for RFT with propofol TCI and esketamine would result in a reduction in the required dose of propofol by at least 10%, compared with sedation with propofol TCI and remifentanil. The sample size calculation was based on observational data from our hospital sedation database, which showed a mean dose of propofol of 5.80$mg kg^{-1} h^{-1}$ with an SD of 0.65$kg^{-1} h^{-1}$ per RFT. The sample size needed to demonstrate a 10% reduction in propofol

Table 2. Patients' characteristics and baseline values

	Esketamine, n = 40	Remifentanil,n = 40
Age (years)	53.0±13.9	51.9±14.7
Sex (female)	22(55%)	24(60%)
Weight (kg)	62.9±9.6	61.1±10.7
Length (cm)	164.1±7.5	162.2±6.3
BMI (kg/m^2)	23.32±3.16	23.08±2.86
ASA PS	1.8±0.5	1.8±0.6
Cardiovascular disease	3(7.5%)	5(12.5%)
Pulmonary disease	6(15%)	7(17.5%)
diabetes	5(12.5%)	4(10%)
Alcohol	11(27.5%)	14(35%)
smoker	10(25%)	12(30%)
Duration procedure(min)	48.4±6.5	49.0±6.6
Nerve,n(%)		
V1	2(5)	0(0)
V2	8(20)	9(22.5)
V3	13(32.5)	14(35)
V2+V3	17(42.5)	17(12.5)
Baseline measurements		
SBP	107.9±19.4	110.2±16.9
DBP	66.4±12.2	69.4±12.4
Heart rate	69.5±11.8	71.2±13.3
SpO2	98.2±1.4	97.9±1.6

Note: Data presented as mean±SD, or number (%).

Abbreviations: ASA PS, American Society of Anesthesiologists Physical Status; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 3. Outcome Measures

	Esketamine	Remifentanil	*P* value
Cumulative dose of propofol	5.3mg.kg^{-1}.h^{-1} (5.0 to 5.7)	5.8mg.kg^{-1}.h^{-1}(5.3 to 6.3)	.000
Recovery time (min)	10.0±1.6	9.6±1.9	.228
AUC(SBP)	582.6±68.0	538.1±58.1	.002
AUC(DBP)	331.8±64.1	301.4±52.6	.023
NRS	1.3±0.9	1.5±0.9	.777
Surgeons satisfaction	8.5±0.8	8.7±0.7	.081
Patients satisfaction	8.2±0.9	8.2±0.7	.328
PSQI	5.0±2.0	5.3±2.5	.529

Note: Data presented as median [IQR] or mean±SD,

Abbreviations: AUC, area under the curve; DBP, diastolic blood pressure; SBP, systolic blood pressure; NRS, numerical rating scale; PSQI, pittsburgh sleep quality index.

Table 4. Numbers of adverse events in both groups during entire procedure (n)

Events	Esketamine	Remifentanil	*P* value
Desaturation	2	9	.000
Oxygen desaturation (SpO2 75 to 90% for <60 s)	2	8	.087
Severe oxygen desaturation (SpO2<75% at any time or prolonged SpO2<90% for >60 s)	0	1	-
Need for airway manoeuvre	0	2	.494
Bradycardia	2	4	.675
Tachycardia	3	2	-
Hypotension	3	5	.714
Hypertension	7	3	.311
Need for vasoactive drugs	1	4	.359

Note: Median [IQR] values for desaturations were 86 [85 to 88] and 84 [80 to 88] in the esketamine and remifentanil groups, respectively. Crude numbers are total events during the procedure (not split per patient).

requirement, with a power of 0.90 and a significance level of 0.05, would, therefore be 72 (36 per group) patients. However, to account for a dropout rate of 10%, we randomized a total of 80 patients (40 per group).

Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software version 17.0. All analyses were performed with an intention-to-treat analysis and included all data and outcomes from randomization until the first postintervention day. All data were checked for normal distribution using the Kolmogorov–Smirnov test and histograms. For normally distributed, continuous variables, an independent Student's *t* test was used, and the variables were presented as mean ± SD. $P < .05$ was considered statistically significant. For categorical variables, cross tabulation and Fisher's exact test were applied, and variables were allegorized as number and/or percentages of the total. Not normally distributed data were compared using Mann–Whitney U test and data were presented as median and interquartile range (IQR). To compare heart rate (HR), noninvasive blood pressure (NIBP) and Saturation of Peripheral Oxygen (SpO2) between both groups, the area under the curve for each variable was calculated using the trapezoidal rule over the different time points under the curve (AUC) for each variable was calculated using the trapezoidal rule over the different time points. The AUCs were tested for statistical significance using the Mann–Whitney U test.

RESULT

Dosage of Propofol

Patients in group E received significantly less propofol [5.3mgkg^{-1}h^{-1} (5.0 to 5.7)] than that in group R [5.8 mgkg^{-1}h^{-1} (5.3 to 6.3), $P = .000$] .

The AUC values of SBP, DBP

The AUC values for both SBP and DBP were significantly higher in group E than that in group R (SBP:582.6±68.0 vs 538.1±58.1, $P = .002$; DBP:331.8±64.1 vs 301.4±52.6, $P = .023$). (Table 3).

The MOAA/S Scores and Recovery Time

The MOAA/S scores were not significantly different between groups at any postoperative point. Median recovery time was 10.02±1.62 min in group E and 9.55±1.86 min in group R ($P = .228$).

The NRS Values

The NRS values were not significantly different between groups after 24hrs after operation of RFT for the treatment of trigeminal neuralgia. (1.30±0.88 vs 1.48±0.93, $P = .777$) (Table 3).

Satisfaction and the Pittsburgh Sleep Quality Index (PSQI)

There was no difference in the two groups with regard to surgeons and patient satisfaction. The PSQI within 24 hrs of surgery was not different between groups E and R (22.85±2.34 vs. 22.98±3.14, $P = .133$)(Table 3)

The Incidence of Adverse Reactions

The Desaturation was observed in 5% of patients of group E, which was lower than that of group R ($P = .048$), regarding hypotension, hypertension, bradycardia, tachycardia and the usage of vasoactive drugs; however, they were not statistically different (Table 4).

DISCUSSION

The purpose of this current randomized controlled study was to evaluate and compare the efficacy and safety of low-dose esketamine with those of remifentanil in ASA I to III Chinese patients. We found that sedation with esketamine and propofol TCI results in a dose reduction of propofol to achieve satisfactory sedation conditions compared with a remifentanil and propofol TCI regimen for RFT, with a decline of respiratory depression event. Patients in the esketamine group had a significantly higher BP than patients in the remifentanil group. The analgesic effect and recovery time of esketamine and remifentanil are both similar in short-time hypoirritant surgical procedures. There were no significant differences in the occurrence of cardiovascular events and psychotomimetic events between groups.

In the conventional radiofrequency thermocoagulation of the trigeminal nerve, mild sedation and analgesia were given in the first stage. Following the radiofrequency needle reaching the foramen ovale, the target nerve bundle was determined by electrical stimulation, and then local anesthetics were given to eliminate the stronger pain stimulation caused by radiofrequency thermocoagulation.[23] Patients, however, were often unable to cooperate during the Operation because of tension or incomplete block, which makes patients and surgeons dissatisfied. Consequently, general anesthesia based on propofol and fentanyl or remifentanil has become the preferred choice.[7] In recent years, opiod-free general anesthesia has become a new choice for minor surgery, thus avoiding the respiratory and circulatory depression caused by opioid drugs in most surgeries.[24,25] In the present study, esketamine was the new choice for opioid-free anesthesia because of its dual analgesic and sedative properties.

In most routine RFT surgeries, a two-stage approach to anesthesia is used (i.e., in the first stage, a narcotic analgesic is used to relieve the pain caused by puncture, and in the second stage, a small amount of local anesthetic is injected into the foramen ovale (FO) to relieve the neuralgia caused by RFT). In our study, only propofol and analgesics were used for general anesthesia in the whole process, without a midazolam or dexmedetomidine combination, making sedation more comparable between the two groups. The MOAAS was set as the target value of 2 for the depth of anesthesia, which prompts patient could quietly cooperate with the doctor during the electrical stimulation, instead of dividing the anesthesia process into two stages, which reduced the Operation of the anesthesiologist. In this trial, no patients in either group were unable to cooperate because of agitation or were too deeply seaged to respond to stimulation.

In our study, patients in the esketamine group used significantly less propofol than those in the remifentanil group. Esketamine has a dual sedative and analgesic effect, and its sedative effect is stronger than remifentanil, thus reducing the amount of propofol. In addition, while there was a statistical difference in blood pressure between the two groups, the increase in blood pressure in the esketamine group was within the acceptable range, meaning it could be used in patients with hemodynamic instability. This needs to be assessed by further studies. Aydoghan et al.[26] found that the combination of propofol and ketamine causes shorter recovery time, better hemodynamic stability, and higher satisfaction than propofol alone in patients undergoing upper gastrointestinal endoscopy. Ramkiran et al.[15] studied the effect of the depth of anesthesia using combinations of propofol-ketamine and propofol-dexmedetomidineby BIS in patients who were candidates for ERCP. They concluded that the combination of propofol and low-dose ketamine led to less consumption of propofol, faster recovery, and more favorable hemodynamic effects.

In terms of respiratory, patients in the remifentanil group had more respiratory depression/desaturation episodes. This is likely due to the more amount of propofol and the intrinsic respiratory depression funtion of renmifentanil that was necessary to achieve satisfactory sedation levels. Akhondzadeh et al.[27] demonstrated a 31% reduction of apnoeas using ketamine instead of a fentanyl adjunct to a propofol and midazolam sedation regimen. Hasanein et al.[28] also reported a significant reduction in hemodynamic and respiratory depression due to the lower dose of propofol for patients sedated with ketamine compared with fentanyl. In the present study, two patients in the remifentanil group and none in the esketamine group required airway assistance. In contrast to the results of Bahrami's trial[29] no patients in either study group required tracheal intubation, possibly due to the assessment and adjustment of the dosage of anesthetics every 5 minutes. In Eberl's study,[16] there was no difference in respiratory depression between ketamine and alfentanil, which may be related to the relatively shallow sedation and the supporting effect of the ERCP scope on the upper airway (mainly glossopharyngeal).

Additionally, there were 3 cases of postoperative nausea and vomiting in the remifentanil group and 2 cases in the esketamine group, which was not statistically different. The study from Chen HY[30] have shown that opioid-free anesthesia with esketamine can reduce the incidence of opioid-related nausea and vomiting. But our results are not similar, which may be related to the low usage of esketamine and the rapid internal metabolism of remifentanil without accumulation, but the results after increasing the sample size need further study.

Ketamine is an Nmethyl-*D*-aspartate receptor (NMDAR) that has been shown to relieve a variety of neuropathic pain, such as complex regional pain syndrome[31], PHN[32], cancer pain[33] and trigeminal neuralgia[34], and Esketamine is the dextral form of ketamine and has a higher affinity for NMDARs[10]. Jia-Chun Tao et al.[35] reported that using esketamine PCIA for a woman patient undergoing trigeminal extracranial thermocoagulation produced a good analgesic effect without any adverse events occurring. Although remifentanil can cause postoperative hyperalgesia, there was no significant difference between the two groups in our study, which may be related to the small amount usage of

remifentanil used. Nevertheless, whether intraoperative esketamine inhibits postoperative neuropathic pain remains to be further investigated.

Although esketamine can produce undesirable psychotomimetic symptoms such as vivid dreaming, extracorporeal experiences (sense of floating out of one's body), and illusions (misperceptions of real and external sensory experiences), the Eberl et al.[16] and Mortero et al.[22] did not show an increase in esketamine psychotomimetic symptoms, similar to our current findings, Nagata A et al [36] deemed the absence of psychotomimetic effects could be that propofol inhibits ketamine-induced c-fos expression in the posterior cingulate cortex. However, for patients with mental disorders, low doses of esketamine may also cause non-negligible effects, so the expansion of clinical use of esketamine needs to be cautious.

Our study has great clinical significance for patients undergoing radiofrequency thermocoagulation of trigeminal neuralgia, and it is also very helpful for practitioners to achieve effective and safe sedation in such non-intubated patients, which is the dream of surgeons.

Our study still has some limitations. There were no cases of psychiatric symptoms such as postoperative delirium in our study, and there was no significant difference in PQSI between the two groups. This may be related to a small number of elderly patients and patients with ASA PS classIII, and the absence of patients with ASA PS class IV. This may have distorted the results and is a limitation of this study. The study population consisted primarily of low-risk patients. Hence, for high-risk patients, these findings need to be further evaluated in future studies. At present, we are currently conducting a study on esketamine combined with remazolam for fibrobronchoscopy in elderly patients to further explore its clinical practicability by expanding the sample size, changing the target population, and making full use of the characteristics of esketamine to dilate bronchus and stabilize circulation.

CONCLUSION

Compared with remifentanil, low-dose esketamine combined with propofol for sedation in RFT patients reduced the dosage of propofol and the incidence of respiratory depression. This can provide a safer and more effective sedation and analgesia option for minor surgery.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Somaza S, Montilla EM, Mora MC. Gamma knife radiosurgery on the trigeminal ganglion for idiopathic trigeminal neuralgia: results and review of the literature. *Surg Neurol Int*. 2019;10:89. doi:10.25259/SNI-134-2019
2. Maarbjerg S, Di Stefano G, Bendtsen L, Cruccu G. Trigeminal neuralgia - diagnosis and treatment. *Cephalalgia*. 2017;37(7):648-657. doi:10.1177/0333102416687280
3. Di Stefano G, Truini A, Cruccu G. Current and Innovative Pharmacological Options to Treat Typical and Atypical Trigeminal Neuralgia. *Drugs*. 2018;78(14):1433-1442. doi:10.1007/s40265-018-0964-9
4. Tang YZ, Jin D, Bian JJ, Li XY, Lai GH, Ni JX. Long-term outcome of computed tomography-guided percutaneous radiofrequency thermocoagulation for classic trigeminal neuralgia patients older than 70 years. *J Craniofac Surg*. 2014;25(4):1292-1295. doi:10.1097/SCS.0000000000000591
5. Hall JC, Ung TH, McCleary TL, et al. Stereotactic radiosurgery for trigeminal neuralgia secondary to tumor: a single-institution retrospective series. *Neurosurg Focus*. 2022;53(5):E3. doi:10.3171/2022.8.FOCUS22381
6. Sterman-Neto H, Fukuda CY, Duarte KP, et al. Balloon compression vs radiofrequency for primary trigeminal neuralgia: a randomized, controlled trial. *Pain*. 2021;162(3):919-929. doi:10.1097/j.pain.0000000000002070
7. Yang Y, Tang Q, Liu H. Comparison of intravenous anesthesia methods in trigeminal gasserian ganglion radiofrequency thermocoagulation. *Chinese Journal of Pain Medicine*. 2011;17(04):249-250.
8. Baldo BA, Rose MA. Mechanisms of opioid-induced respiratory depression. *Arch Toxicol*. 2022;96(8):2247-2260. doi:10.1007/s00204-022-03300-7
9. Khanna AK, Bergese SD, Jungquist CR, et al; PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY (PRODIGY) Group Collaborators. Prediction of Opioid-Induced Respiratory Depression on Inpatient Wards Using Continuous Capnography and Oximetry: An International Prospective, Observational Trial. *Anesth Analg*. 2020;131(4):1012-1024. doi:10.1213/ANE.0000000000004788
10. Jonkman K, van Rijnsoever E, Olofsen E, et al. Esketamine counters opioid-induced respiratory depression. *Br J Anaesth*. 2018;120(5):1117-1127. doi:10.1016/j.bja.2018.02.021
11. Hustveit O, Maurset A, Oye I. Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. *Pharmacol Toxicol*. 1995;77(6):355-359. doi:10.1111/j.1600-0773.1995.tb01041.x
12. Ihmsen H, Geisslinger G, Schüttler J. Stereoselective pharmacokinetics of ketamine: R(-)-ketamine inhibits the elimination of S(+)-ketamine. *Clin Pharmacol Ther*. 2001;70(5):431-438.
13. Wang J, Huang J, Yang S, 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;13:4135-4144. doi:10.2147/DDDT.S224553
14. Trimmel H, Helbok R, Staudinger T, et al. S(+)-ketamine : current trends in emergency and intensive care medicine. *Wien Klin Wochenschr*. 2018;130(9-10):356-366. doi:10.1007/s00508-017-1299-3
15. Ramkiran S, Iyer SS, Dharmavaram S, Mohan CV, Balekudru A, Kunnavil R. BIS Targeted Propofol Sparing Effects of Dexmedetomidine Versus Ketamine in Outpatient ERCP: A Prospective Randomised Controlled Trial. *J Clin Diagn Res*. 2015;9(5):UC07-UC12. doi:10.7860/JCDR/2015/12435.5991
16. Eberl S, Koers L, van Hooft J, 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. doi:10.1097/EJA.0000000000001134
17. Association SOCCMCM. [Guidelines for analgesia and sedation treatment in intensive care unit of Chinese adults]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2018;30(6).
18. Al-Rifai Z, Mulvey D; ZAl-Rifai. DMulvey. Principles of total intravenous anaesthesia: basic pharmacokinetics and model descriptions. *BJA Educ*. 2016;16(3):92-97. doi:10.1093/bjaceaccp/mkv021
19. Goldberg TE, Chen C, Wang Y, et al. Association of Delirium With Long-term Cognitive Decline: A Meta-analysis. *JAMA Neurol*. 2020;77(11):1373-1381. doi:10.1001/jamaneurol.2020.2273
20. Han Q, Liu B, Lin S, et al. Pittsburgh Sleep Quality Index score predicts all-cause mortality in Chinese dialysis patients. *Int Urol Nephrol*. 2021;53(11):2369-2376. doi:10.1007/s11255-021-02842-6
21. Mason KP, Green SM, Piacevoli Q; International Sedation Task Force. Adverse event reporting tool to standardize the reporting and tracking of adverse events during procedural sedation: a consensus document from the World SIVA International Sedation Task Force. *Br J Anaesth*. 2012;108(1):13-20. doi:10.1093/bja/aer407
22. Mortero RF, Clark LD, Tolan MM, Metz RJ, Tsueda K, Sheppard RA. The effects of small-dose ketamine on propofol sedation: respiration, postoperative mood, perception, cognition, and pain. *Anesth Analg*. 2001;92(6):1465-1469. doi:10.1097/00000539-200106000-00022
23. Lee JY, Park JH, Hong JH. Analysis of the Hemodynamic Response During Radiofrequency Thermocoagulation in Trigeminal Neuralgia. *Pain Physician*. 2022;25(7):E1057-E1062.
24. Aguerreche C, Cadier G, Beurton A, et al. Feasibility and postoperative opioid sparing effect of an opioid-free anaesthesia in adult cardiac surgery: a retrospective study. *BMC Anesthesiol*. 2021;21(1):166. doi:10.1186/s12871-021-01362-1
25. Urvoy B, Aveline C, Belot N, Catier C, Beloeil H. Opioid-free anaesthesia for anterior total hip replacement under general anaesthesia: the Observational Prospective Study of Opiate-free Anesthesia for Anterior Total Hip Replacement trial. *Br J Anaesth*. 2021;126(4):e136-e139. doi:10.1016/j.bja.2021.01.001
26. Harun, Aydoğan & Aydogan, Timucin & Uyanikoglu, Ass.Prof.M.D.Ahmet & Kucuk, Ahmet & Yuce, Hasan & Karahan, mahmut alp & Buyukfirat, Evren & Yalcin, Saban. (2013). Propofol-ketamine combination has shorter recovery times with similar hemodynamics compared to propofol alone in upper gastrointestinal endoscopy in adults. A randomized trial. *Acta Medica Mediterranea*. 29.
27. Akhondzadeh R, Ghomeishi A, Nesioonpour S, Nourizade S. A comparison between the effects of propofol-fentanyl with propofol-ketamine for sedation in patients undergoing endoscopic retrograde cholangiopancreatography outside the operating room. *Biomed J*. 2016;39(2):145-149. doi:10.1016/j.bj.2015.11.002
28. Hasanein, R., & El-Sayed, W. Ketamine/propofol versus fentanyl/propofol for sedating obese patients undergoing endoscopic retrograde cholangiopancreatography (ERCP). *Egyptian Journal of Anaesthesia*, 29, 207 - 211.
29. Bahrami Gorji F, Amri P, Shokri J, Alereza H, Bijani A. Sedative and Analgesic Effects of Propofol-Fentanyl Versus Propofol-Ketamine During Endoscopic Retrograde Cholangiopancreatography: A Double-Blind Randomized Clinical Trial. *Anesth Pain Med*. 2016;6(5):e39835. doi:10.5812/aapm.39835
30. Chen HY, Meng XY, Gao H, et al. Esketamine-based opioid-free anaesthesia alleviates postoperative nausea and vomiting in patients who underwent laparoscopic surgery: study protocol for a randomized, double-blinded, multicentre trial. *Trials*. 2023;24(1):13. Published 2023 Jan 6. doi:10.1186/s13063-022-07003-3
31. Sigtermans MJ, van Hilten JJ, Bauer MCR, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain*. 2009;145(3):304-311. doi:10.1016/j.pain.2009.06.023
32. Kim YH, Lee PB, Oh TK. Is magnesium sulfate effective for pain in chronic postherpetic neuralgia patients comparing with ketamine infusion therapy? *J Clin Anesth*. 2015;27(4):296-300. doi:10.1016/j.jclinane.2015.02.006
33. Culp C, Kim HK, Abdi S. Ketamine Use for Cancer and Chronic Pain Management. *Front Pharmacol*. 2021;11:599721. doi:10.3389/fphar.2020.599721
34. Rabben T, Skjelbred P, Oye I. Prolonged analgesic effect of ketamine, an N-methyl-D-aspartate receptor inhibitor, in patients with chronic pain. *J Pharmacol Exp Ther*. 1999;289(2):1060-1066.
35. Wang JL, Leigheb M. New Year's greeting and overview of *World Journal of Orthopedics* in 2021. *World J Orthop*. 2021;12(2):56-60. doi:10.5312/wjo.v12.i2.56
36. Nagata A, Nakao S, Miyamoto E, et al. Propofol inhibits ketamine-induced c-fos expression in the rat posterior cingulate cortex. *Anesth Analg*. 1998;87(6):1416-1420. doi:10.1213/00000539-199812000-00040