Submitted: 26 February, 2024 Accepted: 06 May, 2024 Published: 08 October, 2024 DOI:10.22514/sv.2024.126

Open Access
Signa Vitae

ORIGINAL RESEARCH

Efficacy and safety of propofol in combination with different esketamine doses for anesthesia during loop electrosurgical excision procedure

Qian Wu[1], Yonggang Hao[1,*], Shanqiu Wang[1]

[1]Department of Anesthesiology, The First Affiliated Hospital of Chongqing Medical University, 400016 Chongqing, China

***Correspondence**
hyg203385@hospital-cqmu.com
(Yonggang Hao)

Abstract

To investigate the efficacy and safety of propofol combined with different doses of esketamine (ESK) for anesthesia during loop electrosurgical excision procedure (LEEP). Ninety female patients undergoing LEEP were randomly allocated to three groups: group P (2 mg/kg propofol + saline), group propofol + esketamine (PK)1 (1.5 mg/kg propofol + 0.5 mg/kg ESK), and group PK2 (1.5 mg/kg propofol + 0.25 mg/kg ESK). Parameters including mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), oxygen saturation (SPO_2), and venous carbon dioxide (P_vCO_2) were recorded. Additionally, the need for supplemental propofol, jaw thrust maneuver or ventilation, postoperative awakening time, and adverse reactions were assessed. After induction, there was a significant decrease in MAP and HR observed in group P, while an increase was noted in group PK1 (both $p < 0.05$), with no notable change in group PK2 ($p > 0.05$). By the 5-minute mark post-induction, group PK1 exhibited RR and P_vCO_2 levels similar to pre-induction levels ($p > 0.05$), whereas group PK2 demonstrated an increase in RR and a decrease in P_vCO_2 ($p < 0.05$). The occurrence of jaw thrust maneuvers in group PK1 and group P was higher than in group PK2 ($p < 0.05$). Moreover, fewer patients necessitated additional intraoperative propofol in groups PK1 and PK2 compared to group P ($p < 0.05$). The time to awakening was shorter in group PK2 than in groups PK1 and P ($p < 0.05$). Additionally, the frequency of postoperative vertigo was higher in group PK1 compared to groups P and PK2 ($p < 0.05$), the incidence of nausea did not significantly differ among the three groups ($p > 0.05$). Notably, neither irritation nor delirium was reported in any of the three groups. This study suggested that propofol combined with low-dose esketamine characterized minimal disruption to circulatory and respiratory parameters, reduced occurrences of adverse reactions, and faster postoperative awakening.

Keywords

Esketamine; LEEP; Propofol

1. Introduction

Loop electrosurgical excision procedure (LEEP) is a widely used surgical treatment for cervical lesions such as cervical intraepithelial neoplasia (CIN), cervical erosion, and cervicitis [1]. It involves the application of high-frequency electric waves via a loop electrosurgical device, which generates intense heat upon tissue contact, facilitating tissue resection. Despite its simplicity, LEEP often induces significant pain and discomfort, with reported mean Visual Analog Scale (VAS) scores reaching as high as 4, even under local anesthesia [2]. Patient movement during the procedure can severely impact surgical accuracy, highlighting the need for an effective anesthesia regimen to ensure successful LEEP outcomes.

Propofol is a widely used intravenous anesthetic for LEEP due to its sedative and amnestic properties, as well as its fast onset and recovery [3]. However, it lacks analgesic effects and can lead to dose-dependent hemodynamic and respiratory depression. Esketamine (ESK), an enantiomer of ketamine derived from phencyclidine, shares similar sedative and analgesic properties with ketamine but is known for its faster clearance and lower toxicity incidence [4].

To date, only a few studies have explored the combination of propofol with other analgesics for LEEP, such as fentanyl, ketamine or dezocine [5, 6]. Thus, this study aims to evaluate the anesthetic effectiveness and safety of propofol in combination with different doses of ESK in LEEP.

2. Materials and methods

2.1 Patients information

A total of ninety female patients who underwent LEEP between January and October 2022 were recruited for this study. Eligible participants were aged between 20 and 60 years, had a body mass index (BMI) ranging from 18 to 30 kg/m^2, and an American Society of Anesthesiologists (ASA) physical status classification of grade I or II.

Exclusion criteria encompassed the following: (1) Patients who declined participation; (2) Individuals with a history of hypertension, hyperthyroidism, neurological or mental disorders; (3) Patients currently using or having used opioids and non-steroidal anti-inflammatory drugs within 48 hours prior to surgery; (4) Participation in other drug clinical trials within the preceding 4 weeks; (5) Allergy to ESK or propofol; (6) History of opioid or ESK addiction.

The random-number table method was utilized to allocate patients into control and observation groups. Patients were categorized into three groups: propofol (2 mg/kg) + normal saline (group P), propofol (1.5 mg/kg) + ESK (0.5 mg/kg) (group PK1), and propofol (1.5 mg/kg) + ESK (0.25 mg/kg) (group PK2). In group P, patients received an intravenous injection of an equivalent dose of normal saline followed by 2 mg/kg of propofol. Group PK1 received an intravenous injection of 0.5 mg/kg ESK followed by 1.5 mg/kg of propofol. Similarly, group PK2 received an intravenous injection of 0.25 mg/kg ESK followed by 1.5 mg/kg of propofol. The rate of propofol induction did not exceed 40 mg/10 seconds.

Dosages of propofol and ESK were calculated by a blinded researcher based on total body weight. ESK was diluted with normal saline in a 10 mL syringe. The researchers responsible for randomization and blinding procedures were not involved in the subsequent follow-up study. Neither other investigators nor patients were informed of the study grouping or the experimental drugs until the end of the study.

2.2 Method of anesthesia

All patients fasted for 6 hours for food and 2 hours for water before the surgery. Upon admission to the operating room, peripheral venous access was established. Patients' vital signs, including heart rate (HR), peripheral oxygen saturation (SpO_2), and blood pressure, were continuously monitored using a 3-lead electrocardiogram (ECG), pulse oximeter, and non-invasive blood pressure monitor, respectively. Additionally, patients received 5 L/min of pure oxygen via an oxygen mask at least 3 minutes before anesthesia and throughout the surgical procedure.

Surgery started upon achieving a modified Observer Assessment of Alertness/Sedation scale (MOAA/S) score of <2 [7], as detailed in Table 1. If physical movement occurred during surgery (defined as any movement of the body, such as opening the eyes, clenching the legs, or raising the hands), an additional 1 mg/kg of propofol was administered. In instances where SpO_2 dropped below 95% during the procedure, a jaw thrust maneuver or face mask ventilation was performed. After surgery, the patients were transferred to the recovery room to monitor vital signs, including HR, respiratory rate (RR), non-invasive blood pressure (NIBP), and SpO_2. Discharge from the recovery room was approved upon achieving an MOAA/S score of 5.

TABLE 1. Modified Observer's Alertness/Sedation scale score (MOAA/S).

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

2.3 Outcome measures

The HR, RR, MAP and SpO_2 were recorded upon admission to the operating room, as well as at 1 minute and 5 minutes post-anesthesia. Venous carbon dioxide (P_vCO_2) levels were assessed at admission and 5 minutes post-anesthesia. The number of additional instances of propofol usage, occurrences of jaw thrust maneuvers or face mask ventilation, postoperative awakening time (defined as achieving a MOAA/S score >4), and incidences of postoperative vertigo, nausea, agitation and delirium were documented for all three groups.

2.4 Statistical analysis

The study sample size was determined based on the results of a small-sample pre-experiment using awakening time as the primary outcome. Utilizing the PASS 11 software (NCSS, Kaysville, Utah), it was calculated that 27 patients would be needed in each group to achieve a power of 0.90 and a type I error rate of 0.05. Considering a dropout rate of 10%, the sample size was adjusted to 30 patients per group, resulting in a total of 90 patients for randomization. Data were analyzed using the SPSS v26.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables with a normal distribution are presented as mean $\pm$ standard deviation ($\bar{x} \pm s$) and compared using the t-test or one-way analysis of variance (ANOVA). Categorical data are expressed as frequency or percentage (%) and compared using the χ^2 test or Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

3. Results

Of the initial 96 patients assessed for eligibility in this study, six patients declined to participate. Thus, the remaining 90 patients were randomly assigned to the different study groups, as illustrated in Fig. 1.

3.1 Demographics

Data analysis showed no significant differences among the three groups in terms of patients' age, BMI, operation time, ASA classification, or underlying conditions such as diabetes and motion sickness ($p > 0.05$) (Table 2).

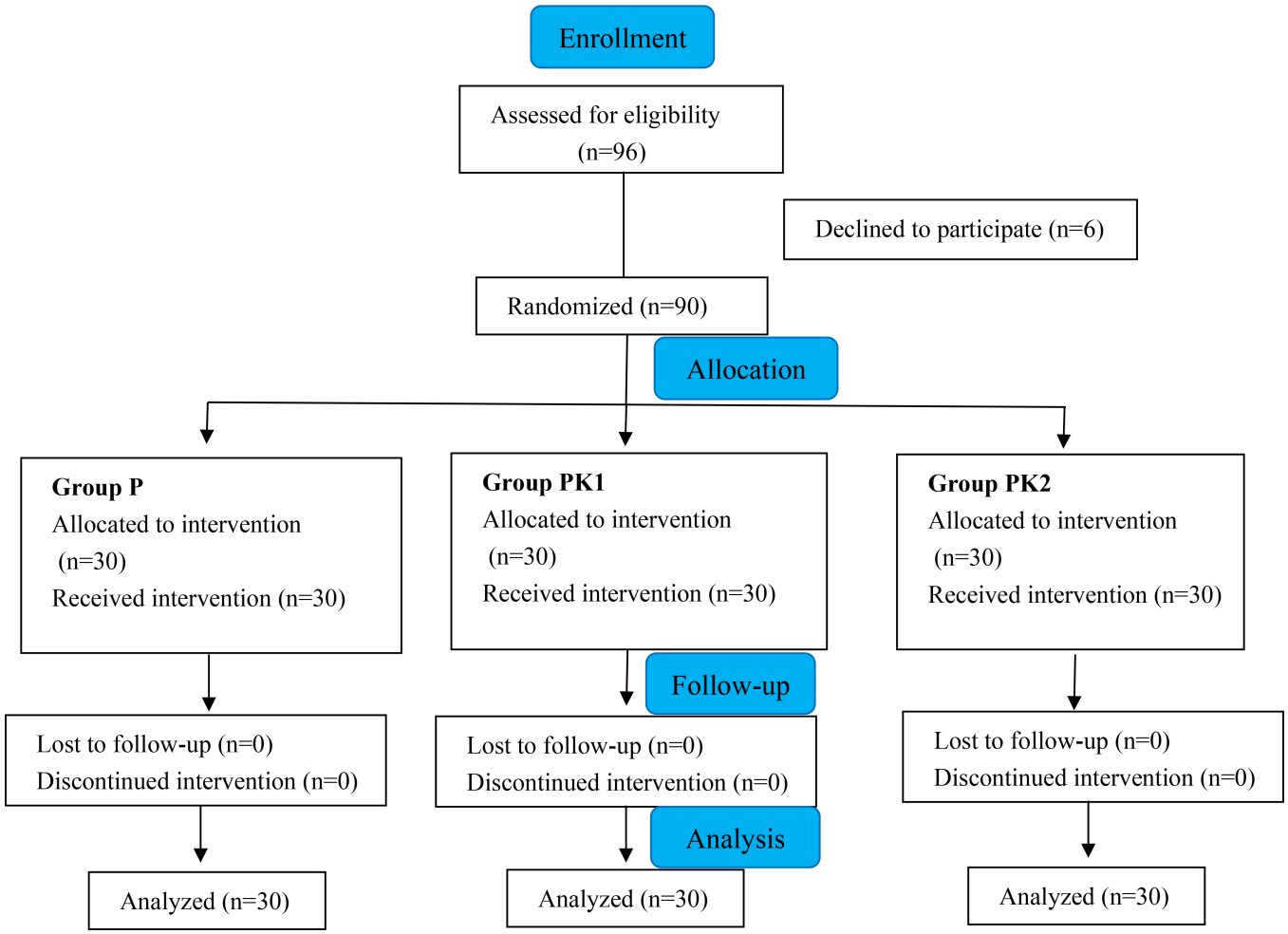

FIGURE 1. CONSORT flow chart of patient selection and study group allocation. PK: propofol + esketamine.

TABLE 2. Patients' baseline characteristics.

Characteristics	Group P	Group PK1	Group PK2
Sample size, n	30	30	30
Age (yr)	37.0 ± 3.9	39.6 ± 7.5	39.4 ± 5.9
BMI (kg/m^2)	22.2 ± 1.5	22.0 ± 2.4	22.7 ± 2.0
Operation time (min)	6.0 ± 1.0	5.6 ± 0.7	6.1 ± 1.3
ASA (I/II) (n)	28/2	26/4	29/1
Diabetes, n (%)	1 (3.3)	2 (6.7)	0 (0.0)
Motion sickness, n (%)	2 (6.7)	1 (3.3)	1 (3.3)

Data are presented in n (%) or $\bar{x} \pm s$. BMI: body mass index; ASA: American Society of Anesthesiologists; PK: propofol + esketamine.

3.2 Comparison of MAP, HR and RR

In group P, patients showed significantly lower MAP at 1 minute and 5 minutes post-induction compared to pre-induction levels ($p < 0.05$). Conversely, patients in group PK1 demonstrated significantly higher MAP at 1 minute post-induction ($p < 0.05$), with comparable MAP at 5 minutes post-induction compared to pre-induction levels ($p > 0.05$). However, no significant changes in MAP were observed at 1 minute and 5 minutes post-induction in group PK2 ($p > 0.05$) (Fig. 2).

Moreover, HR was notably reduced at 1 minute and 5 minutes post-induction in group P ($p < 0.05$) but significantly increased at 1 minute and 5 minutes post-induction in both groups PK1 and PK2 ($p < 0.05$). In regard to RR, the results showed that RR was significantly decreased at 1 minute post-induction in groups P ($p < 0.05$), PK1 ($p < 0.01$) and PK2 ($p < 0.01$). However, while there was no change in RR at 5 minutes post-induction in group PK1 ($p > 0.05$), RR significantly increased at 5 minutes post-induction in group PK2 ($p < 0.05$).

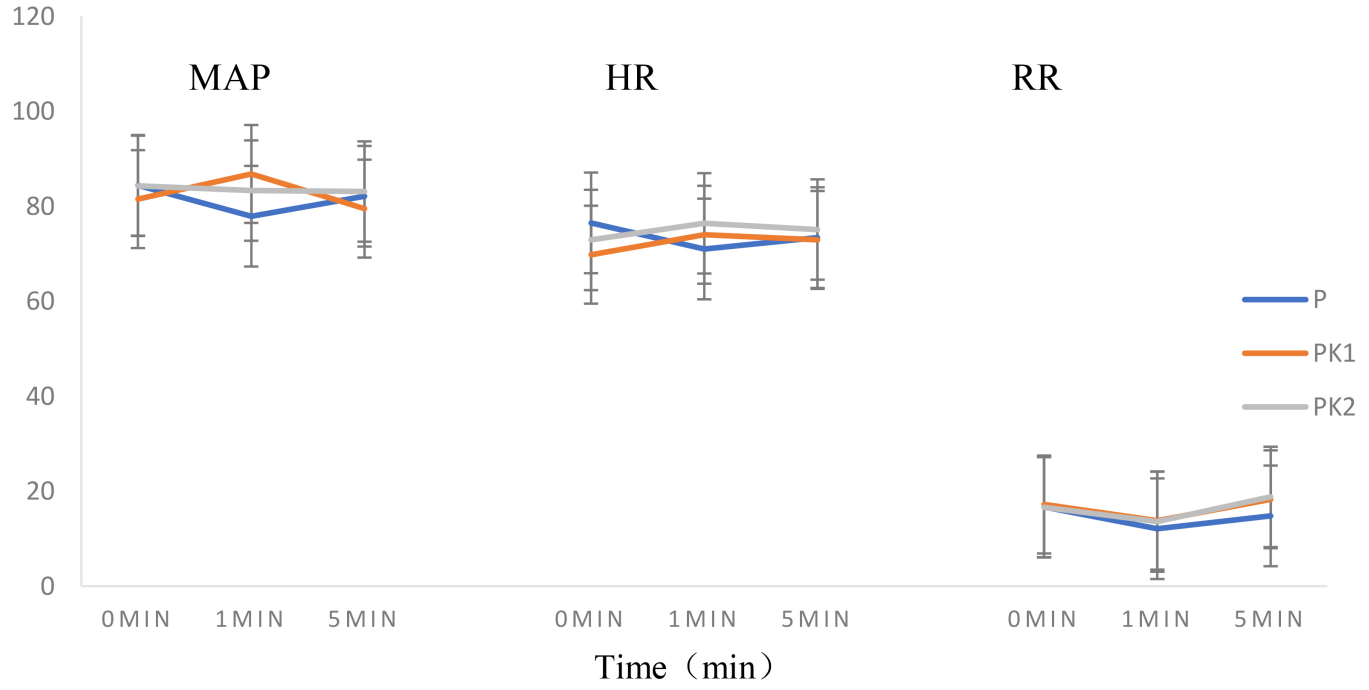

FIGURE 2. The MAP, HR and RR before induction and at 1 minute and 5 minutes post-induction. MAP: mean arterial pressure; HR: heart rate; RR: respiratory rate; PK: propofol + esketamine.

3.3 Change in P_vCO_2

At 5 minutes post-induction, there was a significant increase in P_vCO_2 observed in group P ($p < 0.05$), while no significant change was noted in group PK1 ($p > 0.05$). Comparatively, the P_vCO_2 significantly decreased at 5 minutes post-induction in group PK2 ($p < 0.05$), as illustrated in Fig. 3.

3.4 Additional propofol usage, jaw thrust maneuver and adverse reactions

The number of additional propofol usages was significantly lower in groups PK1 and PK2 compared to group P ($p < 0.05$), with similar rates between groups PK1 and PK2 ($p > 0.05$). The frequency of jaw thrust maneuvers was comparable between groups PK2 and P, but lower in group PK2 than in group PK1 ($p < 0.05$). Incidence of vertigo was significantly higher in group PK1 than in groups P and PK2 ($p < 0.05$), while no significant difference was found between the latter two groups ($p > 0.05$). There was no significant difference in the incidence of nausea among the three groups ($p > 0.05$). Awakening time was significantly shorter in group PK2 than in groups P and PK1 ($p < 0.05$) but similar between groups P and PK1 ($p > 0.05$) (Table 3).

4. Discussion

Propofol is widely favored in clinical anesthesia due to its rapid onset and recovery. It acts by enhancing the activity of the inhibitory neurotransmitter, γ-Aminobutyric acid (GABA). However, as propofol lacks analgesic effects, it is often used in combination with analgesics. ESK represents a novel N-methyl-D-aspartate (NMDA) receptor blocker with significantly higher affinity—3 to 4 times greater—for the NMDA receptor phencyclidine binding site, and a 2-fold higher affinity for the opioid receptor compared to ketamine [8]. Jia *et al.* [9] demonstrated that ESK exhibits more potent anesthetic and analgesic effects, with a faster onset (within 30 seconds of intravenous infusion) and shorter elimination half-life than ketamine. Theoretically, the advantages and disadvantages of propofol and ESK can complement each other.

This study demonstrates that both propofol combined with 0.5 mg/kg ESK and a subanesthetic dose of 0.25 mg/kg ESK can achieve deep sedation (MOAAS <2), indicating the effectiveness of propofol + ESK for LEEP anesthesia. Furthermore, the lower number of additional propofol usages in patients receiving propofol + ESK compared to those receiving propofol alone aligns with the sedative and analgesic properties of ESK. Conversely, awakening time was significantly shorter in the propofol + 0.25 mg/kg ESK group than in the propofol alone and propofol + 0.5 mg/kg ESK groups, but similar between the latter two groups, thereby suggesting that post-anesthetic awakening time could be influenced by the dose of ESK.

The study findings indicate that at 1 minute and 5 minutes post-induction, MAP and HR significantly decreased in group P, increased in group PK1, and remained unchanged in group PK2. These observed changes can be attributed to the dose-dependent stimulatory effect of ESK on the cardiovascular system, primarily mediated by its sympathomimetic effect and augmentation of endogenous catecholamine release, as well as inhibition of norepinephrine reuptake [10, 11]. Additionally, the concurrent administration of propofol and ESK results in a reduction in the propofol dosage, mitigating its suppressive impact on the circulatory system [7]. Importantly, the study highlights that propofol combined with low-dose ESK has a diminished effect on patient circulation.

Ensuring minimal depression of RR and tidal volume is crucial for LEEP anesthesia safety. This study found that the

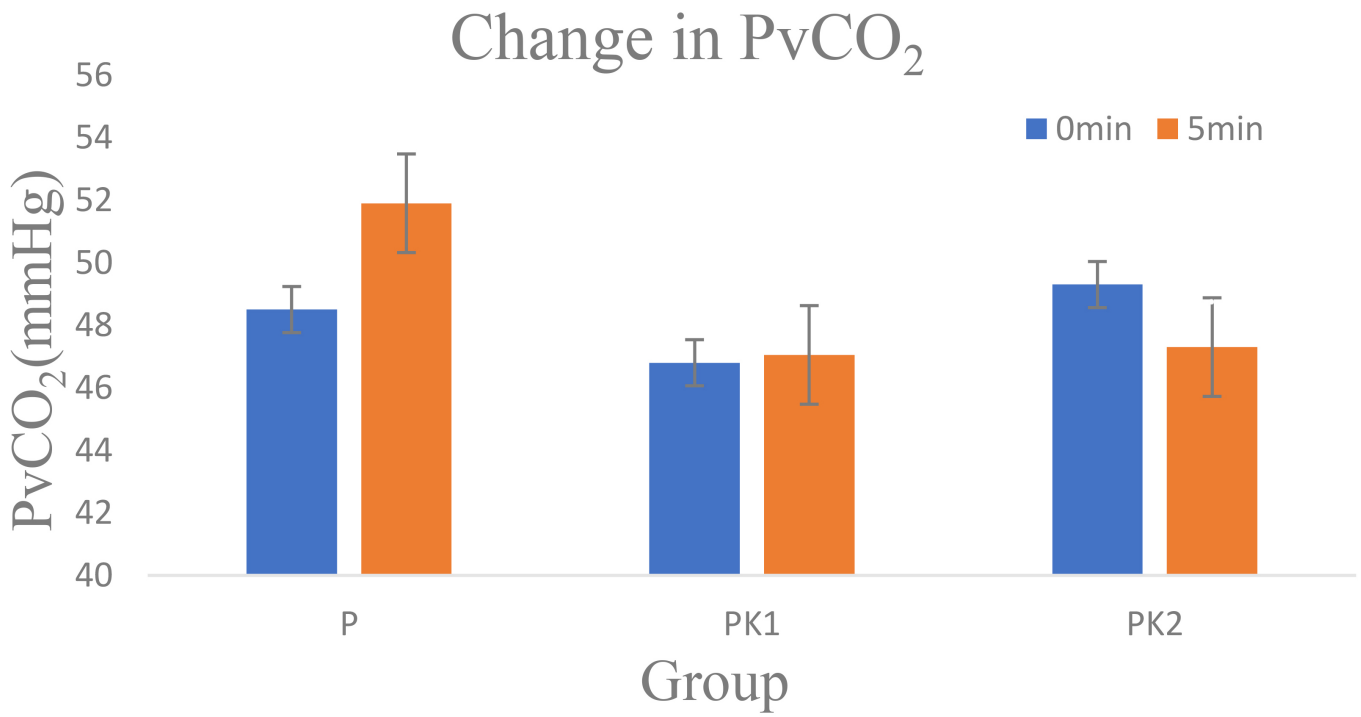

FIGURE 3. P_vCO_2 before induction and at 5 minutes post-induction. P_vCO_2: venous carbon dioxide; PK: propofol + esketamine.

TABLE 3. Comparison of other outcome measures between the study groups.

Outcomes	Group P (n = 30)	Group PK1 (n = 30)	Group PK2 (n = 30)	Group P & PK1	Group P & PK2	Group PK1 & PK2
Additional propofol	19 (63)	3 (10)	10 (33)	$p = 0.015$	$p = 0.039$	$p = 0.028$
Jaw thrust maneuver or ventilation	16 (53)	10 (33)	3 (10)	$p = 0.118$	$p = 0.001$	$p = 0.028$
Vertigo	6 (20)	18 (60)	9 (30)	$p = 0.002$	$p = 0.037$	$p = 0.020$
Nausea	1 (3)	3 (10)	0 (0)	$p = 0.605$	$p = 1.000$	$p = 0.237$
Awakening time (min)	6.2 ± 1.3	6.4 ± 1.6	4.5 ± 1.3	$p = 0.598$	$p = 0.001$	$p = 0.001$

Data are presented in n (%) or $\bar{x} \pm s$. PK: propofol + esketamine.

frequency of jaw thrust maneuvers or face mask ventilation, indicating transient hypoxia (SpO_2 <95%), was lower in the propofol + ESK groups compared to the propofol alone group, with the lowest occurrence observed in group PK2. This finding aligns with previous research on propofol combined with ESK in procedures like gastrointestinal endoscopy and fiberoptic bronchoscopy [12, 13]. ESK-induced respiratory stimulation mechanisms may involve its sympathomimetic effect, N-methyl-D-aspartate receptor blockade, or its metabolite hydroxynorketamine [14]. This respiratory stimulation advantage is absent when combining propofol with other drugs like fentanyl during anesthesia. Furthermore, in this study, the RR decreased following induction but returned to preoperative levels alongside P_vCO_2 in the PK1 group after five minutes. Conversely, the PK2 group exhibited a faster RR and lower P_vCO_2 than baseline, suggesting ESK's respiratory system effects may be dose-dependent and require further investigation.

The common adverse events associated with ESK include vertigo, nausea, vomiting and mental symptoms. However, these adverse effects are reported to be lower with ESK compared to ketamine [15]. In our present study, none of the patients experienced vomiting or mental symptoms, and the incidence of nausea was similar among the groups. Vertigo, attributed to ESK's stimulation of the thalamus and limbic system [16], was more prevalent in group PK1 than in groups P and PK2 but similar between the latter two groups. These findings suggest that administering ESK at an appropriate dose could reduce the occurrence of adverse reactions.

The present study had several limitations. Firstly, it is a single-center study with a small sample size and limited sample diversity, which may affect the generalizability of the results. Therefore, future studies should aim to expand the sample size to provide more robust evidence for clinical treatment. Additionally, the assessment of the patients' anesthetic status relied solely on the MOAA/S score, and the inclusion of other methods, such as the Bispectral Index (BIS), could further validate the results. Furthermore, this study only investigated the effects of 0.5 mg/kg and a sub-anesthetic dose of 0.25 mg/kg ESK. Future research could explore additional doses, such as 0.3 mg/kg and 0.4 mg/kg, to provide a more comprehensive

understanding of ESK's effects.

5. Conclusions

Propofol combined with ESK was found to be a safe and effective anesthetic strategy for female patients undergoing LEEP. Notably, propofol combined with low-dose ESK exhibited reduced impact on circulation, minimal influence on RR and depth, lower incidence of adverse effects, and shorter awakening time.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

QW, YGH and SQW—designed the research study; analyzed the data. QW and YGH—performed the research; wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This prospective, double-blind, randomized controlled study was conducted following the ethical standards of the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Approval no. 2022-71) and registered in the ClinicalTrials.gov (NCT06574945), and followed the principles outlined in the 1964 Helsinki Declaration and its subsequent amendments regarding ethical research involving human subjects. Informed consent was obtained from all participants prior to their inclusion in the study.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Ramírez SI, Lutzkanin A. Management of cervical dysplasia using office loop electrosurgical excision procedure. Primary Care. 2021; 48: 583–595.

[2] Limwatanapan N, Chalapati W, Songthamwat S, Saenpoch S, Buapaichit K, Songthamwat M. Lidocaine spray versus paracervical block during loop electrosurgical excision procedure: a randomized trial. Journal of Lower Genital Tract Disease. 2018; 22: 38–41.

[3] Yan T, Zhang GH, Wang BN, Sun L, Zheng H. Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: a prospective, randomized and controlled study. BMC Anesthesiology. 2018; 18: 131.

[4] Song N, Yang Y, Zheng Z, Shi W, Tan A, Shan X, *et al*. Effect of esketamine added to propofol sedation on desaturation and hypotension in bidirectional endoscopy. JAMA Network Open. 2023; 6: e2347886.

[5] Oh C, Kim Y, Eom H, Youn S, Lee S, Ko YB, *et al*. Procedural sedation using a propofol-ketamine combination (Ketofol) *vs.* propofol alone in the loop electrosurgical excision procedure (LEEP): a randomized controlled trial. Journal of Clinical Medicine. 2019; 8: 943.

[6] Liu Z, Zou X, Sun X, Fan W. Loop electrosurgical excision procedure under propofol intravenous anesthesia combined with nano-silver gel in the treatment of cervicitis. Cellular and Molecular Biology. 2022; 68: 96–104.

[7] 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. European Journal of Anaesthesiology. 2020; 37: 394–401.

[8] Li H, Wu H, Peng J. Evaluation of low-dose esketamine on sleep quality in elderly patients undergoing painless gastroscopy. Tropical Journal of Pharmaceutical Research. 2023; 22: 887–891.

[9] Jia T, Teng J. New narcotic analgesics: esketamine. Chinese Journal of Clinical Pharmacology and Therapeutics. 2022; 27: 834–840.

[10] Yang H, Zhao Q, Chen H, Liu W, Ding T, Yang B, *et al*. The median effective concentration of propofol with different doses of esketamine during gastrointestinal endoscopy in elderly patients: a randomized controlled trial. British Journal of Clinical Pharmacology. 2022; 88: 1279–1287.

[11] Chen H, Ding X, Xiang G, Xu L, Liu Q, Fu Q, *et al*. Analysis of the efficacy of subclinical doses of esketamine in combination with propofol in non-intubated general anesthesia procedures—a systematic review and meta-analysis. BMC Anesthesiology. 2023; 23: 245.

[12] Lu C, Ren J, Guo X, Qian J. Effects of remimazolam combined with esketamine anesthesia on circulatory and respiratory function during painless gastroenteroscopy. Contrast Media & Molecular Imaging. 2022; 2022: 1079099.

[13] Nie J, Chen W, Jia Y, Zhang Y, Wang H. Comparison of remifentanil and esketamine in combination with propofol for patient sedation during fiberoptic bronchoscopy. BMC Pulmonary Medicine. 2023; 23: 254.

[14] Jonkman K, van Rijnsoever E, Olofsen E, Aarts L, Sarton E, van Velzen M, *et al*. Esketamine counters opioid-induced respiratory depression. British Journal of Anaesthesia. 2018; 120: 1117–1127.

[15] Eberl S, Koers L, van Hooft JE, de Jong E, Schneider T, Hollmann MW, *et al*. Sedation with propofol during ERCP: is the combination with esketamine more effective and safer than with alfentanil? Study protocol for a randomized controlled trial. Trials. 2017; 18: 472.

[16] Trujillo KA, Heller CY. Ketamine sensitization: influence of dose, environment, social isolation and treatment interval. Behavioural Brain Research. 2020; 378: 112271.

How to cite this article: Qian Wu, Yonggang Hao, Shanqiu Wang. Efficacy and safety of propofol in combination with different esketamine doses for anesthesia during loop electrosurgical excision procedure. Signa Vitae. 2024; 20(10): 56-61. doi: 10.22514/sv.2024.126.