

ORIGINAL RESEARCH

AMBULTORY ANESTHESIA

Clinical application of esketamine-induced mild sedation technique in outpatient oral surgery

Zhijun Xin¹, Tao Yu^{2#}, Lian Lian Wang³, Weidong Qu⁴, Ning Wang^{5*}, Meiling Yao^{6**}

Author affiliations:

1. Zhijun Xin, Department of Anesthesiology, Yantai Stomatology Hospital of Binzhou Medical University, Yantai, Shandong 264000, China: E-mail: zhijun1711@126.com
2. Tao Yu, Department of Oral and Maxillofacial Surgery, Yantai Stomatology Hospital of Binzhou Medical University, Yantai, Shandong 264000, China; E-mail: yutao199608@163.com
3. Lian Lian Wang, Department of Anesthesiology, Yantai Stomatology Hospital of Binzhou Medical University, Yantai, Shandong 264000, China: E-mail: 117119971@qq.com
4. Weidong Qu, Department of Oral and Maxillofacial Surgery, Yantai Stomatology Hospital of Binzhou Medical University, Yantai, Shandong 264000, China; E-mail: qwd0109@163.com
5. Ning Wang, Department of Anesthesiology, Yantai Stomatology Hospital of Binzhou Medical University, Yantai, Shandong 264000, China: E-mail: 951981202@qq.com
6. Meiling Yao, Department of Clinical laboratory, Yantai Stomatology Hospital of Binzhou Medical University, Yantai, Shandong 264000, China; E-mail: ytyaoml@163.com

#Co-first author: Tao Yu; E-mail: yutao199608@163.com

*Corresponding author: Ning Wang; E-mail: 951981202@qq.com

**Co-corresponding author: Meiling Yao, E-mail: ytyaoml@163.com

ABSTRACT

Background & Objective: Sedation is often required in outpatient surgical procedures, performed under local analgesia, to allay the anxiety of the patient, which may lead to involuntary movements of the patient, thus interfering in the smooth course of the surgery. Various sedative drugs have been used by the anesthetists. We compared the effects of mild sedation techniques induced by remifentanyl combined with propofol and esketamine combined with propofol on the cardiopulmonary indices of intraoperative patients, and to explore the application of mild sedation techniques in oral outpatient surgery.

Methodology: A total of 62 patients undergoing oral surgery were randomly divided into a control group (31 cases, receiving remifentanyl combined with propofol) and an observation group (31 cases, receiving esketamine combined with propofol). The vital signs of the patients were monitored at five time points: admission (T0), anesthesia induction (T1), local anesthesia (T2), the beginning of surgery (T3), and the end of surgery (T4), including heart rate (HR), mean arterial pressure (MAP), bispectral index (BIS), respiratory rate, and oxygen saturation (SPO₂). Postoperative memory of each step was recorded, and the sedative effect was evaluated by physician and patient using the visual analogue scale (VAS).

Results: During surgery, 6 patients in the control group had SpO₂ < 90%, and 8 patients experienced coughing or tongue fall, while 1 patient in the observation group had a transient increase in blood pressure. After intravenous administration, all patients had a decrease in HR, and the decrease in the observation group was significantly less than that in the control group (P < 0.05). The BIS values in the observation group were significantly higher than those in the control group during T2 and T3.

Conclusion: In oral outpatient surgery, the combination of propofol and esketamine-induced mild sedation can stabilize the hemodynamic indices of patients during surgery, reduce the incidence of complications, and improve patient satisfaction.

Abbreviations: BIS- Bispectral Index; HR- Heart Rate; RASS- Richmond Agitation-Sedation Scale; SBP- Systolic Blood Pressure; VAS- Visual Analogue Scale

Key words: Mild Sedation; Esketamine; Propofol; Remifentanyl; Oral Surgery

Citation: Xin Z, Yu T, Wang LL, Qu W, Wang N, Yao M. Clinical application of esketamine-induced mild sedation technique in outpatient oral surgery. *Anaesth. pain intensive care* 2022;27(6):715–720; **DOI:** 10.35975/apic.v27i6.2234

Received: May 28, 2023; **Revised:** October 24, 2023; **Accepted:** November 08, 2023

1. INTRODUCTION

In the recent years, the development of intravenous sedation technology has provided safe and comfortable surgical conditions for patients, so it has been widely accepted by doctors and patients. Mild sedation is the use of one or more drugs to produce a state of depression in the central nervous system that enables treatment, but throughout the sedation period, the patient is able to purposefully respond to verbal cues, either alone or in combination with mild tactile stimulation.¹ Mild sedation has the effect of maintaining independent and sustained airway patency without any intervention, adequate spontaneous ventilation, and thus maintenance of cardiovascular function.² Therefore, moderate sedation is used in a variety of outpatient procedures, such as endoscopy, colonoscopy, bronchoscopy, and oral outpatient procedures. In recent years, propofol has been widely used in combination with opioids for sedation.

Esketamine, which has both sedative and analgesic functions, can be used in combination with propofol. Its sympathomimetic properties can counteract the effects of propofol, thereby reducing the risk of cardiovascular and respiratory depression.³ No studies have been reported on the specific experience of using esketamine for oral clinical treatment under mild sedation. In this study, propofol combined with esketamine and remifentanyl combined with esketamine were used to induce mild sedation. The effects of different drug-induced mild sedation techniques on cardiopulmonary parameters were compared, and the application of mild sedation techniques in oral outpatient surgery was discussed.

2. METHODOLOGY

2.1. General Information

In this study, 62 patients who underwent outpatient oral surgery under intravenous sedation at Yantai Stomatological Hospital of Binzhou Medical University from March 2021 to December 2022 were selected for comparative analysis. The patients were randomly divided into two groups of 31 each using a random number system: the remifentanyl combined with the propofol group (control group) and the esketamine combined with the propofol group (observation group).

Inclusion criteria were: (1) The patients who have good general condition, able to tolerate surgery, American Society of Anesthesiologists (ASA) classification grade

I or II, and no respiratory system diseases; (2) dental anxiety and a score greater than 4 on the Dental Anxiety Scale; (3) expected surgery time less than one hour; (4) the patients and their family understood and accepted the possible risks and complications of surgery and propofol intravenous sedation and agreed to treatment and voluntarily signed an informed consent form.

Exclusion criteria were surgical contraindications and those who were allergic or had contraindications to the drugs used in this study. This study was approved by the Medical Ethics Committee of Yantai Stomatological Hospital of Binzhou Medical University (ethics approval number: 2021-11).

2.2. Anesthesia and Surgical Methods

After collecting basic patient information, routine examinations were performed before surgery to exclude contraindications for surgery and anesthesia. Patients were fasted and prohibited from eating and drinking for 6 h before surgery. They were placed in the same operating room equipped with a standard anesthesia workstation. After entering the room, intravenous access was established, and nasal oxygen therapy was initiated at a flow rate of 5 L/min. The patient was positioned supine with the head elevated by 30°. In the experimental group, intravenous injection of 0.25 mg/kg of esketamine was administered followed by intravenous infusion of 0.5 mg/kg of propofol as a loading dose, and maintenance continued at a rate of 2.5–5 mg/kg/h. In the control group, intravenous injection of 0.5 mg/kg of propofol was used as the loading dose, and maintenance was continued at a rate of 2.5–5 mg/kg/h, followed by intravenous infusion of 0.1–0.15 µg/kg/h of remifentanyl. Local infiltration anesthesia with lidocaine with adrenaline was used for all patients during surgery. Sedation, local anesthesia, and surgical procedures were performed by the same experienced surgical anesthesia team.

Bispectral index (BIS) monitoring was performed during surgery, with BIS values maintained between 70–90 representing sedation. If the BIS value exceeded 90 and lasted for more than 2 min, an additional 0.5 mg/kg of propofol was administered IV. If the patient's SpO₂ dropped below 90% during surgery, the patient's name was immediately called out loudly, and they were instructed to take deep breaths. If necessary, the operation was temporarily suspended, and the chin was lifted to open the airway. If the systolic blood pressure (SBP) fell by more than 20% from the baseline during

surgery, ephedrine was administered intravenously; if the SBP rose by more than 20% from the baseline value, urapidil was administered intravenously. If the HR dropped below 50 beats/min during surgery, atropine was administered IV. The depth of sedation was assessed every 5 min during surgery using the Richmond Agitation-Sedation Scale (RASS). When RASS was between 0-3, the patient was considered to be in a lightly sedated state with preserved consciousness.

The vital signs of patients were monitored at five time points: admission to the OR (T0), anesthesia induction (T1), local anesthesia (T2), the start of surgery (T3), and the end of surgery (T4). The recorded vital signs included heart rate (HR), mean arterial pressure (MAP), bispectral index (BIS), respiratory rate (RR), and blood oxygen saturation (SpO₂). After the surgery, we recorded the patient's memory of each stage of the surgery, evaluated the patient's satisfaction level using the visual analog scale (VAS), with 0 representing completely dissatisfied and 10 representing very satisfied.

2.3. Statistical Analysis

The data were analyzed using SPSS 20.0 software. After checking the normality of the data, normally distributed metric data were expressed as mean \pm standard deviation ($\bar{x} \pm s$), and the t-test was used for group comparisons. Count data were represented by n (%), and the chi-square test or Fisher's exact probability test were used. A P < 0.05 was considered statistically significant.

3. RESULTS

A total of 62 patients participated in this study, with ages ranging from 9 to 38 years old, with a mean age of 21.5 years old, and a male-to-female ratio of 35:27. Among

them, there were 22 cases of root cyst excision, 36 cases of tooth extraction, and 4 cases of lingual frenectomy, all of which were successfully completed within less than

Table 1. Occurrence of adverse events during anesthesia

Adverse events	Control group (n = 31)	Observation group (n = 31)
SpO ₂ < 90%	6 (19.35)	3 (9.68)
Elevation of blood pressure	0	1 (3.2)
Hypotension	3 (9.68)	0
Bradyarrhythmia	3 (9.68)	0
Body movement	6 (19.35)	5 (16.1)
Bucking	8 (25.8)	3 (9.68)
Summation	18 (58.08)	9 (29.04)

one hour of surgery time. Frequency of adverse events during the surgical procedures in the two groups are given in Table 1. All patients had complete amnesia of the various stages of the surgery, and there was a no recall of communication between the doctors and patients during the surgery. Among the observation group, 6 patients reported having dreams during the surgery, with strong feelings of pleasure and excitement. One week after the surgery, all 62 patients had no apparent postoperative anesthesia or surgical complications.

3.1. Vital data record

Compared with the time point T0 when all patients were given intravenous administration, the heart rate (HR) of all patients decreased, and the decrease in the observation group was significantly less than that in the control group (P < 0.05). After intravenous administration, the bispectral index (BIS) of both groups of patients decreased significantly, and it slightly increased when local anesthesia was administered. During the operation, the BIS of the observation group was significantly higher than that of the control group at

Table 2: Vital signs data of two groups of patients at different time points

Time point		T0	T1	T2	T3	T4
Control group (n=31)	HR (beats/min)	93.13 \pm 12.50	89.46 \pm 14.53 [#]	86.42 \pm 16.72 [#]	83.92 \pm 15.61 [#]	85.13 \pm 16.09 [#]
	MAP (mmHg)	89.35 \pm 10.41	90.22 \pm 14.01	87.42 \pm 11.36	87.12 \pm 12.24	87.08 \pm 10.09
	BIS	97.73 \pm 1.24	86.28 \pm 4.43 [#]	88.32 \pm 4.41 [#]	85.83 \pm 5.65 [#]	86.08 \pm 4.66 [#]
	RR (breaths/min)	18.11 \pm 3.02	16.83 \pm 3.27	17.35 \pm 2.81	17.15 \pm 1.83	16.85 \pm 2.43
	SpO ₂ (%)	99.28 \pm 0.41	98.42 \pm 2.50	98.32 \pm 2.41	98.03 \pm 2.87	99.01 \pm 2.37
Observation group (n=31)	HR (beats/min)	92.81 \pm 15.50	90.63 \pm 16.56 [#]	89.92 \pm 15.92 ^{**}	86.22 \pm 13.42 ^{**}	86.33 \pm 13.39 ^{**}
	MAP (mmHg)	89.08 \pm 11.11	90.67 \pm 12.21	88.61 \pm 10.56	90.42 \pm 10.23 [*]	88.36 \pm 10.24
	BIS	98.15 \pm 1.33	87.58 \pm 4.94 [#]	90.81 \pm 3.21 ^{**}	88.83 \pm 4.25 ^{**}	87.08 \pm 5.61 [#]
	RR (breaths/min)	18.43 \pm 4.02	17.23 \pm 3.19	18.55 \pm 1.81	17.55 \pm 1.81	17.25 \pm 2.26
	SpO ₂ (%)	99.12 \pm 0.52	98.50 \pm 2.47	98.66 \pm 2.44	98.38 \pm 3.02	98.63 \pm 2.87

Note: Compared with the control group, *P < 0.05; compared with T0, [#]P < 0.05.

Table3: Comparative surgeon and patient satisfaction between the two groups.

Group	Surgeon satisfaction	Patient satisfaction
Control group (n = 31)	8.9 ± 1.2	9.2 ± 1.4
Observation group (n = 31)	9.2 ± 1.3	9.1 ± 1.5

time points T2 and T3. The mean arterial pressure (MAP) of the observation group was significantly higher than that of the control group at the start of surgery (T3) (Table 2).

3.2. Surgeon and patient satisfaction

No significant difference was found in the surgeon satisfaction and the patients' satisfaction between the two groups (Table 3).

4. DISCUSSION

Intravenous sedation techniques can easily control the degree of sedation and are the most widely used in modern anesthesia. Propofol is a short-acting intravenous anesthetic used for induction and maintenance of general anesthesia. However, the analgesic effect of propofol is very weak, and high-dose propofol sedation may lead to progression from deep sedation to general anesthesia. Cote et al. showed that 12.8% of patients who received propofol for endoscopic sedation experienced hypoxemia.⁴ Therefore, to minimize these risks is an important goal to make the sedation process safer. The commonly used method is to reduce the dose of propofol by using it in combination with other drugs. Remifentanyl is currently clinically used as a combination drug with propofol. It has a fast onset and obvious analgesic effect. Propofol can effectively inhibit sympathetic nerve activity and reduce hormone levels (such as catecholamines and cortisol). When used in combination with remifentanyl, it can increase plasma concentration, inhibit the sensitivity of baroreceptors, play a sedative and analgesic role, reduce stress and inflammatory reactions, and stabilize hemodynamics.^{5,6} However, remifentanyl has a short half-life, and the ester bond in its molecular structure is easily hydrolyzed by nonspecific esterases, which destroys pharmacokinetics.^{7,8} Moreover, remifentanyl has a certain respiratory inhibitory effect, which may compromise the respiratory and circulatory systems.⁹ In this study, 3 patients in the control group had bradycardia during surgery, 6 patients had $SpO_2 < 90\%$, 3 patients had hypotension, and 8 patients had bucking during surgery, which was significantly more than that in the observation group. This may be related to the combined hemodynamic and respiratory inhibitory effects of propofol and remifentanyl.

Ketamine was first developed by Parke Davis in 1962. Around 2020, esketamine was introduced to China,

which is the s-enantiomer of racemic ketamine and has a higher affinity for NMDA receptors. It has both sedative and analgesic functions and has stronger analgesic effects and higher in vivo clearance than traditional ketamine. Its dose is only half that of ketamine.^{10,11} Esketamine can indirectly stimulate the sympathetic nervous system and excite the cardiovascular system. The overall performance is an increase in HR and blood pressure.¹² In this study, one patient in the observation group experienced a transient increase in blood pressure, and the MAP of the observation group was significantly higher than that of the control group at the start of surgery (T3), which may be related to the excitatory effect of esketamine on the sympathetic nervous system. Its pseudo-sympathetic properties can counteract the hemodynamic inhibition of propofol, increase sympathetic nerve tension, maintain autonomous respiration and airway excursion, thereby reducing the risk of cardiovascular and respiratory depression. Jonkman et al. demonstrated that low-dose esketamine not only reduced opioid consumption but also stabilized breathing.¹³ Their study showed that esketamine counteracts respiratory depression by antagonizing CO_2 chemosensitivity due to remifentanyl-induced respiratory depression. Tu et al.¹⁴ found that compared with sufentanil, esketamine improved hemodynamics, reduced surgical stress and inflammatory reactions, promoted postoperative cognitive recovery. Esketamine is usually used for bronchoscopy in children, which is beneficial for patient sedation and reducing the incidence of delirium.¹⁵ Esketamine can relax bronchial smooth muscle, inhibit histamine-induced bronchoconstriction, thereby reducing tracheal and bronchial muscle spasms. Tu et al.¹⁴ found that the combined application of propofol and esketamine had good safety and high reliability, was more conducive to stable hemodynamics, reduced surgical stress and inflammatory reactions, promoted postoperative recovery in elderly surgical patients, and had relatively mild adverse reactions. Eberl et al.¹⁶ pointed out that using esketamine during surgery can reduce propofol dosage by about 20%. Zhan Y et al. found that in painless gastrointestinal endoscopy examination, combined use of propofol and 0.2 mg/kg esketamine had a shorter induction time than a single use of propofol alone, with lower coughing and limb movement rates, less use of propofol alone, no significant effect on recovery time, hemodynamic stability, postoperative cognitive function, adverse event rate or pseudo-psychotic symptoms.¹⁷ Eberl S et al. showed that the synergistic effect of esketamine and propofol during ERCP can reduce individual drug doses, thereby providing better safety and satisfaction than

combined use with opioid drugs. A potential problem with esketamine may be its psychostimulant effects such as visual impairment, dizziness or nausea which may affect patient satisfaction.

The application of low-dose esketamine may be more effective in short oral surgery.¹⁸ In this study, six patients in the observation group reported having dreams during surgery with strong pleasure and excitement feelings which might be related to the psychostimulant effect of esketamine. This was consistent with the observation that BIS of patients in the observation group was significantly higher than that in the control group at T2, T3 during surgery time.

During sedation, if the patients are not sedated enough, they may cough or move. If they are over-sedated, they may experience respiratory and circulatory suppression and delayed awakening. The key to determining a safe and satisfactory level of sedation for a patient is the concentration of the drug and the level of sedation. Administering drugs intravenously through a micro-infusion pump can accurately titrate and help control and adjust the level of sedation during medical procedures. Therefore, oral treatment should be performed under the supervision of an anesthesiologist, and clinicians should be able to handle adverse events related to accidental over-sedation, such as respiratory suppression, blood pressure changes, and hypoxia. Local anesthesia must be used in conjunction with conscious sedation to avoid compensating for poor local anesthesia by deepening the level of sedation, as deep sedation in dentistry can lead to serious complications such as glossocoma, coughing, and choking. Of course, the psychostimulant effect of esketamine is also a direction that needs attention in future sedation during and after surgery.

5. CONCLUSION

This study found that in outpatient oral surgery, the use of a combination of propofol and esketamine for mild sedation resulted in more stable hemodynamic indicators during surgery, a lower incidence of bucking and hypoxemia, and good patient satisfaction compared to the group using remifentanyl combined with propofol. This can provide a reference for the development of oral treatment under intravenous mild sedation.

6. Data availability

The numerical data generated during this research is available with the authors.

7. Acknowledgement

This study was strongly supported by Yantai Stomatological Hospital affiliated to Binzhou Medical University, and we would like to thank all the doctors and teachers who cooperated with us.

8. Funding

This study was approved by Yantai City Science and Technology Bureau policy guidance projects (2022YD100).

9. Conflict of interest

The authors did not declare any conflicts of interest, and no external or industry funding was involved.

10. Authors' contribution

All authors contributed in the design and conduct of this study. All authors have read the final manuscript and approve it.

11. REFERENCES

1. Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018: A Report by the American Society of Anesthesiologists Task Force on Moderate Procedural Sedation and Analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology. *Anesthesiology*. 2018;128(3):437-479. [PubMed] DOI: [10.1097/ALN.0000000000002043](https://doi.org/10.1097/ALN.0000000000002043)
2. Galeotti A, Garret Bernardin A, D'Antò V, Ferrazzano GF, Gentile T, Viarani V, et al. Inhalation Conscious Sedation with Nitrous Oxide and Oxygen as Alternative to General Anesthesia in Precooperative, Fearful, and Disabled Pediatric Dental Patients: A Large Survey on 688 Working Sessions. *Biomed Res Int*. 2016;2016:7289310. [PubMed] DOI: [10.1155/2016/7289310](https://doi.org/10.1155/2016/7289310)
3. 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 Oct 11;18(1):472. [PubMed] DOI: [10.1186/s13063-017-2197-8](https://doi.org/10.1186/s13063-017-2197-8)
4. Coté GA, Hovis RM, Ansstas MA, Waldbaum L, Azar RR, Early DS, et al. Incidence of sedation-related complications with propofol use during advanced endoscopic procedures. *Clin Gastroenterol Hepatol*. 2010 Feb;8(2):137-42. [PubMed] DOI: [10.1016/j.cgh.2009.07.008](https://doi.org/10.1016/j.cgh.2009.07.008)
5. Hulsman N, Hollmann MW, Preckel B. Newer propofol, ketamine, and etomidate derivatives and delivery systems relevant to anesthesia practice. *Best Pract Res Clin Anaesthesiol*. 2018;32(2):213-221. [PubMed] DOI: [10.1016/j.bpa.2018.08.002](https://doi.org/10.1016/j.bpa.2018.08.002)
6. Tian HT, Duan XH, Yang YF, Wang Y, Bai QL, Zhang X. Effects of propofol or sevoflurane anesthesia on the perioperative inflammatory response, pulmonary function and cognitive function in patients receiving lung cancer resection. *Eur Rev Med Pharmacol Sci*. 2017 Dec;21(23):5515-5522. [PubMed] DOI: [10.26355/eurrev_201712_13943](https://doi.org/10.26355/eurrev_201712_13943)
7. Wąsowicz M, Jerath A, Luksun W, Sharma V, Mitsakakis N, Meineri M, et al. Comparison of propofol-based versus volatile-based anaesthesia and postoperative sedation in cardiac surgical patients: a prospective, randomized, study. *Anaesthesiol Intensive Ther*. 2018;50(3):200-209. [PubMed] DOI: [10.5603/AIT.a2018.0012](https://doi.org/10.5603/AIT.a2018.0012)
8. Forget P, Cata J. Stable anesthesia with alternative to opioids: Are ketamine and magnesium helpful in stabilizing hemodynamics during surgery? A systematic review and meta-

- analyses of randomized controlled trials. *Best Pract Res Clin Anaesthesiol.* 2017;31(4):523-531. [PubMed] DOI: [10.1016/j.bpa.2017.07.001](https://doi.org/10.1016/j.bpa.2017.07.001)
9. Wang Y, Qiu R, Kong G, Liu J. Effects of propofol combined with remifentanyl anesthesia on the NO, endothelin and inflammatory cytokines in the plasma of patients with liver cirrhosis during the perioperative period. *Exp Ther Med.* 2019;17(5):3694-3700. [PubMed] DOI: [10.3892/etm.2019.7367](https://doi.org/10.3892/etm.2019.7367)
 10. Lee C, Jones TA. Effects of Ketamine Compared with Urethane Anesthesia on Vestibular Sensory Evoked Potentials and Systemic Physiology in Mice. *J Am Assoc Lab Anim Sci.* 2018;57(3):268-277. [PubMed] DOI: [10.30802/AALAS-JAALAS-17-000131](https://doi.org/10.30802/AALAS-JAALAS-17-000131)
 11. Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, et al. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. *JAMA Psychiatry.* 2017 Apr 1;74(4):399-405. [PubMed] DOI: [10.1001/jamapsychiatry.2017.0080](https://doi.org/10.1001/jamapsychiatry.2017.0080)
 12. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacol Rev.* 2018 Jul;70(3):621-660. [PubMed] DOI: [10.1124/pr.117.015198](https://doi.org/10.1124/pr.117.015198)
 13. 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 May;120(5):1117-1127. [PubMed] DOI: [10.1016/j.bja.2018.02.021](https://doi.org/10.1016/j.bja.2018.02.021)
 14. Tu W, Yuan H, Zhang S, Lu F, Yin L, Chen C, et al. Influence of anesthetic induction of propofol combined with esketamine on perioperative stress and inflammatory responses and postoperative cognition of elderly surgical patients. *Am J Transl Res.* 2021 Mar 15;13(3):1701-1709. [PubMed]
 15. Ozturk T, Acikel A, Yılmaz O, Topçu I, Çevikkalp E, Yuksel H. Effects of low-dose propofol vs ketamine on emergence cough in children undergoing flexible bronchoscopy with sevoflurane-remifentanyl anesthesia: a randomized, double-blind, placebo-controlled trial. *J Clin Anesth.* 2016 Dec;35:90-95. [PubMed] DOI: [10.1016/j.jclinane.2016.06.025](https://doi.org/10.1016/j.jclinane.2016.06.025)
 16. 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 May;37(5):394-401. [PubMed] DOI: [10.1097/EJA.0000000000001134](https://doi.org/10.1097/EJA.0000000000001134)
 17. Zhan Y, Liang S, Yang Z, Luo Q, Li S, Li J, et al. Efficacy and safety of subanesthetic doses of esketamine combined with propofol in painless gastrointestinal endoscopy: a prospective, double-blind, randomized controlled trial. *BMC Gastroenterol.* 2022 Aug 20;22(1):391. [PubMed] DOI: [10.1186/s12876-022-02467-8](https://doi.org/10.1186/s12876-022-02467-8)
 18. Xin Z, Wang N, Qu W, Wang H, Wang C, Wang T, Li J, Wang H. Application of low-dose ketamine in short-time oral and maxillofacial surgery under general anesthesia. *J Oral Sci Res.* 2023;39(1):46-51. DOI: [10.13701/j.cnki.kqxyyj.2023.01.009](https://doi.org/10.13701/j.cnki.kqxyyj.2023.01.009)