

Original Research Article

Evaluation of low-dose esketamine on sleep quality in elderly patients undergoing painless gastroscopy

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Sent for review: 9 November 2022

Revised accepted: 25 March 2023

Abstract

Purpose: To investigate the effect of low-dose esketamine on sleep quality in elderly patients undergoing painless gastroscopy.

Methods: A total of 84 patients (ASA grade II - III, > 65 years old) who were to undergo painless gastroscopy in Guanggu District, Wuhan Third Hospital from June to July 2021 were enrolled. The diagnosis of sleep disorder was performed using Pittsburgh Sleep Quality Index (PSQI) before surgery. Patients with PSQI ≥ 5 were diagnosed with a sleep disorder (group E, $n = 42$), while those with PSQI < 5 were normal (group C, $n = 42$). Patients in both groups were given a single intravenous injection of esketamine 0.2 mg/kg 3 min before anesthesia induction, followed by an intravenous loading dose of propofol 1.5 mg/kg. Maintenance of anesthesia was achieved by intravenous pumping with propofol at 4 mg/kg per hour.

Results: Sleep quality of patients in both groups improved after surgery, but the PSQI scores decreased more than that of group E ($p < 0.05$), especially on the night after surgery. Compared with group C, anesthesia induction time was longer and the number of propofol supplementation was increased in group E ($p < 0.05$). Groups C and E manifested no significant differences in postoperative satisfaction and occurrence of adverse reactions ($p > 0.05$).

Conclusion: Low-dose esketamine improves the sleep quality of elderly patients with painless gastroscopy without increasing the risk of circulating breathing during surgery. However, multi-center large-scale studies will be required in further investigations in order to validate the findings of this study.

Keywords: Esketamine, Sleep quality, Painless gastroscopy, Pittsburgh Sleep Quality Index

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INTRODUCTION

Sleep disorders are important factors that affect the recovery of patients after surgery. In severe cases, it may lead to postoperative delirium [1,2], cognitive dysfunction, and other mental diseases [3], and even lead to increased mortality. For older patients, total sleep time and deep sleep

time decrease, and sleep latency and non-REM sleep increase [4,5]. Therefore, sleep quality may have some impact on elderly patients undergoing painless gastroscopy. Esketamine is D-ketamine that is sedative and analgesic, and its sympathomimetic activity may resist circulatory respiratory depression with propofol, making the anesthesia more stable for patients [6,7].

However, some studies have confirmed that long-term use of ketamine in large quantities potentially leads to prolonged sleep latency, while acute use of low-dose ketamine can increase early slow-wave sleep activity and amplitude [8]. This study investigated the effect of low-dose esketamine sedation on sleep quality in elderly patients.

METHODS

General information

This trial adopted a single-center, controlled, randomized, and double-blind design. A total of 84 patients (> 65 years old) who underwent elective painless gastroscopy in the outpatient clinic of Guanggu District, Wuhan Third Hospital from June to July 2021 were enrolled.

The study excluded patients with uncontrolled hypertension, heart disease, and mental illness, hyperthyroidism, high intracranial and intraocular pressure, difficulty in respiratory tract management (modified Markov score level IV), drug allergies, and intermittent or long-term use of opioids or sedatives within 2 months prior to admission. All patients were diagnosed with a sleep disorder by the Pittsburgh Sleep Quality Index (PSQI) before surgery. Patients with PSQI ≥ 5 were diagnosed with a sleep disorder (group E, $n = 42$), while those with PSQI < 5 were normal (group C, $n = 42$).

Ethical considerations

According to the Declaration of Helsinki and STROBE guidelines [9], this study was approved by the Ethical Committee of Guanggu District, Wuhan Third Hospital (approval no. KY2021-013). Written informed consent was obtained from all patients.

Administration of anesthesia

Preoperative preparation

All patients fasted for 8 h and water for 4 h before examination. Endoscopic diagnosis and treatment operations were performed by one of the three senior physicians in gastroenterology in the Guanggu District, Wuhan Third Hospital. Anesthesia was performed by a senior anesthesiologist, and an anesthesia resident was responsible for collecting relevant clinical data.

Anesthesia process

Electrocardiograms, pulse oxygen saturation, and non-invasive blood pressure were routinely

monitored after admission. Patients were intravenously injected with a balanced salt solution at a dose 4 mL/kg per hour and inhaled with oxygen at 10 L/min in the right lateral decubitus position. Two groups of patients received a single intravenous injection of esketamine at 0.2 mg/kg 3 mins before anesthesia induction, followed by an intravenous injection of a loading dose of propofol at 1.5 mg/kg, anesthesia maintenance: intravenous infusion of propofol 4 mg/kg per hour. Patients underwent gastroscopy when the eyelash reflex completely disappeared. Propofol 25 mg was supplemented when body dynamic responses occurred during the surgery. If the patient suffers from respiratory distress, the mask is pressurized to give oxygen to assist breathing. After 5 min of observation, the surgery should be continued depending on the patient's condition. For patients with hypotension (blood pressure decline $\geq 30\%$) during surgery, the fluid infusion rate is accelerated and ephedrine 5 mg is concurrently administered intravenously. In patients with bradycardia (HR < 50 beats/min), atropine was administered intravenously at 5 μ g/kg.

Parameters evaluated

The sleep status of the patients was investigated using PSQI and patients' satisfaction and willingness to undergo painless examination again was investigated by VAS score. Also, adverse reactions such as coughing, nausea, vomiting, hypotension, respiratory depression, etc. were recorded. The recovery of patients was investigated using a modified observer's assessment of alert/sedation (MOAA/S = 5: patients respond sensitively to calling in a normal tone of voice; MOAA/S = 1: patients respond to pain stimuli).

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 22.0 was employed for statistical analysis. Measurement data were expressed as mean \pm standard deviation (SD) and analyzed using independent samples *t*-test for normally distributed data or Bonferroni test for non-normally distributed data. For categorical data, data analysis was done with χ^2 test or Fisher's exact test. $P < 0.05$ was considered statistically significant.

RESULTS

General patient profile

No significant difference existed in basic information such as age, gender, height, weight,

Table 1: General data of patients (n=42)

| Indicator | Group C | Group E | P-value |
|---------------------------------------|--------------|--------------|---------|
| Age (years) | 71.86±5.33 | 70.90±5.07 | 0.404 |
| Gender (Male/female) | 23/19 | 22/20 | 0.827 |
| Body mass index (kg/cm ²) | 21.73±2.58 | 22.82±2.55 | 0.055 |
| ASA grade (II/III) | 10/32 | 13/29 | 0.463 |
| Endoscopy duration (min) | 317.83±74.06 | 339.43±72.04 | 0.179 |

ASA: American Society of Anesthesiologists classification

ASA classification, and endoscopy duration between patients with or without sleep disorders ($p > 0.05$, Table 1).

PSQI scores

Esketamine had no significant effect on the postoperative PSQI scores of group C ($P > 0.05$), and PSQI scores increased at T1, which may be related to the hyperactivity of one patient, but there was no difference compared with preoperative status. At T2 and T3, patients' sleep returned to normal ($P > 0.05$).

However, the PSQI scores in group E decreased at T1 ($P < 0.05$). Although the PSQI scores at T2 and T3 were lower than those at T, the difference was not statistically significant ($P > 0.05$, Table 2).

Table 2: PSQI scores at different time points

| Time | Group C | Group E |
|--------------------|-------------|--------------|
| T | 3.64 ± 0.48 | 9.023 ± 2.16 |
| T1 | 4.02 ± 0.55 | 7.93 ± 1.39* |
| T2 | 3.67 ± 0.61 | 8.14 ± 1.22 |
| T3 | 3.64 ± 0.66 | 8.17 ± 1.25 |
| F (Between groups) | 0.349 | 4.09 |
| P (Between groups) | 0.79 | 0.08 |

Note: T is before gastroscopy, T1 is the night after surgery, T2 is the first night after surgery, and T3 is the second night after surgery. * $P < 0.05$ compared to T at different time points

Patient satisfaction and willingness to receive gastroscopy again

Without considering the cost of anesthesia, no significant difference was presented between the two groups in terms of patient satisfaction and willingness to receive gastroscopy again ($P > 0.05$, Table 3).

Table 3: Patient satisfaction and willingness to receive gastroscopy again

| Indicator | Group C | Group E | P-value |
|----------------------------|-----------|------------|---------|
| Patients' satisfaction | 4.78±0.42 | 4.67±0.477 | 0.226 |
| re-examination willingness | 4.62±0.49 | 4.43±0.63 | 0.127 |

Incidence of adverse events

During the sedation process, the anesthesia induction time and the number of propofol supplementation in group E were more than those in group C ($P < 0.05$). The recovery time and the number of patients with hypotension, nausea, and vomiting in group C had no statistical significance in group E ($p > 0.05$).

DISCUSSION

Sleep disorder is a common problem in the elderly, with more than half of old people suffering from sleep problems [10]. The structure, duration, and quality of sleep change with age [11,12]. In addition, elderly patients are prone to anxiety, resulting in difficulty in falling asleep and insomnia due to underlying diseases, lack of professional knowledge of the disease, and worry about the efficacy and prognosis. The use of anesthetics is also one of the causes of postoperative sleep disorder.

Esketamine, the D-isomer of ketamine, has a higher affinity for NMDA receptors and opioid μ receptors. Esketamine has a stronger sedative and analgesic efficacy and a lower incidence of side effects than ketamine [7,13,14]. After ketamine treatment in patients with depressive disorder, sleep mode changes, mainly manifested as increased slow wave activity and increased amplitude in early sleep, but these changes appear in the first period after administration. During the second night's sleep, slow-wave sleep activity and amplitude decrease [8]. Animal experiments have confirmed that ketamine increases delta sleep intensity (the characteristic wave of stage 3 sleep in non-REM sleep), and its mechanism may be through increasing synaptic plasticity and BDNF levels, thereby increasing sleep slow wave activity [8]. Similar to ketamine, the rapid antidepressant effects of esketamine are associated with increased total sleep time, slow-wave sleep, slow-wave activity, and rapid eye movement sleep, decreased wakefulness, enhanced delta sleep intensity [15,16], and increased BDNF level. The study results showed that esketamine had no significant effect on postoperative sleep-

in patients with normal sleep, but improved postoperative sleep in patients with sleep disorder.

Some limitations present in the study, include the relatively small number of study cases, and a lack of long-term research, and further study on the mechanism will be necessary.

CONCLUSION

Combined low-dose esketamine/propofol intravenous anesthesia improves postoperative sleep quality in patients undergoing painless gastrointestinal endoscopy and has the advantages of less impact on breathing and circulation, rapid recovery time, and high patient satisfaction. However, multi-center large-scale studies will be required in further investigations in order to validate the findings of this study.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

This study was approved by the Ethical Committee of Guanggu District, Wuhan Third Hospital (approval no. KY2021-013).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Huan Li and Huizhen Wu conceived and designed the study, and drafted the manuscript. Huan Li and Jian Peng collected, analyzed, and interpreted the experimental data. Huizhen Wu and Jian Peng revised the manuscript for important intellectual

content. All authors read and approved the final manuscript.

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REFERENCES

- Guo L, Lin F, Yu M, Dai H, Huang H, Pan L. Effect of preoperative sleep quality on the occurrence of postoperative delirium in elderly patients. *J Clin Anesthesiol* 2018; 34(7): 673-677.
- Cao Y, Liu H, Chen B, Shen Z, Xu Y, Dong Y. Association between preoperative fragmented sleep and postoperative delirium in patients with esophageal cancer. *J Clin Anesthesiol* 2021; 37(7): 728-731.
- Li R, Chen N, Wang E, Tang C. Correlation between preoperative sleep disorder and postoperative delayed neurocognitive recovery in elderly patients. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2021; 46(11): 1251-1259.
- Tatineny P, Shafi F, Gohar A, Bhat A. Sleep in the Elderly. *Mo Med* 2020; 117(5): 490-495.
- Roepke SK, Sonia AI. Sleep disorders in the elderly. *Indian J Med Res* 2010; 131: 302-310.
- Zhang Z, Xu Y, Zhang Y, Liu X, Zhang Y. Effective dose of propofol combined with low-dose esketamine inhibiting response to gastroscopy insertion. *J Clin Anesthesiol* 2021; 37(9): 949-952.
- Eberl S, Koers L, van Hooft J, de Jong E, Hermanides J, Hollmann MW, Preckel B. The effectiveness of a low-dose esketamine versus an alfentanil adjunct to propofol sedation during endoscopic retrograde cholangiopancreatography. *Eur J Anaesthesiol* 2020; 37(5): 394-401.
- Sun W, Ran T, Ping D, Deng J, Yang Z, Sun H. Research Progress on the Effect of Ketamine on Nocturnal Sleep. *Chin J Drug Dependence* 2016; 25(1): 14-17.
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Das Strengthening the Reporting of Observational Studies in Epidemiology (STROBE-) Statement (The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting of observational studies). *Internist (Berl)* 2008; 49(6): 688-693.
- Yaremchuk K. Sleep Disorder in the Elderly. *Clin Geriatr Med* 2018; 34(2): 205-216.

11. Mander BA, Winer JR, MP W. Sleep and human aging1. *Neuron* 2017; 94(1): 19-36.
12. Shi L, Bao YP, Chen SJ, Ma MY, Han Y, Wang YM, Shi J, Vitiello MV, Lu L. Reply to Sanguaneko and Upala on "Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis". *Sleep Med Rev* 2019; 43: 133-134.
13. Wang J, Huang J, Yang S, Cui C, Ye L, Wang SY, Yang GP, Pei Q. 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.
14. van de Bunt JA, Veldhoen ES, Nievelstein RAJ, Hulsker CCC, Schouten ANJ, van Herwaarden MYA. Effects of esketamine sedation compared to morphine analgesia on hydrostatic reduction of intussusception: A case-cohort comparison study. *Paediatr Anaesth* 2017; 27(11): 1091-1097.
15. Borentain S, Williamson D, Turkoz I, Popova V, McCall WV, Mathews M, Wiegand F. Effect of sleep disturbance on the efficacy of esketamine in treatment-resistant depression: findings from randomized controlled trials. *Neuropsychiatr Dis Treat* 2021; 17: 3459-3470.
16. Raith H, Schuelert N, Duveau V, Roucard C, Plano A, Dorner-Ciossek C, Ferger B. Differential effects of traxoprodil and S-ketamine on quantitative EEG and auditory event-related potentials as translational biomarkers in preclinical trials in rats and mice. *Neuropharmacol* 2020; 171: 108072.