EGYPTIAN JOURNAL OF ANAESTHESIA
2023, VOL. 39, NO. 1, 128–133
https://doi.org/10.1080/11101849.2023.2166653

Evaluation of paradoxical effect of small dose ketamine as adjuvant in deep sedation for endoscopy patients

Mohammed M Maarouf, Azza M Youssef and Akram M Amer

Department of Anesthesiology, Intensive Care and Pain Management, Ain Shams University Faculty of Medicine, Cairo, Egypt

ABSTRACT

Background: This study tested the hypothesis that use of ketamine as an adjuvant to propofol in the induction of deep sedation for endoscopy patients could lead, paradoxically, to faster emergence.

Methods: We conducted a single-center, prospective randomized controlled study on 154 adult ASA I or II patients, admitted for gastrointestinal endoscopies. Patients were sedated with 25 µg fentanyl and 1 mg/kg propofol bolus over 30 s. Patients were divided into two groups: Group P ($n = 77$), sedated with propofol only, and Group PK ($n = 77$), who received additionally a single dose of ketamine (0.1 mg/kg) at induction. If the patient moved or Ramsay Sedation Score (RSS) regressed to <4, increments of 0.25 mg/kg of propofol were given. After the end of the procedure, emergence from sedation was assessed with modified Aldrete score, 5 and 10 m after admission to the recovery room.

Results: Adding a small dose of ketamine did not significantly achieve deep sedation (RSS ≥4) more quickly or result in lesser propofol increments. Patients who received ketamine showed a statistically significant improvement in the Modified Aldrete score when recorded 5 min after admission to the recovery room (Group P 8.73 ± 1.02, Group PK 9.1 ± 0.96, P value = 0.02), but not after 10 min (Group P 9.03 ± 0.74, Group PK 9.21 ± 0.8, P value = 0.146).

Conclusion: Inclusion of a small single dose of ketamine in the induction of sedation for gastrointestinal endoscopy significantly improves emergence from sedation.

ARTICLE HISTORY
Received 17 November 2022
Revised 27 December 2022
Accepted 3 January 2023

KEYWORDS
Propofol sedation; ketamine paradoxical effect; gastrointestinal endoscopy

1. Introduction

Propofol is the drug of choice in anesthetic induction, as well as the drug of choice as sedative agent for diagnostic and ambulatory procedures [1]. Used alone or in conjunction with other drugs, propofol is used in different types of procedures. It can be administered either in boluses or via continuous infusion to achieve the required level of sedation or anesthesia [2].

But propofol's utility comes with considerable risks, including respiratory depression, apnea, loss of protective reflexes, and hemodynamic suppression [3]. To attenuate these adverse effects, propofol has been combined with opioids or ketamine to decrease its induction dosage [4].

Ketamine is an *N*-methyl D-aspartate (NMDA) antagonist with amnestic and analgesic effects. Due to its cardiovascular boosting effect, ketamine is frequently used in conjunction with or in lieu of other anesthetics. Combining ketamine with propofol in sedating upper gastrointestinal (UGI) and colonoscopic endoscopies has been proven advantageous in achieving adequate levels of sedation while consuming lower doses of propofol. Adding ketamine to propofol sedation also avoids hemodynamic instability, and has a lower incidence of nausea and vomiting, and respiratory complication rates. Still, propofol–ketamine combination is associated with a relatively longer recovery period [5].

Clinical trials to reverse anesthetic effects or accelerate recovery have been in vogue for the past few years. Trials target the thalamus, the cholinergic system, and the dopaminergic system [6,8,9].

Ketamine induction produces effects similar to the traits associated with rapid eye movement (REM) sleep, including high-frequency cortical activity, high cholinergic tone in the cortex, and dreams [9,10]. Hambrecht-Wiedbusch et al. administered subanesthetic ketamine during isoflurane anesthesia in rodents, and their trial showed that ketamine provided paradoxically deeper anesthesia and faster emergence time [11].

Ketamine is frequently used as a combination drug with propofol in sedating endoscopy patients; however, it is used at moderately high doses (0.5–1 mg/kg), which results in delayed emergence from sedation [5,12], in addition to postoperative hallucinations which have long been a deterrent to the drug's use [13,14].

In our study, we investigated whether using small doses of ketamine, alongside standard propofol dosage, might achieve deep sedation quickly, as well as faster emergence at the end of the endoscopy procedure, while avoiding its associated adverse effects.

CONTACT Mohammed M Maarouf mm.maarouf@med.asu.edu.eg Istithmari Buildings, Number 4, Mostaqbal City, 11831, Cairo, Egypt

2. Methods

2.1. Study design and participants

This single-center prospective randomized controlled study was conducted in the Gastrointestinal Endoscopy Unit of Ain Shams University Hospitals during the period from July to October 2022. Ethics approval was received from the Research Ethical Committee of Faculty of Medicine, Ain Shams University (FMASU R 108/2022). Participants in the study were selected during routine preoperative anesthetic consultation, based on their age, medical condition, and type of endoscopy.

The researchers approached the patients and their relatives and provided them with a detailed explanation of what the study and their participation entailed as well as the way the randomization process worked. Finally, written consents were obtained from the patients.

The inclusion criteria for the patients in this study were as follows:

- American Society of Anesthesiologists Physical Status Classification System (ASA) I or II
- Upper gastrointestinal or colonoscopic endoscopies
- Age 20–60 years
- BMI 20–35 kg/m^2, body weight 50–100 kg

Exclusion criteria were:

- Tachycardia (>110 b/mim) or any sort of arrhythmia, hypotension (<90/60 mm Hg), or any hemodynamic instability
- History of seizures
- History of suspected propofol or ketamine allergy
- Moderate-to-severe renal or hepatic impairment

2.2. Randomization

The patients were divided into two groups: the control group, Group P (n = 77), receiving only propofol sedation, and the study group, Group PK (n = 77), where the patients, in addition to propofol sedation, received a single dose of ketamine (0.1 mg/kg) during the induction of sedation.

Computer-generated randomization was used to assign participants to either Group P or Group PK.

3. Procedures

In the endoscopy room, the patient was given 25 µg fentanyl, then put into position (lateral decubitus), and oxygen via nasal prongs (4 L/min) was provided. Patients in the PK group received a small dose of ketamine (0.1 mg/kg) immediately before the injection of propofol. Sedation was then instituted with an initial bolus of 1 mg/kg propofol, over 30 s. Sedation levels were tested using Ramsay Sedation Score (RSS) every minute (Table 1), and endoscopy was commenced when the patient reached a score of ≥4. Increments of 0.25 mg/kg of propofol were added if the patient did not achieve this level of sedation within 2 min. During the procedure, if the patient moved or the RSS appeared to regress to lower than 4, increments of 0.25 mg/kg of propofol were given.

Table 1. Ramsay Assessment Scale for the level of sedation.

Description	Score
Patient anxious, agitated, or restless	1
Patient cooperative, oriented, and tranquil	2
Patient sedated but responds to commands	3
Patient asleep but responds to glabellar tap	4
Patient asleep but responds to nail bed pressure	5
Patient asleep, no response to nail bed pressure	6

Desaturation (SpO_2 <92%) and apneas were managed with head repositioning and jaw thrust, and there was no need for interruption of the endoscopy procedure for resuscitation for any of the patients.

In the recovery room, oxygen via nasal prongs (4 L/min) was provided, and patients were monitored with pulse oximetry. Modified Aldrete score (MAS) (Table 2) was recorded, 5 and 10 min after admission to the recovery room.

4. Outcomes

The primary outcome of this clinical trial was to find the difference in full emergence from sedation between patients sedated using propofol only and those sedated with propofol and a small dose of ketamine as an adjuvant. This was measured by recording the Modified Aldrete score, 5 and 10 min after admission to the recovery room.

The secondary outcome observed during this clinical trial was the effect of a small dose of ketamine on the depth of sedation, which was measured through the time taken to achieve RSS ≥4, and the number of propofol boluses/per 5 min of procedure to sustain this level of sedation.

5. Statistical analysis

Recorded data were analyzed using the Statistical Package for Social Sciences, version 24.0 (SPSS Inc., IBM Corporation). Quantitative data are expressed as mean ± standard deviation (SD). Independent samples t-test of significance was used when comparing two means. Categorical data are presented as frequencies and appropriate proportions. Comparison between proportions was done using Chi-square test. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. P value <0.05 was considered significant while a P value <0.001 was considered highly significant.

Table 2. Post-anesthesia recovery score – Modified Aldrete Score.

Category	Description	Score
Consciousness	• Fully awake and orientated (name, place, date)	• 2
	• Arousable on calling	• 1
	• Not responding	• 0
Activity	• Moves all 4 extremities voluntarily or on command	• 2
	• Moves 2 extremities	• 1
	• Unable to move extremities	• 0
Respiration	• Breathes deeply and coughs freely	• 2
	• Dyspnea, limited breathing, or tachypnea	• 1
	• Apneic or on mechanical ventilation	• 0
Circulation	• Blood pressure ±20% of preanesthetic level	• 2
	• Blood pressure ±20–49% of preanesthetic level	• 1
	• Blood pressure ±50% of preanesthetic level	• 0
Oxygen Saturation	• SpO_2 >92% on room air	• 2
	• Supplemental O_2 required to maintain SpO_2 >90%	• 1
	• SpO_2 <92% with O_2 supplementation	• 0
Maximum Score		• 10

The sample size was calculated by the Community Department, Faculty of Medicine, Ain Shams University. A sample size of at least 77 cases per group was found to achieve a power of 80% to detect a medium effect size (0.5) comparing mean time to recovery in the two groups using two-independent samples *t*-test with a significance level of 0.05. The sample size was inflated by 20% to compensate for dropouts.

6. Results

A total of 154 patients [56.5% (*N* = 87) male], aged 21–60 years were recruited into the study between July and October 2022.

There were no statistically significant differences between the study groups with regard to gender, age, and body mass index distribution (Table 3).

A total of 113 patients (73.4%) underwent upper gastrointestinal endoscopies [Group P 58 patients (75.3%), Group PK 55 patients (71.4%)], while 41 patients underwent colonoscopies [Group P 19 patients (24.7%), Group PK 22 patients (28.6%)]. Overall, there was no statistically significant difference in the type of procedure across both groups (*P* value = 0.57). Also, the average duration for endoscopies across both groups was quite similar (Group P 11.56 min ± 4.28, Group PK 12.82 min ± 5.28, *P* value = 0.106).

Patients who received the small dose of ketamine were found to achieve deep sedation (RSS ≥ 4) slightly faster than those in the control group (Group P 92.33 ± 14.23 s vs Group PK 89.74 ± 21.45 s), but the difference was not statistically significant (*P* = 0.377). Also, the patients who received the small induction dose of ketamine were less likely to need incremental propofol injections than the patients in the other group (Group P 2.1 ± 0.97 vs Group PK 1.91 ± 0.94), but once again the difference was not statistically significant (*P* = 0.239) (Table 4) (Figure 1).

Table 3. Demographic variables.

	Group P (*n* = 77)	Group PK (*n* = 77)	*P*-value
Sex			
• Male	46 (59.7%)	41 (53.2%)	0.416
• Female	31 (40.3%)	36 (46.8%)	
Age	49.1 ± 8.9	46.9 ± 9.6	0.159
Body mass index (BMI)	24.67 ± 4.45	25.52 ± 5.05	0.273

There was a statistically significant improvement in Modified Aldrete score (MAS) recorded 5 min after admission to the recovery room in the patients who received ketamine (Group P 8.73 ± 1.02, Group PK 9.1 ± 0.96, *P* value = 0.02). However, when the Modified Aldrete score was recorded once again, 10 min after admission to the recovery room, that difference turned out to be statistically not significant (Group P 9.03 ± 0.74, Group PK 9.21 ± 0.8, *P* value = 0.146) (Table 4) (Figure 2).

7. Discussion

In a study conducted on rats, a small subanesthetic dose of ketamine was shown to increase the depth of anesthesia and, paradoxically, to accelerate emergence at the end of anesthesia. This paradoxical effect is presumably mediated through ketamine's action on cholinergic centers in the arousal system of the brain [11].

Our study was done to test the effect of a small dose of ketamine (0.1 mg/kg) on the depth of propofol sedation and emergence from sedation for paients who unerwent gastrointestinal endoscopy. A small induction dose of fentanyl (25 µg) was added to provide smoother and deeper sedation as well as to preempt mild pain and discomfort associated with upper GI and colonoscopy procedures.

Regarding the effect of ketamine on the depth of sedation, our study shows that adding a small dose of ketamine did not significantly reduce the time required to achieve appropriate deep sedation (RSS ≥ 4) (Group P 92.33 ± 14.23 s vs Group PK

Table 4. Comparison between the two groups regarding sedation and recovery.

	Group P (n = 77)	Group PK (n = 77)	P-value
Time to achieve RSS ≥4 (s)	92.33 ± 14.23	89.74 ± 21.45	0.377
Propofol bolus/5 min of procedure	2.1 ± 0.97	1.91 ± 0.94	0.239
Aldrete Score at 5 min	8.73 ± 1.02	9.1 ± 0.96	0.02
Aldrete Score at 10 min	9.03 ± 0.74	9.21 ± 0.8	0.146

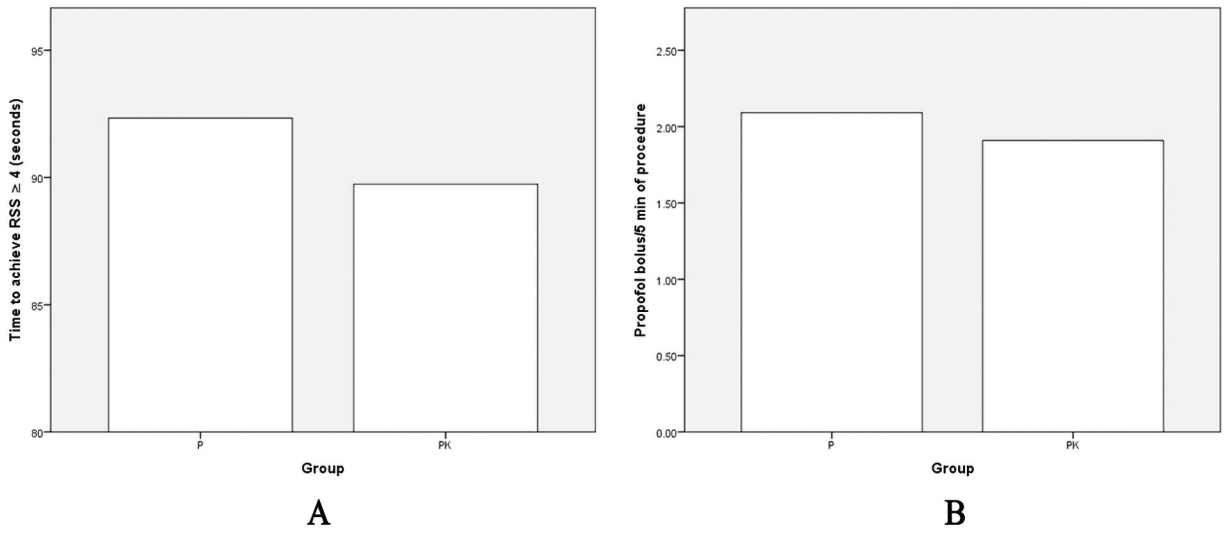

Figure 1. Effect on depth of sedation. (a) Mean time to RSS ≥4. (b) Mean propofol bolus/5 min of procedure.

89.74 ± 21.45 s, P = 0.377). It also did not significantly decrease the number of incremental propofol boluses required to maintain RSS ≥ 4 (Group P 2.1 ± 0.97 vs Group PK 1.91 ± 0.94, P = 0.239).

Our results contradict many research trials that examined ketamine's role as a sedative for endoscopy procedures, but in most of these studies, the drug was used in standard sedative doses, which are higher than the dose chosen in our study. Most studies show that adding ketamine helped achieve sedation quickly and sustained it for longer periods of time.

In their study on colonoscopy patients, Baykal et al. showed that a propofol–ketamine combination (1:1 combination) achieved sedation (RSS ≥4) in a shorter period of time in comparison to patients who received propofol only (3.3 ± 4.2 vs 2.4 ± 1.6 min; P = 0.038) [5].

Another clinical trial by Schmitz et al. (conducted between March 2012 and September 2014) examined sedation for magnetic resonance imaging (MRI) in pediatrics, using propofol with or without ketamine for induction. In the patient subset that received ketamine (1 mg/kg at induction, then propofol infusion rate of 5 mg/kg/h), a greater number of patients

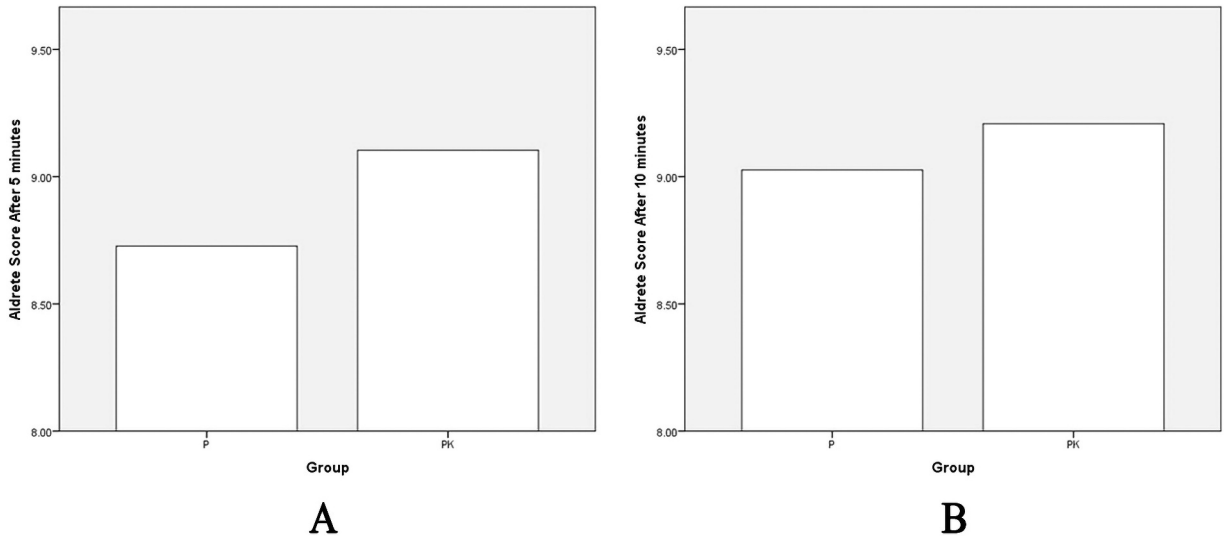

Figure 2. Effect of ketamine as an adjuvant on emergence. (a) Modified Aldrete Score at 5 min. (b) Modified Aldrete Score at 10 min.

achieved sedation more rapidly [98 (59.8%) vs 60 (35.9%); $P < 0.001$] compared to the number of patients in the subset who had been sedated with propofol only (propofol infusion rate of 10 mg/kg/h). However, induction time was not significantly reduced in the ketamine-propofol subset relative to the propofol-only subset [7 [5,7–9,9] vs 7.5 [5,7–9,9] min; $P = 0.3$] [4].

In our study, there was a statistically insignificant difference in time to achieve sedation (RSS ≥ 4) between the two groups, probably owing to the comparatively smaller dose of ketamine used in our study.

In the same Baykal et al. study, they found out that patients sedated with propofol-ketamine were less likely to need an additional dosage of the sedative drug in comparison to patients who received propofol-only sedation (33.3% vs 66%, $P = 0.001$). In our study, the subset of patients sedated with the small dose of ketamine needed a number of additional doses comparable to that of the patients who received propofol-only sedation. A result, again, probably owing to the smaller dose of ketamine used in this study.

One of the more interesting findings in our study was a statistically significant improvement in the Modified Aldrete score, when recorded 5 min after admission to the recovery room, in the patients who received ketamine (Group P 8.73 ± 1.02, Group PK 9.1 ± 0.96, P value = 0.02). But that improvement was not maintained when the Modified Aldrete score was tested 10 min after admission to the recovery room (Group P 9.03 ± 0.74, Group PK 9.21 ± 0.8, P value = 0.146).

Once again, this result is different from that of many clinical trials, where emergence from sedation from ketamine-based injections is usually delayed. In the Baykal et al. study, patients who received a propofol–ketamine combination (1:1) achieved MAS ≥ 9 significantly slower than the propofol-only preparation [1 [4] vs 5(12.7) min; $P = 0.005$] [5].

A similar result is seen in the trial by Damps et al., 2019, conducted on children admitted for gastroscopy. Patients were divided into two subsets: a group received a propofol–ketamine combination (1.5 mg/kg ketamine + 1.5 mg/kg propofol induction, then continuous propofol infusion 6 mg/kg/h) while the other received a propofol–remifentanil combination (1.5 mg/kg propofol induction, then 6 mg/kg/h infusion + remifentanil infusion 0.1 µg/kg/min). The trial showed that the patients who received a propofol–ketamine combination awoke significantly slower than those who received a propofol–remifentanil combination [6 (4) vs 4(4.5) min; $P = 0.007$] [15].

Similar results are also observed in the study by Zhang et al., conducted on laparoscopic cholecystectomy patients, in which the patients in the study group were given a small dose of esketamine (*S*-enantiomer of ketamine) at 0.2 mg/kg, before TIVA anesthesia. The recovery time for patients who received esketamine was significantly longer (22.04 ± 1.48 min vs 17.54 ± 1.46 min, $P = 0.036$). Recovery time in this study was recorded as the time between the cessation of TIVA till endotracheal extubation [16].

The faster emergence results of our study mirror some aspects of the pioneering study of Hambrecht-Wiedbusch et al., studying the effect of subanesthetic ketamine during isoflurane anesthesia on recovery from anesthesia in rats. In their study, a single dose of subanesthetic ketamine caused a significant 44% reduction in emergence time (saline: 877 ± 335 s vs ketamine: 494 ± 108 s; $P = 0.0005$; $n = 10$ per treatment). Rats injected with ketamine also had a significant 317% increase in cortical acetylcholine release after isoflurane anesthesia was discontinued [11].

Other similar results to our study can be found in the clinical trial by Schmitz et al. conducted on children sedated for MRI. The patient subset that received ketamine (1 mg/kg at induction, then propofol infusion rate of 5 mg/kg/h) showed significantly shorter recovery times [38 (22–65) vs 54 (37–77) min; median difference 14 (95% CI: 8, 20) min; $P < .001$] compared to the subset of patients who had been sedated with propofol only (propofol infusion rate of 10 mg/kg/h). Recovery times were measured as time from the end of procedure till MAS = 10 [4].

The results obtained from our study should be interpreted while keeping in mind its limitations, like studying just a single dose of ketamine, and that while there was a statistically significant difference in emergence, as measured by MAS, 5 min after admission to the recovery room, that difference turned out to be statistically not significant when MAS was repeated at the 10 min mark.

8. Recommendations

Based on this study, the researchers recommend further exploration of the role of ketamine as an adjuvant in deep sedation and anesthetic procedures.

Further studies, across various sedative and anesthetic protocols, for a myriad of diagnostic and surgical procedures, are needed to test the effect of ketamine as an adjuvant and to fine-tune its appropriate dose, with regard to depth of sedation and recovery. Studying its effect on intraoperative awareness probably should also be an essential part of any future research.

9. Conclusions

Use of small doses of ketamine as an adjuvant in deep sedation for gastrointestinal endoscopies significantly enhances emergence from deep sedation.

Ethics approval and consent to participate

Approval for this study was obtained from the Research Ethical Committee of Faculty of Medicine, Ain Shams University (code number: FMASU R 108/2022), and written informed consent was obtained from patients. The study was also registered in the Pan African Clinical Trials Registry (identification number: PACTR202208588389635).

Acknowledgments

This study is directly inspired by the Hambrecht-Wiedbusch et al. study published in 2017, exploring the role of a subanesthetic dose of ketamine in isoflurane anesthesia in rats. The researchers would like to thank all patients that participated in the study and their families. Furthermore, the researchers would like to acknowledge the contributions of the members of the anesthesia team, as well as of the surgical and internal medicine staff in the Gastrointestinal Endoscopy Unit, Ain Shams University Hospitals, Cairo, Egypt.

Disclosure statement

The researcher declares no competing interests.

Funding

The authors certify that except for local institutional resources, they received no fund for this research from any source.

ORCID

Mohammed M Maarouf http://orcid.org/0000-0001-8303-2013

References

[1] Vuyk J, Sitsen E, Reekers M. Intravenous Anesthetics. 8th ed. Miller's anesthesia. Saunders; 2015. p. 821–863.
[2] Rudner R, Jalowiecki P, Kawecki P, et al. Conscious analgesia/sedation with remifentanil and propofol versus total intravenous anesthesia with fentanyl, midazolam, and propofol for outpatient colonoscopy. Gastrointest Endosc. 2003;57(5):657–663.
[3] Goudra B, Gouda G, Mohinder P. Recent developments in drugs for gi endoscopy sedation. Dig Dis Sci. 2022;2022:1.
[4] Schmitz A, Weiss M, Kellenberger C, et al. Sedation for magnetic resonance imaging using propofol with or without ketamine at induction in pediatrics—A prospective randomized double-blinded study. Paediatr Anaesth. 2018;28(3):264–274.
[5] Baykal TZ, Gulec H, Derelı N, et al. Propofol-ketamine combination: a choice with less complications and better hemodynamic stability compared to propofol? On a prospective study in a group of colonoscopy patients. Ir J Med Sci. 2016;185 (3):699–704.
[6] Alkire MT, McReynolds JR, Hahn EL, et al. thalamic microinjection of nicotine reverses sevoflurane-induced loss of righting reflex in the rat. Anesthesiology. 2007;107(2):264–272.
[7] Hudetz AG, Wood JD, Kampine JP. Cholinergic reversal of isoflurane anesthesia in rats as measured by cross-approximate entropy of the electroencephalogram. Anesthesiology. 2003;99(5):1125–1131.
[8] Solt K, Cotten JF, Cimenser A, et al. Methylphenidate actively induces emergence from general anesthesia. Anesthesiology. 2011;115(4):791–803.
[9] Blagrove M, Morgan CJA, Curran HV, et al. The incidence of unpleasant dreams after sub-anaesthetic ketamine. Psychopharmacology (Berl). 2009;203 (1):109–120.
[10] Pal D, Hambrecht-Wiedbusch VS, Silverstein BH, et al. Electroencephalographic coherence and cortical acetylcholine during ketamine-induced unconsciousness. British Journal of Anaesthesia. 2015;114(6):979–89.
[11] Hambrecht-Wiedbusch VS, Li D, Mashour GA. Paradoxical emergence. Anesthesiology. 2017;126 (3):482–494.
[12] Khajavi M, Emami A, Etezadi F, et al. Conscious sedation and analgesia in colonoscopy: ketamine/propofol combination has superior patient satisfaction versus fentanyl/propofol. Anesthesiol Pain Med. 2013;3 (1):208–213.
[13] Abdalla MW, El SSM, El SAI, et al. Propofol dexmedetomidine versus propofol ketamine for anesthesia of endoscopic retrograde cholangiopancreatography (ERCP) (A randomized comparative study). Egypt J Anaesth. 2015;31(2):97–105.
[14] Seleem WM, El Hossieny KM, Abd-Elsalam S. Evaluation of different sedatives for colonoscopy. Curr Drug Saf. 2020;15(1):20–4.
[15] Damps M, Stołtny L, Siemek-Mitela J, et al. Comparison of propofol-ketamine versus propofol-remifentanil in children anaesthetized for gastroscopy. Anaesthesiol Intensive Ther. 2019;51(4):262–7.
[16] Zhang C, He J, Shi Q, et al. Subanaesthetic dose of esketamine during induction delays anaesthesia recovery a randomized, double-blind clinical trial. BMC Anesthesiol. 2022;22(1):4–9.