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# A randomized controlled trial for measuring effects on cognitive functions of adding ketamine to propofol during sedation for colonoscopy

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**Abstract**

**Background:** The purpose of this study was to evaluate the effects of adding ketamine to propofol on cognitive functions in patients undergoing sedation for colonoscopy.

**Methods:** In this randomized, double-blinded, and controlled study, 200 patients were randomly allocated to ketamine/propofol admixture group (Group KP, n = 100), and propofol group (Group P, n = 100). Patients in Group KP received 0.25 mg/kg of ketamine and 0.5 mg/kg of propofol. Patients in Group P received 0.5 mg/kg propofol. Cognitive functions were measured using CogState battery before and after the colonoscopy procedure. Ninety five patients in Group KP and 92 patients in Group P had completed the CogStates tests and were included in the data analysis.

**Results:** Compared with before procedure baseline, the performance on detection and identification tasks were significantly impaired after the procedure in both Group KP ($P = .004$, $P = .001$) and Group P patients ($P = .005$, $P < .001$). However, one-card learning accuracy and One-back memory was only impaired in Group KP patients ($P = .006$, $P = .040$) after the endoscopy but left intact in Group P patients. Group KP patients showed more severe impairment in one-card learning accuracy compared with Group P patients ($P = .044$). Group KP patients have better 5 minutes MAP ($P = .005$) and were also less likely to suffer from complications such as respiratory depression ($P = .023$) and hypotension ($P = .015$). OAA/S scores, BIS, MAP, complications, recovery times, and endoscopist and patient satisfaction were similar between the 2 groups.

**Conclusion:** Although adding ketamine to propofol for sedation in colonoscopy provided fewer complications such as respiratory depression and hypotension, it also causes more impairment in cognitive functions.

**Abbreviations:** ASA = American Society of Anesthesiologists, BIS = bispectral index, MAP = mean arterial pressure, MMT = Mini-Mental Test, POCD = postoperative cognitive dysfunction.

**Keywords:** cognitive, colonoscopy, ketamine, propofol

## 1. Introduction

Colonoscopy is a highly accurate diagnostic technique for large intestine and colon disease, and could also be used as a therapeutic approach under certain conditions. Sedation during colonoscopy procedures is widely used to alleviate patients' anxiety, fear, and pain.[1] Although the goal of sedation is to facilitate the endoscopy, sedation may also result in undesired side effects such as cognitive impairment that may delay discharge or result in patients being discharged from hospital with levels of impaired cognitive function that undermines complex daily activities. It is therefore important to shorten the recovery time of cognitive function after sedation so that most patients could resume safe, normal life soon after the procedure.

Propofol, an ultra-short-acting sedative agent with a rapid recovery profile, has been used extensively in gastrointestinal endoscopy.[2] Despite its benefits, propofol alone for sedation causes higher costs, deeper sedation, and adverse effects.[3] Propofol combined with other adjuvants can reduce the dosage of propofol and improve patient comfort, but they could also delay the time required to return to normal cognitive function when their duration of action exceeds that of propofol.

Ketamine is an N-methyl D-aspartate receptor antagonist with the properties of sedation, analgesia, and amnesia without

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causing respiratory depression.[4] Its drawbacks are vomiting and recovery agitation. The combination of ketamine and propofol can produce synergy and reduce each other's untoward effects.[5] Ketamine is commonly used for several procedures including gastrointestinal endoscopic procedures.[6–8] Ketamine displays neuroprotective effects including the prevention of excitotoxic injury and apoptosis, inhibited systemic inflammatory responses. In patients undergoing abdominal, orthopedic, or cardiac surgery, a bolus of ketamine at the induction of anesthesia led to a 65% decrease in the risk of postoperative cognitive dysfunction (POCD).[9] However, whether ketamine/propofol admixture has a reduced effect on cognitive function compared with propofol in colonoscopy is not known.

In this study, we aimed to detect whether there were differences in postprocedural cognitive function between ketamine/propofol admixture and propofol in colonoscopy. In addition, operating conditions, complications, recovery times, and satisfaction with care were compared between the 2 groups.

## 2. Methods

After approval of the ethical research committee in the First People's Hospital of Lianyungang China and obtaining informed written consent, we selected patients aged above 18 years, who were of physical status I–II according to the American Society of Anesthesiologists (ASA), and were scheduled for elective colonoscopy procedure. Exclusion criteria were patient refusal, Mini-Mental Test (MMT) scores of <26, advanced cardiopulmonary or psychiatric disease, alcohol or drug addiction, morbid obesity (body mass index >30 kg/m), history of undergoing anesthesia in the last 7 days, and known allergy to the drugs studied.

The study is a prospective, randomized, double-blind, controlled study. Patients were randomized into either the propofol (Group P) or the ketamine/propofol admixture (Group KP) group by using random numbers generated by computer placed in sealed envelopes. Participants were enrolled, and blinding was provided by an anesthesiologist who did not participate in anesthesia application. He had access to the randomization list when the patient was admitted to the colonoscopy suite and met criteria for study inclusion. He prepared appropriate anesthesia-inducing drugs for each group. Each milliliter of ketamine/propofol admixture contained 5 mg propofol (batch 1709025; Guorui Medicine, Sichuan, China) and 5 mg ketamine (batch 17110516; Hengrui Medicine, Jiangsu, China), and 20 mL of ketamine/propofol admixture was prepared for Group KP in a ratio of 1:2 as follows: 50 mg ketamine (50 mg/mL) diluted with 5% glucose to reach a volume of 10 mL, mixed with 10 mL 1% propofol (10 mg/mL). Group P was administered 10 mL 5% glucose mixed with 10 mL of 1% propofol (10 mg/mL). Randomization took place in the preprocedure room, separated from the procedure room and the recovery room. Patients, endoscopists, and postoperative observers were blind to group allocation.

Demographic data were recorded and the CogState brief computerized cognitive test battery were completed after consensus was acquired in order to establish a before procedure baseline. After patients were brought to the endoscopy room, IV access was obtained, and oxygen was administered at 4 L/min via a clear plastic mask. Noninvasive blood pressure, peripheral oxygen saturation, and electrocardiogram were attached to the patient. BIS were placed on the skin of the forehead after cleansing with alcohol. Prior to induction, all patients received 2 mL of lidocaine intravenously to lessen pain on injection.

Anesthesia induction was achieved with 0.1 mL/kg ketamine/propofol admixture (0.25 mg/kg of ketamine and 0.5 mg/kg of propofol) or propofol (0.5 mg/kg) in 30 seconds. The level of sedation was assessed by the anesthetic personnel using the OAA/S score.[10] The sedation score was observed and maintained at the level 3 (responds only after name is called loudly and/or repeatedly) throughout the procedure. Oxygen saturation, heart rate, and arterial blood pressure were recorded every 5 minutes during sedation. OAA/S score were tested every 1 minute. After the process of colonoscopy had started, additional bolus propofol doses of 0.5 mg/kg were applied to both groups when the patient moved, or BIS value >80, or had an OAA/S score of >3. The total propofol dose were calculated and recorded. At the end of the procedure, the endoscopist's satisfaction to the sedation for the procedure was recorded on a 5-point Likert scale.[11]

Adverse reaction such as respiratory depression ($SpO_2$ <90% or rate <10/min), hypotension (decrease in blood pressure by 20% from baseline), bradycardia (heart rate <50/min), postprocedural pain, and postoperative vomiting during the procedure were recorded. The duration from the endoscopy insertion to the end of endoscopy removal was accepted as the period of colonoscopy. Time until OAA/S = 5, time in PACU, and time until hospital discharge were all measured using the time of endoscopy removal as the starting point. Once the patients were ready for hospital discharge according to the Chung discharge criteria (score >9 of 10),[12] cognitive testing was repeated and patient satisfaction with sedation was recorded on a 5-point Likert scale.

The CogState brief computerized test battery (CogstateTM, Melbourne, Australia) consisted of 4 tests that required approximately 10 minutes to complete. The tests measured psychomotor function (Detection task: "Has the card turned over?"), attention (Identification task: "Is the card red?"), visual memory (One Card Learning task: "Have you seen this card before in this task?"), and working memory (One Back Memory task: "Is the card the same as the previous card?"). These tasks were administered according to standard instructions.[13,14]

The primary end point for this study was the difference in accuracy on CogState tests between the discharge and baseline assessments between the 2 experimental groups. Secondary end points included OAA/S scores, BIS, MAP, complications, recovery times, and endoscopist and patient satisfaction with sedation. The CogState tests were conducted right before patients were discharged.

### 2.1. Statistical analysis

Detection time and identification time in CogSate task measurements were non-normally distributed and therefore log-transformed.[15,16] Similarly, arcsine transformation was applied to the accuracy measurements of CogSate one-card learning and one-card memory tasks to make these measurements closer to normal distribution. Paired two-tailed *t* tests were applied to compare the difference of cognitive function at baseline and discharge time for each treatment group and each of the 4 CogState tasks (Table 1). Effect size of before after comparison was measured as Cohen's *d* distance, computed in R 3.5.2 using the effectsize package cohen.d () function, with parameters POOL=True and paired=True. Unpaired two-tailed *t* test was applied to compare the change of cognitive function from

**Table 1**

**Cognitive testing baseline and discharge.**

| Cognitive task | Group | Baseline | Discharge | *P* | Effect size (Cohen *d*) |
|---|---|---|---|---|---|
| Detection ($log_{10}$ms) | KP (n = 95) | 2.55 ± 0.10 | 2.61 ± 0.11 | <.001 | −0.571 |
| | P (n = 92) | 2.56 ± 0.11 | 2.60 ± 0.12 | .003 | −0.381 |
| Identification ($log_{10}$ms) | KP (n = 95) | 2.73 ± 0.09 | 2.77 ± 0.10 | .005 | −0.421 |
| | P (n = 92) | 2.72 ± 0.08 | 2.77 ± 0.09 | <.001 | −0.588 |
| One-card learning (arcsine) | KP (n = 95) | 0.85 ± 0.13 | 0.8 ± 0.12 | .006 | 0.404 |
| | P (n = 92) | 0.84 ± 0.12 | 0.83 ± 0.11 | .316 | 0.087 |
| One-back memory (arcsine) | KP (n = 95) | 1.15 ± 0.22 | 1.09 ± 0.18 | .040 | 0.298 |
| | P (n = 92) | 1.15 ± 0.23 | 1.13 ± 0.21 | .581 | 0.091 |

Cogstate tasks reported as mean ± SD. $log_{10}$ms = milliseconds log transformed; arcsine = proportion correct arcsine transformed. An increase in reaction time (detection and identification) and a decrease in accuracy (one-card learning and one-back memory) indicate impairment.

baseline to discharge between Group KP and Group K. Effect size was measured as Cohen *d* distance with parameters POOL=True and paired=False.

A pilot study of 30 patients each group found that arcsine accuracy of One Card Learning tasks has changed by –0.04 in Group KP and by 0.01 in Group P, with pooled standard deviation of 0.11. Based on these results, for an alpha error of 0.05, and a power of 80%, 76 participates were needed for each group. Accounting for potential loss of patients during the experiment, we allocated 100 patients for each group.

Continuous data were tested for normality and then summarized using mean (SD) if normally distributed or median (interquartile range [IQR]) if non-normally distributed. Normally distributed data were compared using unpaired two-tailed *t* tests (between groups) or paired two-tailed *t* tests (within groups). Skewed data were compared using Wilcoxon ranked sum test.

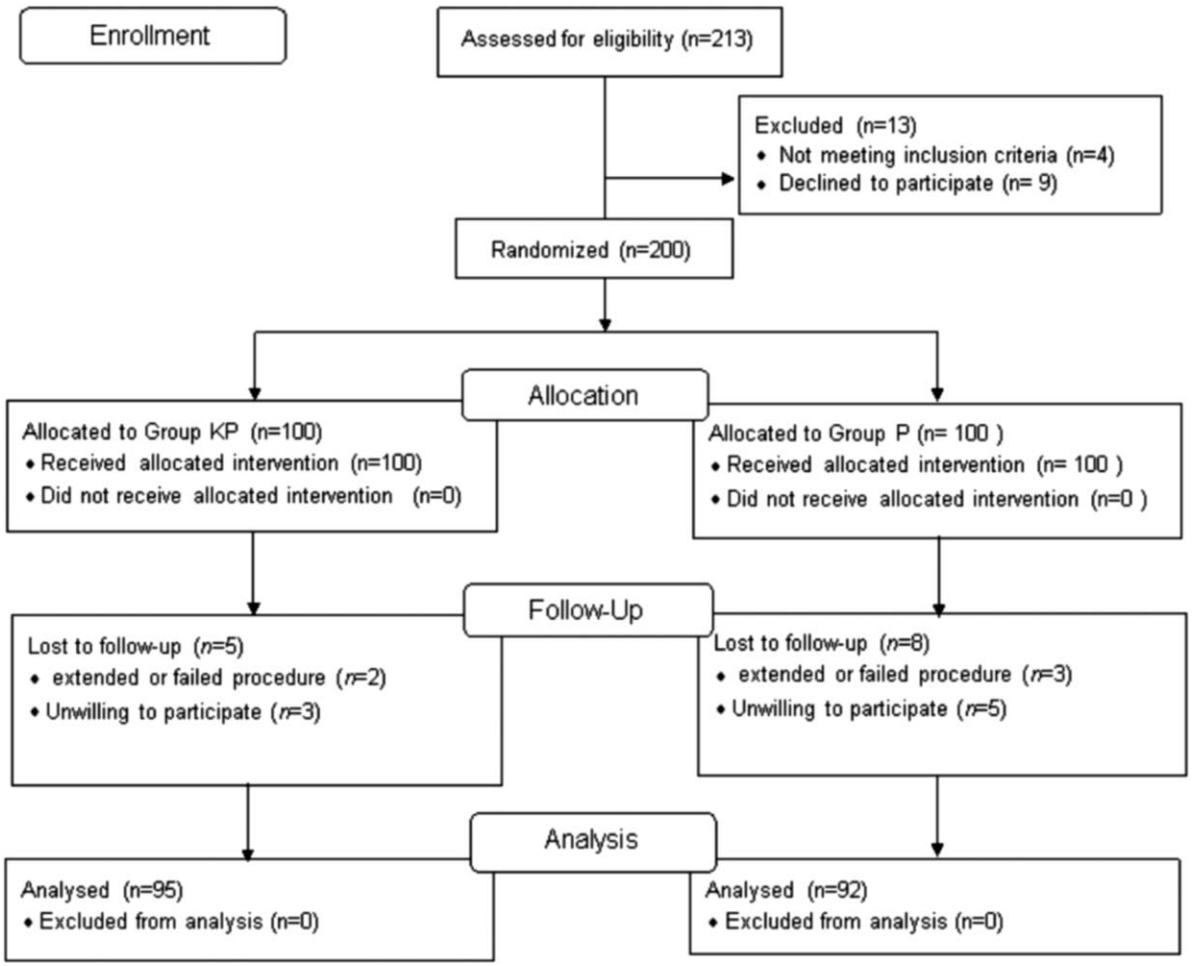


**Figure 1.** Consolidated Standards of Reporting Trials diagram.

**Table 2**

**Comparison of demographics, baseline monitoring (HR, MAP, $SPO_2$, BIS) between the 2 groups.**

| Demographic | Group KP (n = 95) | Group P (n = 92) | P |
|---|---|---|---|
| Age, yr | 45.7 ± 13.9 | 43.4 ± 14.3 | .406 |
| Weight, kg | 68.1 ± 12.3 | 65.5 ± 11.3 | .281 |
| Sex (F/M) | 36/59 | 42/50 | .746 |
| ASA (I/II) | 58/37 | 61/31 | .544 |
| HR, pulse/min | 77.6 ± 15.2 | 74.1 ± 16.5 | .271 |
| MAP, mm Hg | 90.8 ± 10.1 | 87.9 ± 11.9 | .193 |
| $SPO_2$ (%) | 98 (96,100) | 98 (95,100) | .622 |
| BIS | 97 (92.99)[95.98] | 97 (93.99)[96.98] | .818 |

Data presented as mean ± SD (normally distributed data), median (range) [interquartile range](skewed data), or number (%) (categorical data). ASA = American Society of Anesthesia; BIS = bispectral index; HR = heart rate; KP = ketamine-propofol; MAP = mean arterial pressure; P = propofol, $SPO_2$ = oxygen saturation.

Categorical data were summarized using number (%) and were compared using chi-squared test. $P < .05$ was considered statistically significant.

## 3. Results

Two hundred thirteen patients were enrolled in the study and 100 of them were randomly assigned into propofol group and ketamine/propofol admixture group respectively. Ninety two patients in propofol group and 95 patients in ketamine/propofol admixture group completed the discharge cognitive test and were included the analysis of the primary outcome, see the Fig. 1 flow diagram for details.

Group KP and Group P patients were similar in terms of age, body weight, and sex composition (Table 2). Baseline physiological metrics such as heart rate, mean arterial pressure (MAP), BIS, SPO2 are also not statistically different between the 2 groups (Table 2).

Colonoscopy time (time from endoscope insertion to endoscope removal) was not statistically different between the Group KP (16.0 ± 6.4 minutes) and Group P (14.6 ± 6.3 minutes). The dosage of propofol in KP group was significantly lower than that in P group ($P = .004$). Recovery time (time from endoscopy removal to OAA/S = 5), time in PACU, and time to hospital discharge (same as time to CogState test) were also similar between Group KP and Group P patients (Table 3). Five minutes MAP were higher in Group KP patients than Group P patients ($P = .005$). Patients in Group KP were also less likely to suffer from complications such as respiratory depression ($P = .023$) and hypotension ($P = .015$). Ratio of patients who had bradycardia, postprocedural pain, and postoperative vomiting were similar between the 2 groups as well (Table 3). The satisfaction scores for endoscopists and patients were both similar regardless of the sedation drugs administered (Table 3).

**Table 3**

**Sedation, procedure, and recovery characteristics.**

| Characteristics | Group KP (n = 95) | Group P (n = 92) | P |
|---|---|---|---|
| Colonoscopy time, min | 16 ± 6.4 | 14.6 ± 6.3 | .281 |
| Total propofol dose, mg | 142.9 ± 22 | 189.7 ± 27.9 | .004 |
| Median BIS | 62 (28,89)[54,71] | 63 (32,85)[55,70] | .493 |
| 5 min MAP | 82.3 ± 13.7 | 75.4 ± 16.7 | .005 |
| Respiratory depression | 7/88 | 17/75 | .023 |
| Hypotension | 10/85 | 22/70 | .015 |
| Bradycardia | 4/91 | 5/87 | .878 |
| Postprocedure pain | 15/80 | 19/73 | .388 |
| Postoperative vomiting | 2/93 | 3/89 | .970 |
| Endoscopists highly satisfied | 84/11 | 80/12 | .760 |
| Patient highly satisfied | 93/2 | 88/4 | .384 |
| Time until OAA/S = 5 | 3.7 ± 2.4 | 3.5 ± 2.2 | .473 |
| Time in PACU | 19.7 ± 7.5 | 17.8 ± 7.3 | .250 |
| Time until hospital discharge | 36.1 ± 12.3 | 33.8 ± 11.5 | .173 |

Data presented as mean ± SD (normally distributed data), median (range) [interquartile range](skewed data), or number (%) (categorical data). Duration of colonoscopy = time from endoscope insertion to endoscope removal. Oxygen saturation, heart rate, arterial blood pressure were recorded every 5 minutes during sedation. OAA/S score were test every 1 minute. 5 Min MAP = 5 minute after induction. Respiratory depression (rate <10/min or SPO2 <90), hypotension (a decrease of 20% in MBP compared with initial values), bradycardia HR <50/min. Satisfaction measured on 5-point Likert scale from 1 = very dissatisfied to 5 = very satisfied. For sedation satisfaction those highly satisfied = number (%) who scored 4 or 5 on Likert scale. Time until OAA/S = 5, time from endoscope removal to OAA/S = 5, time in PACU = time from endoscope removal to PACU discharge.

Performance of CogState tasks at baseline and at discharge time were summarized in Table 1. For patients in both groups, performance at discharge had declined significantly from baseline for the Detection (Group KP, $P < .001$; Group P, $P = .003$) and Identification (Group KP, $P = .005$ Group P, $P < .001$) tasks. However, Group P patients were not impaired in the One-card Learning task at discharge time compared with baseline ($P = .316$), while Group KP patients displayed significant reduction in the accuracy of One-card learning task ($P = .006$). Similarly, for One-back memory task, Group P patients showed similar performance level at discharge time compared with baseline ($P = .581$), while Group KP patients showed mild yet statistically significant reduction in accuracy ($P = .040$).

The above data suggested that the cognitive function was more impaired in Group KP patients compared with Group P patients during the procedure. To confirm this, the change in performance of the 4 CogState tasks were computed and compared between the 2 groups. Indeed, Group KP patients had stronger reduction in accuracy of the One-card learning task ($P = .044$) and One-back memory task ($P = .028$) from baseline than Group P patients. The 2 groups were similar in terms of the increase in

**Table 4**

**Change of cognitive function from baseline to discharge.**

| Cognitive task | Group P (n = 95) | Group KP (n = 92) | P | Effect size (Cohen d) |
|---|---|---|---|---|
| Detection ($log_{10}$ms) | 0.07 ± 0.10 | 0.05 ± 0.13 | .201 | −0.173 |
| Identification ($log_{10}$ms) | 0.04 ± 0.11 | 0.05 ± 0.08 | .370 | 0.105 |
| One-card learning (arcsine) | (−0.05) ± 0.14 | (−0.02) ± 0.09 | .044 | 0.261 |
| One-back memory (arcsine) | (−0.06) ± 0.1 | (−0.02) ± 0.13 | .028 | 0.348 |

Cogstate tasks reported as mean ± SD. $log_{10}$ms = milliseconds log transformed; arcsine = proportion correct arcsine transformed. An increase in reaction time (detection and identification) and a decrease in accuracy (one-card learning and one-back memory) indicate impairment.

reactive time in Detection task ($P = .201$) and Identification task ($P = .370$) in Table 4.

## 4. Discussion

Fast recovery and preservation of cognitive function is an important subject of research in endoscopic procedures.[17] To the best of our knowledge, our trial is the first to directly investigate postprocedural cognitive function between ketamine/propofol admixture and propofol on patients undergoing elective colonoscopy. Contrary to our initial hypothesis, the use of ketamine plus propofol did not result in less cognitive impairment at discharge than the use of propofol alone. Ketamine/propofol admixture causes more impairment on certain dimensions of cognitive functions.

Use of ketamine and propofol for procedural sedation and analgesia (PSA) has widely been assessed. According to the published reviews and meta-analyses of randomized controlled trials, administration of ketamine/propofol admixture for sedation is an advisable consideration with several benefits such as hemodynamic stability, analgesia, and a lower incidence of respiratory depression, as compared with propofol.[18] The current study found little difference between KP and P group in terms of sedation depth, patients' satisfaction, and endoscopists' satisfaction. This suggests both ketamine/propofol admixture and propofol could provide sufficient sedation for colonoscopy. However, ketamine/propofol admixture has the benefits of using less propofol and causes fewer complications such as respiratory suppression and hypotension.

Ketamine/propofol admixture (1:1 ketamine propofol ratio) has better postoperative analgesia results compared with propofol while resulting in longer recovery time,[8] probably due to the higher metabolism rate and shorter half-life of propofol. Thus, reduction of ketamine dose in ketamine/propofol admixture might shorten the post procedure recovery time. The ketamine/propofol admixture solution used in this study has a 1:2 ratio between ketamine and propofol. We found that the 2 groups had no significant difference between post-procedure pain and recovery time. Ketamine/propofol admixture at even lower dosage of ketamine might lose the benefits on blood circulation and sedation effects. Aydogmus et al[19] has compared ketamine/propofol admixtures with the ratio of ketamine and propofol at 1:2 and 1:4, and found no significant difference between their post-procedure recovery time. However, patients who received ketamine/propofol admixture with 1:2 ketamine:propofol ratio showed more stable blood circulation, better sedation, and higher patient satisfaction.

In this study, propofol group only demonstrated impairment in psychromotor function and attention, while ketamine/propofol admixture group showed impairment in all 4 tests in the measurement post-procedure cognitive function. Ketamine has been found to exhibit neuroprotective effects in a variety of laboratory experiments, potentially through reducing apoptosis, inflammation, or microthrombosis.[20] Clinical studies of small sample sizes showed that ketamine could mitigate postoperative cognitive impairment.[21,22] However, studies from Hwa et al[23] showed that the incidence of POCD was not significantly influenced by a bolus dose of ketamine (0.5 mg/kg) after orthopedic surgery in elderly patients. An international, double blinded, multiple-center, randomized clinical tests of 672 patients also challenged ketamine's effect in reducing postoperative cognitive impairment, by showing that a single subanesthetic dose of ketamine did not decrease delirium in older adults after major surgery, and might cause harm by inducing negative experiences.[24] There are many risk factors for postoperative cognitive impairment, such as advanced age, mental disorders and long-term surgical interventions, perioperative inflammatory response, long-term sedation, and pain, etc.[25] Due to relative lower level of anesthetic and surgical trauma, colonoscopy patients only suffer from temporary cognitive function impairment, such as memory, attention, and executive function.[14] Ketamine is also a psychoactive drug. Given its hallucination properties, ketamine may also have negative impacts on postoperative cognitive function.[26] Short-term ketamine infusion was shown to cause impairment of working memory and reduction in the encoding of information into episodic memory.[27] We found that compared with propofol, ketamine/propofol admixture group had larger change in working memory and visual memory after the procedure, which could be due to the residual effect of ketamine.

## 5. Limitations

In our study, we could not measure the long-term impacts on cognitive functions due to discharge protocol of endoscopy center in our hospital. Based on previous studies, cognitive impairment after ketamine/propofol admixture analgesia was temporary and self-healing. Cogstate tests started to show normal cognitive function approximately 40 minutes since stopping the sedation in outpatient colonoscopy using propofol and remifentanil as the analgesia.[14] Two hours after intranasal administration of esketamine (the S-enantiomer of ketamine racemate), healthy participants started show normal performance in Cogstate tests.[28] Since esketamine has 3 to 4 times higher affinity for NMDA receptors than ketamine, it is likely that ketamine/propofol admixture will not have long-term negative effects on cognitive function.

Due to technical difficulty of bolus injection of anesthetics, we were not able to precisely control the level anesthesia depth during the procedure. Even though BIS values between the 2 groups were not statistically significant different, as shown in Table 3, the BIS value did vary a lot across individual subjects. The difference of recovery time in postoperation might be masked by the variance of BIS level on individual subject. It is worth to reexamine this point in future studies.

## 6. Conclusion

To conclude, although adding ketamine to propofol for sedation in colonoscopy provided fewer complications, it also causes more impairment in cognitive functions. This suggests that the negative impact on cognitive functions of adding ketamine to propofol for sedation should also be considered when choosing the optimal sedation drugs for colonoscopy. To minimize the adverse impacts on cognitive function, the types and dosage of adjuvants can be further optimized in the future.

## Author contributions

**Conceptualization:** Zhiyuan Zhang, Liang Tian, Hongguang Bao.
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**Writing – review & editing:** Liang Tian, Zhiyuan Zhang.

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