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Safety and efficacy of dexmedetomidine vs ketamine vs midazolam combined with propofol in gastrointestinal endoscopy for cancer patients: A randomized double-blinded trial

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ABSTRACT

Background: A wide range of drugs are used for sedation in gastrointestinal (GI) endoscopy procedures, including midazolam, dexmedetomidine, and ketamine. Therefore, this study aimed to compare the effects of these drugs in combination with propofol among cancer patients undergoing GI endoscopy.

Methods: This randomized, double-blinded study was carried out on 75 cancer patients who underwent GI endoscopy. Patients were categorized into three equal groups. Group D: received dexmedetomidine 0.5 µg/kg bolus infusion over 10 min. Group K: received ketamine 0.5 mg/kg. Group M: received midazolam 0.05 mg/kg. With these drugs, 0.5 mg/kg propofol was administered intravenously with incremental 20 mg till achievement of Ramsey sedation score (RSS) 3–4. After that, 0.5 mg/kg propofol boluses were offered for rescue sedation.

Results: The endoscopy duration was comparable in the three groups. Time of RSS 3–4 achievement and total propofol dose ($P < 0.05$) were significantly lower in group D and group K compared to group M. Time to eye-opening were significantly lower in groups D, and K compared to group M, with insignificant difference between group K and group D. Moreover, the heart rate (HR) and mean arterial pressure (MAP) of group K at 10 min, 15 min, 20 min, 25 min, and 30 min, and PACU were significantly greater than D and M groups ($P < 0.05$). Incidence of hypotension and bradycardia were comparable in the three groups.

Conclusions: In cancer patients who underwent GI endoscopy, dexmedetomidine-propofol and ketamine-propofol had better sedation efficacy [lower achievement time of RSS 3–4, total propofol dose, and eye-opening time] compared to midazolam-propofol group with superior sedative effect of ketamine-propofol than dexmedetomidine-propofol. While ketamine-propofol had more stable HR and MAP.

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Introduction

Endoscopic procedures of the gastrointestinal (GI) tract are extensively utilized to screen, diagnose, and treat GI cancer and other conditions [1,2]. Propofol, midazolam, dexmedetomidine, and ketamine are among the medications used for sedation during GI endoscopic operations [3].

Propofol is an intravenous sedative medication with fast onset and a brief duration of action [4]. A recent meta-analysis [5] demonstrated that propofol is a superior option for all patients undergoing upper GI endoscopy. However, it has no analgesic effect, and its usage is correlated with a dose-dependent reduction in blood pressure due to its direct myocardial depressive action and reduction in systemic vascular resistance [6].

Midazolam is widely applied for conscious sedation. Its sedative effects start immediately and end rapidly. Its metabolite has a prolonged half-life and induces sleepiness and respiratory depression as a result of a diminished carbon dioxide response. The wide variation in midazolam dosage makes stable sedation problematic. Midazolam may generate paradoxical agitation [7].

Dexmedetomidine is an alpha-2 receptor agonist with analgesic, anxiolytic, and sedative properties. It is used for sedation in intensive care units [8]. In addition to its sedative action, it also has analgesic properties. Although minor respiratory depression is a significant benefit, the drug may induce bradycardia and hypotension. Therefore, it should be used with care. Dexmedetomidine is used to induce mild-to-moderate sedation [9].

Ketamine is an N-methyl D aspartate (NMDA) receptor antagonist; it causes dissociative anesthesia and has an amnestic and analgesic effect [10]. While vomiting, increased salivation, sympathomimetic effects, and psychotic emergent responses are its primary side effects [11]. Consequently, when ketamine and propofol (ketofol) are used together, the necessary

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dose is decreased, and a stable structure is established. Its effects are achieved rapidly, although recovery time may be prolonged [12]. A previous study suggested that the administration of ketamine provides an effective endoscopic sedation [13].

A recent meta-analysis showed that dexmedetomidine is an effective alternative to other sedatives during GI endoscopy, with no increase in the risk of the cardiovascular condition [14]. In addition, Samson et al. [15] concluded that dexmedetomidine had improved hemodynamic stability and quicker recovery compared to propofol and midazolam.

To our knowledge, comparing the sedative effects of dexmedetomidine, ketamine, and midazolam coupled with propofol is not well researched. Consequently, the aim of this study was to examine the effects of these agents among cancer patients undergoing GI endoscopy.

Patients and Methods:

This prospective randomized, double-blinded study was conducted on 75 adult cancer patients with ASA II-III physical status aged ≥18 years who underwent GI endoscopy. The patients were recruited from preanesthetic assessment clinic at the National Cancer Institute from November 2020 to December 2022. The ethical committee of the National Cancer Institute, Egypt, approved the trial. The study was registered at ClinicalTrials.gov (NCT: NCT04597268). Signed consent was obtained from the patient.

Patients with allergies to any medications utilized, compromised renal or hepatic functioning, hypertension, and cardiovascular or cerebrovascular illness were excluded.

Randomization and blindness

Patients were randomly computer-generated and allocated into three equal groups by sealed opaque envelopes. **Group D**: received dexmedetomidine 0.5 µg/kg bolus infusion over 10 min. **Group K**: received ketamine 0.5 mg/kg. **Group M**: received midazolam 0.05 mg/kg. Participant and outcome assessors were blinded about which drug patient had received.

Preoperative assessment was done by recording patients' age, sex, body mass index, comorbidity (hypertension and diabetes), kidney and liver function, and type and time of procedures.

Sedation protocol

Ten minutes before endoscopy, patients in group D received a bolus injection of 0.5 µg/kg dexmedetomidine, patients in group M received a bolus injection of 0.05 mg/kg midazolam, and patients in group K received ketamine intravenously as a bolus injection at 0.5 mg/kg.

With these drugs, 0.5 mg/kg propofol was administered intravenously with incremental 20 mg till achievement of Ramsey sedation score (RSS) 3–4. After that, 0.5 mg/kg propofol boluses were offered for rescue sedation. The total dose of required propofol was recorded.

The efficacy of sedation was determined using the time to achievement of RSS 3–4. RSS is a simple scale scored from 1 to 6 as follows: (1. Awake, anxious, and agitated, 2. Awake, cooperative, oriented, and tranquil, 3. Awake and responds to commands only, 4. Asleep, brisk response to a light glabellar tap or loud auditory stimulus, 5. Asleep, slow response to a light glabellar tap or noisy auditory stimulation, and 6. Asleep with no response.)

Hemodynamics, including mean arterial pressure (MAP) as well as heart rate (HR), were recorded at holding, induction, every 5 mins untill 30 mins intraoperatively and in thepost-anesthesia care unit (PAUC). Additionally, the time to eye opening and total propofol dose given (including induction and rescue doses) were recorded. The incidence of hypotension (MAP < 65 mmHg) and bradycardia (HR < 60 beats/min) were also recorded for all groups.

The primary outcome was to detect the time to achievement of RSS 3–4, and the secondary outcomes were total propofol dose, time to eye opening and hemodynamics.

Sample size determination

PASS: Power and Sample Size Calculation Software (Vanderbilt University, Tennessee, USA) Version 3.1.2 was used to determine the sample size. In light of the previous research by Elzohry et al. [16], the mean difference in time to achievement of RSS 3–4 between at least two groups (dexmedetomidine vs. ketamine) was 2 ± 1.6. Using an effect size of 1.25, power 95%, 5% significance level and seven cases were added to overcome dropout; therefore, we recruited 25 cases in each group.

Statistical analysis

The SPSS v26 (IBM Inc., Chicago, IL, USA) was used for statistical analyses. ANOVA (F) test with post hoc test (Tukey) was used for comparing quantitative variables, which were expressed as mean and standard deviation (SD). Chi-square testing was used to interpret the relationships between qualitative variables, which were expressed as frequencies and percentages. A two-tailed P value of <0.05 indicated the statistical significance.

Results

In our study, 106 cases were evaluated for eligibility, 22 patients were out of our criteria, and nine refused

participation. The remaining patients were randomly categorized into three equal groups ($n = 25$). All allocated patients were followed-up and statistically analyzed (Figure 1).

Patient characteristics, type of surgery, and time of procedure were insignificantly different among the three groups (Table 1).

Time to the achievement of RSS 3–4 and total propofol dose were significantly decreased in group D and group K than in group M and in group D than in group K (P value < 0.05). Time to eye opening was significantly lower in group D and group K than in group M (P value < 0.001) and was insignificantly different between group D and group K (Table 2).

HR measurements at holding, induction and 5 min were comparable in the three groups. HR measurements at 10 min, 15 min, 20 min, 25 min, and 30 min and PACU were significantly higher in group

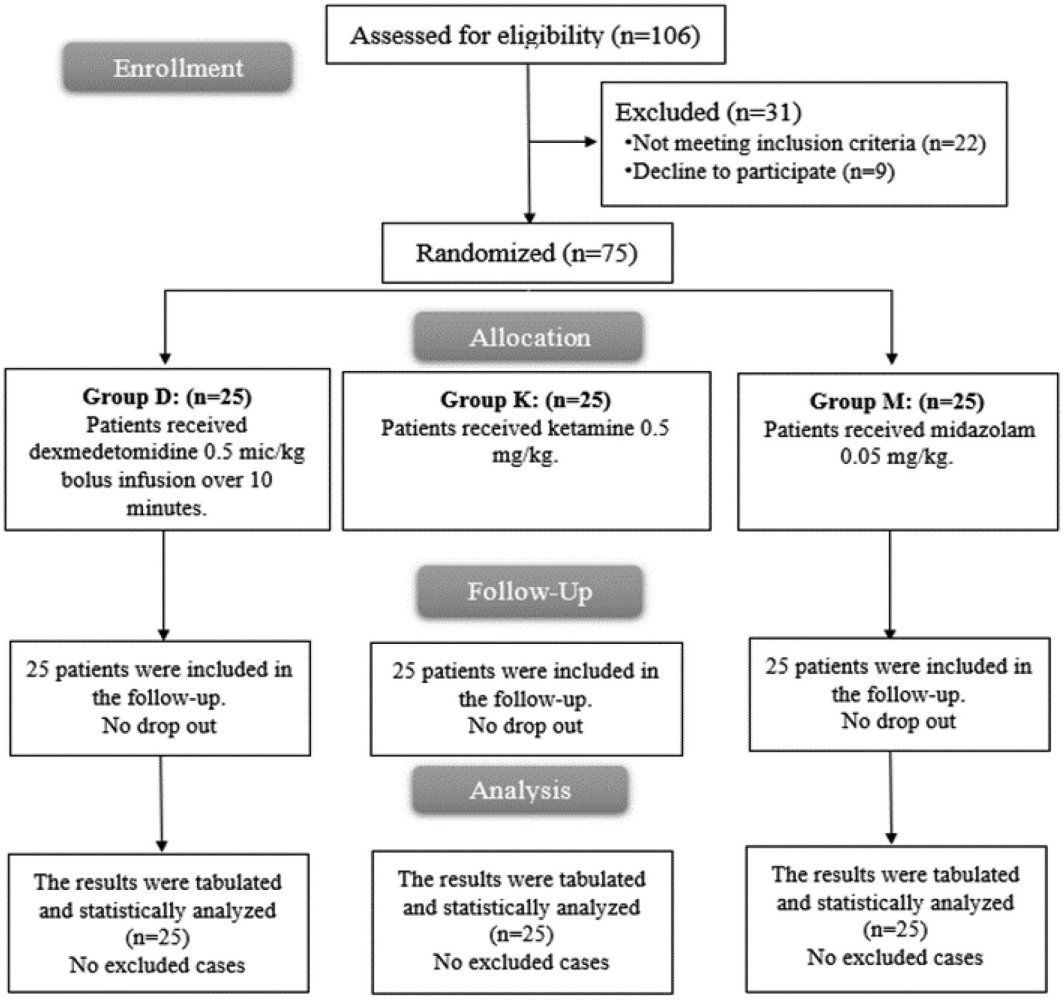

Figure 1. Consort flow chart.

Table 1. Patient characteristics, type of surgery, and time of the procedure of the studied groups.

		Group D ($n = 25$)	Group K ($n = 25$)	Group M ($n = 25$)	P value
Age (years)		4.1 ± 13.53	39.6 ± 11.74	43.6 ± 13.13	.488
Sex	Male	18 (72%)	15 (60%)	17 (68%)	0.657
	Female	7 (28%)	10 (40%)	8 (32%)	
Weight (kg)		64.6 ± 1.78	68.2 ± 1.49	66.8 ± 1.82	.498
Height (cm)		1.65 ± .08	1.65 ± .07	1.66 ± .09	.954
BMI (kg/m^2)		23.7 ± 4.44	25 ± 4.19	24.5 ± 5.04	.609
ASA physical status	II	18 (72%)	16 (64%)	19 (76%)	0.637
	III	7 (28%)	9 (36%)	6 (24%)	
Hypertension		13 (52%)	10 (40%)	15 (60%)	.363
DM		9 (36%)	11 (44%)	8 (32%)	.671
Type of Surgery	Lower endoscopy	16 (64%)	20 (80%)	17 (68%)	0.433
	Both upper and lower endoscopy	9 (36%)	5 (20%)	8 (32%)	
Time of the procedure (min)		22.8 ± 5.27	24.7 ± 3.68	23.5 ± 4.64	.342

Data are presented as mean ± SD or frequency (%), BMI: Body mass index, ASA: American society of anesthesiologists, DM: Diabetes mellitus.

Table 2. Outcomes of the studied groups.

	Group D ($n = 25$)	Group K ($n = 25$)	Group M ($n = 25$)	P value	
Time to achievement of RSS 3–4 (min)	4.7 ± .86	5.9 ± 1.49	7.1 ± 1.94	<.001*	**P1 = 015*** **P2 < 0.001*** **P3 = 0.021***
Time to eye opening (min)	3.2 ± .93	4 ± 1.21	6.4 ± 1.63	<.001*	**P1**=0.079 **P2 < 0.001*** **P3 < 0.001***
Total propofol dose (mg)	128.6 ± 23.91	188.8 ± 33.61	226.8 ± 4.57	<.001*	**P1 < 0.001*** **P2 < 0.001*** **P3 < 0.001***

Data are presented as mean ± SD. RSS: Ramsay sedation score. *: Significant as *P* value ≤ 0.05, P1: *P* value between group D and group K, P2: *P* value between group D and group M, P3: *P* value between group K and group M.

K than group D and group M (*P* value < 0.05) and at 10 min, 15 min, 20 min, and 25 min were insignificantly different between group D and group M (Figure 2).

MAP measurements at holding, induction and 5 min were comparable between the groups. The MAP measurements at 10 min, 15 min, 20 min, 25 min, and 30 min and PACU were significantly higher in group K than group D and group M (*P* value < 0.05) and at 10 min, 15 min, 20 min, 25 min and PACU were insignificantly different between group D and group M (Figure 3).

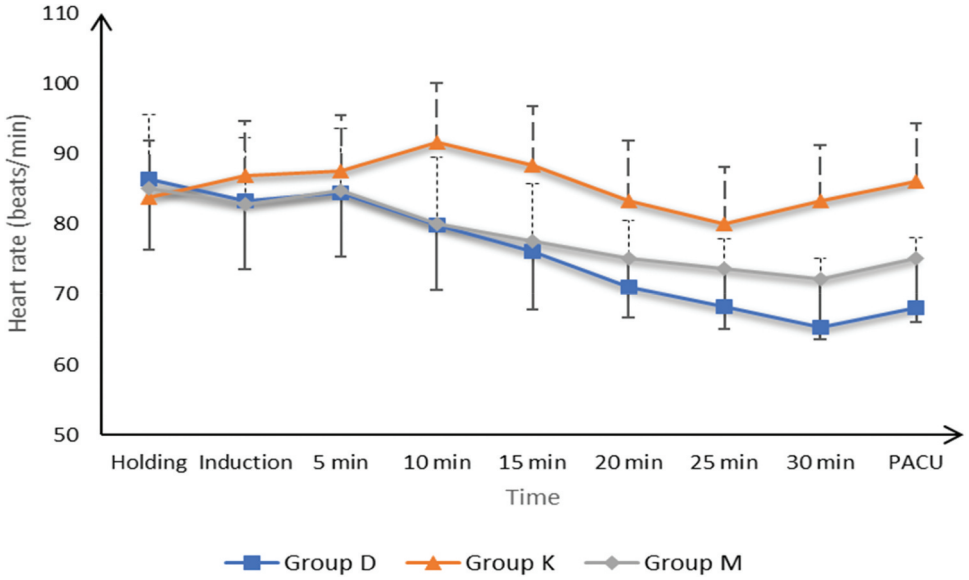

Figure 2. HR (beats/min) of the studied groups.

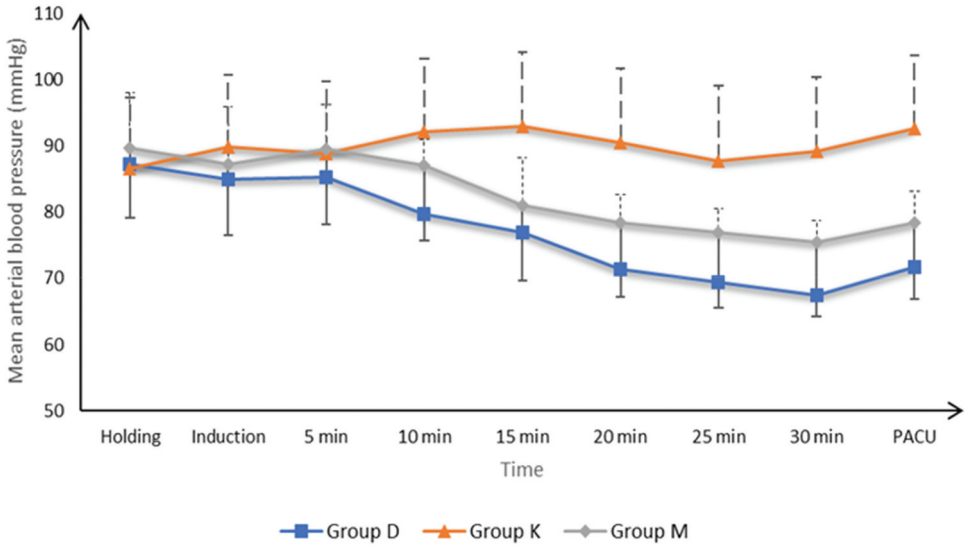

Figure 3. MAP (mmHg) of the studied groups.

Hypotension occurred in seven (28%) patients in Group D, one (4%) patient in Group K, and three (12%) patients in Group M without significant difference among the three groups ($P = 0.051$). Bradycardia occurred in eight (32%) patients in Group D, two (8%) patients in Group K, and three (12%) patients in Group M with insignificant differences among the three groups ($P = 0.056$).

Discussion

While propofol has been suggested for use as a sedative during upper GI endoscopy, its usage is limited, especially in high-risk patients, by the difficulty in accurately estimating the optimum dose and the absence of a direct antagonist [17]. Some advantages may be gained by combining propofol with an adjunctive sedative or analgesic, although this could contribute to additional risks. Adjuvants can potentially improve patients' experience during operations, but they also risk delaying patients' return to normal awareness [18].

ICU patients and those undergoing surgery, heart catheterization, or radiography may be sedated with dexmedetomidine [19]. In addition to its usefulness as a sedative drug during colonoscopy [20]. Dexmedetomidine demonstrated to minimize the anxiety response to surgeries and critical care [21]. The analgesic and sedative roles are due to the activation of locus ceruleus α_2 receptors of the dorsal horn of the spinal cord [22].

For gastroscopy, midazolam is often used alone, but for colonoscopy and endoscopic retrograde cholangiopancreatography, it is typically combined with other agents [20].

Propofol and ketamine combination reduces the ketamine adverse effects such as increased secretion, hallucinations, and vomiting. Meanwhile, the analgesic benefit of ketamine enhances propofol [9].

In the present study, time of RSS 3–4 achievement and total propofol dose were considerably lower in groups D and K compared to group M and in group K than group D. In addition, the time to eye opening was considerably lower in groups D and K compared to group M, with no variation between groups D and K. Moreover, the hemodynamics of group K at 10 min, 15 min, 20 min, 25 min, 30 min and PACU were substantially greater than D and M groups with insignificant differences between D and M groups at 10 min, 15 min, 20 min, and 25 min.

In accordance with our result, Wu et al. [23] compared the dexmedetomidine and midazolam sedation efficacy. They reported that the RSS scores remarkably decreased in the midazolam group compared to the dexmedetomidine group after sedation before endoscopy and after 5 min of endoscopy, with comparable additional sedation and analgesia between both groups.

Moreover, comparable findings were observed by Yin et al. [24]. They found that in comparison to propofol-dexmedetomidine, the hemodynamics during sedation remained stable in the propofol-ketamine, and the recovery time was longer in propofol-dexmedetomidine group with an insignificant difference between groups.

All of the results in our investigation could be elucidated by the pharmacological properties of the medications utilized. Dexmedetomidine was gradually infused over 10 min to minimize the unfavourable hemodynamic alterations brought on by a rapid infusion. It had a prolonged recovery period due to its longer half-life (2–3 h) than that of propofol (30–60 min) [22].

On the contrary, Tekeli et al. [9] indicated that the dexmedetomidine-propofol combination had better sedation and more stable hemodynamics than the ketamine-propofol. The conflicted results could be explained by the different doses of dexmedetomidine, ketamine, and propofol.

El Mourad and his colleagues [25] showed discrepant results; they reported rapid onset of sedation and less additional propofol in ketamine-propofol compared to dexmedetomidine-propofol. In contrast, they were consistent with our results regarding the superior stable hemodynamics in ketamine-propofol compared to dexmedetomidine-propofol.

Confirming this, Elzohry et al. [16] stated that the mean time to RSS 3–4 achievement, recovery Scale Score, and the total propofol requirement in dexmedetomidine-propofol were considerably shorter than ketamine-propofol.

Comparable to our findings, Abbas et al. [26] showed that MAP was significantly increased with ketamine-propofol compared to dexmedetomidine-propofol.

Moreover, Bachula et al. [12] concluded that during GI endoscopy, the early recovery scores and intra- and post-operative hemodynamic measures were better in the ketamine-propofol group.

The particular action mechanism of ketamine remains unknown. Nevertheless, the most probable cause of general anaesthesia is the interruption of corticocortical information flow in a frontal-to-parietal ("top down") distribution [27]. Via various approaches, ketamine stimulates both cardiovascular centres in the medulla directly and the sympathomimetic responses generated (by the inhibition of catecholamine reuptake) indirectly. Combining ketamine with propofol during induction lowers the inhibition of hemodynamic and cardiac processes typically found with propofol only [28].

In line with our results, Koruk et al. [29] found statistically lower total propofol consumption and

recovery period in dexmedetomidine-propofol compared to midazolam-propofol. The hemodynamics was similar between midazolam-propofol and dexmedetomidine-propofol groups.

Comparing the sedation efficacy of midazolam-propofol and dexmedetomidine-propofol, El-Hamamsy et al. [30] were in agreement with our results regarding the total propofol and haemodynamic over time were comparable between dexmedetomidine-propofol and midazolam-propofol groups however, the achievement of consciousness recovery was faster in dexmedetomidine-propofol compared with midazolam-propofol.

Our results observed no significant difference in hypotension between the studied groups, it was observed in 28% in Group D, 4% in Group K, and 12% patients in Group M. Bradycardia occurred in 32% in Group D, 8% patients in Group K, and 12% patients in Group M without a significant difference among the three groups.

In the same context, Hashiguchi et al. [31] stated that bradycardia was recorded in 40% of dexmedetomidine-treated individuals and 10% of midazolam-treated patients. In line with our results, Nishizawa et al. [14] found no significant differences detected between dexmedetomidine and midazolam regarding the incidence of hypotension. A recent randomized clinical trial reported that the dexmedetomidine-propofol group had the highest incidence of hypotension and bradycardia compared ketamine-propfol.

The fact that dexmedetomidine is a highly selective α_2 adrenergic agonist with sedative and analgesic characteristics may explain the greater prevalence of hypotension and bradycardia reported in the dexmedetomidine-propofol group. It promotes sympatholysis, which reduces the stress response, resulting in optimal sedation, and impacts hemodynamic stability [32].

There are a few limitations to this study. This research included both ASA II and ASA III patients. Consequently, high-risk individuals should be included in upcoming research. It was a single-centered study; therefore, the findings cannot be generalized. Further studies using different additives, types, and concentrations of the sedative agents are recommended.

Conclusions

In cancer patients who underwent GI endoscopy, dexmedetomidine-propofol and ketamine-propofol had better sedation efficacy as observed through lower achievement time of RSS 3–4, total propofol dose, and eye-opening time compared to midazolam-propofol group with superior sedative effect of ketamine-propofol than dexmedetomidine- propofol. While ketamine-propofol had better hemodynamics, as observed by more stable HR and MAP.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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