Comparison of two sedation protocols on intraocular pressure and hemodynamic responses during colonoscopy

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Abstract. – OBJECTIVE: Colonoscopy is one of the most frequently performed interventional endoscopic procedures for diagnosis and treatment. During the procedure, the increase in intraabdominal pressure can cause undesirable spikes in intraocular pressure. In the literature, there are no studies on agent combinations that cause the least effect on intraocular pressure and hemodynamic response in colonoscopic procedures, which are performed more frequently in the elderly, the patient group at the greatest risk for glaucoma. This study aimed to compare ketamine-propofol and ketamine-midazolam protocols in terms of their effects on hemodynamic parameters and intraocular pressure.

MATERIALS AND METHODS: The research was a randomized clinical controlled double-blind study. The study was conducted on 60 healthy adults who underwent elective colonoscopy. Ketamin-midazolam and ketamine-propofol combinations were used. Hemodynamic parameters, intraocular pressures at five different times, and the satisfaction levels of the endoscopist and the patient were recorded.

RESULTS: In both groups, there was a statistically significant difference between the pre-procedure intraocular pressure values and the values at the 1st minute of the procedure and at recovery ($p<0.05$). No statistically significant difference was found between the intraocular pressure values of the study groups at any time point ($p>0.05$).

CONCLUSIONS: Both combinations can be used safely. The combination of ketamine and propofol in subanesthetic doses provides better sedation without disturbing the hemodynamics and is preferable.

Key Words:
Intraocular pressure, Colonoscopy, Ketamine, Sedation.

Introduction

The history of anesthesia starts with anesthetic agents given to relieve pain in minor surgical procedures. During the development of surgery and anesthesiology, by complementing each other, resuscitation, fluid replacement, airway method, reduction of surgical stress, and postoperative pain management has become the field of expertise of anesthesiologists[1]. Colonoscopy is one of the most frequently performed interventional endoscopic procedures for screening, diagnosis, and treatment. Although it is a short-term procedure, it is recommended to be performed under sedation because it causes pain and anxiety. During the procedure, the endoscopist gives air to provide dilatation to evaluate the colon clearly, and patients usually feel pain during this process. Therefore, the procedure makes tolerance more difficult for patients. Patients undergoing colonoscopies are usually treated in outpatient clinics.

Sedation must provide increased patient comfort and quality, effective sedation, and rapid recovery. In these applications, patient safety should be prioritized, and the adverse and residual effects of the agents to be selected for sedoanalgesia have gained importance. The fact that the use of a single anesthetic drug causes insufficient sedation and analgesic efficiency increases the number of adverse effects by causing excessive drug consumption, and the use of these agents in combination. For this purpose, the use of opioids and intravenous anesthetics in various combinations increases the potency of drugs and decreases adverse effects.

Glaucoma is a condition that causes damage to the optic nerve with an increased incidence

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and intraocular pressure (IOP) over the age of 40 years (normal range: 12-24 mm Hg). High IOP is one of the most important risk factors for glaucoma. During colonoscopy procedures, the increase in intraabdominal pressure created by air given to enhance the image quality and the drugs used for sedoanalgesic purposes can also increase IOP and cause undesirable spikes in IOP[2,3].

Ketamine, in addition to its sedative, amnestic and hypnotic properties, is a centrally acting strong dissociative anesthetic and analgesic. When used alone, adverse effects, such as tachycardia, hypertension, nausea, laryngospasm due to increased secretion, and hallucinations are common. Therefore, its use alone is limited. Unlike many other anesthetic agents, it increases IOP[2,4].

Although propofol has an amnestic effect, it may cause respiratory depression when used in high doses in painful procedures due to its lack of analgesic activity. It is recommended to be used together with opioids and benzodiazepines to achieve a synergistic effect[5,6].

Midazolam is a benzodiazepine that is frequently used in invasive procedures due to its short half-life and strong anxiolytic-sedative effect. The high amnestic effect increases its frequency of use in endoscopic procedures. Midazolam is considered a good option to reduce anxiety and calm the patient. The most important advantage of midazolam in ocular procedures is that it relaxes the extraocular muscles and lowers IOP[7].

In literature, there are studies on the effects of different agent combinations and anesthetic agents on IOP in other conditions that increase intraabdominal pressure, such as laparoscopy. However, there are no studies on agent combinations that have the least effect on IOP and hemodynamic response in colonoscopic procedures, which are performed more frequently in the elderly, the patient group at the greatest risk for glaucoma. This study aimed to compare ketamine-propofol and ketamine-midazolam protocols in terms of their effects on hemodynamic parameters and IOP.

Material and Methods

The study was conducted on 60 patients who underwent elective colonoscopy in the Gastroenterology Clinic of Ankara Keçiören Training and Research Hospital. Approval for the study was obtained from the Clinical Research Ethics Committee (Number: 874). The research was a randomized clinical controlled double-blind study. Patients with American Society of Anesthesiology (ASA) health status I-II aged 18-60 years were included in the study. The exclusion criteria were patients with ASA III and/or above, age <18 and >60 years, with a history of allergy to any of the drugs, with glaucoma or refractive errors, previous eye surgery, IOP >24 mm Hg in pre-procedure measurements, uncontrolled hypertension, chronic alcohol use, and intracranial space-occupying lesions.

Sixty patients who were scheduled for colonoscopy were divided into two groups of 30 each using computer-assisted randomization: group 1, 0.25 mg/kg ketamine + 0.05 mg/kg midazolam was administered as an IV push, and group 2, 0.25 mg/kg ketamine + 1 mg/kg propofol administered as an IV push.

During the procedure, sedation depth was evaluated using the Observer Assessment of Alertness and Sedation Scale (OAA/S). When OAA/S was 3-4, colonoscopy procedures were allowed to be performed. When OAA/S was >4, sedation was considered insufficient, and 0.25 mg/kg ketamine was administered as an additional dose.

The initial IOPs of the patients were measured and recorded. A second measurement was made 1 minute after the agents were administrated and the colonoscopy procedure was allowed to begin. During the procedure, the measurements were repeated at the hepatic flexure and the ileocecal valve levels. In the recovery unit, the IOP value was measured and recorded for the last time before discharge. A pen-sized applanation tonometer (Tono-Pen AVIA, Reichert Inc., Depew, NY, USA) weighing 71 g, that did not require calibration, was used to measure IOP (measuring range: 5-55 mm Hg) (Figure 1). Tono-Pen gives four independent measurement averages by lightly

Figure 1. The applanation tonometer that was used to measure intraocular pressure (Tono-Pen AVIA, Reichert Inc., Depew, NY, USA).

touching the cornea with a 1.5-mm contact area. A disposable sterile sheath is attached to the end of the device before each measurement.

Studies have shown that patient position is also effective on IOP. It was observed that there was a significant increase in IOP values measured from the inferior side in the lateral decubitus position (LDP)[8]. We also measured IOP in the left eye in all colonoscopies performed in the right LDP so that there would be no positional difference between the measurements. Colonoscopy was performed on all patients by the same specialist physician.

Statistical Analysis

Research data was uploaded to a computer and evaluated using the Statistical Package for the Social Sciences (SPSS) for Windows 22.0 software (SPSS Inc, Armonk, NY, USA). Descriptive statistics are presented as mean standard deviation, median (min-max), frequency distribution, and percentage. Pearson's Chi-square test and Fisher's exact test were used to evaluate categorical variables. The conformity of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Shapiro-Wilk test). For variables that were found to have normal distribution, the Student's *t*-test was used as a statistical method for statistical significance between two independent groups and the paired-sample *t*-test between two dependent groups. For the variables that did not fit normal distribution, the Mann-Whitney U test was used for significance between two independent groups, and the Wilcoxon signed-ranks test was performed between two dependent groups. The statistical significance level was accepted as $p<0.05$.

Results

A total of 60 patients who underwent colonoscopy under anesthesia were evaluated within the scope of the study. The mean age of the patients was 43.78±11.36 (min: 21-max: 60) years, the mean body mass index (BMI) was 24.47±3.95 kg/m^2, and 58.3% (n=35) were female.

Of the 60 patients, 30 were sedated with ketamine and midazolam and 30 were sedated with ketamine and propofol.

Age, height, body weight, BMI values, sex, ASA levels, colonoscopy indications, procedure durations, and sedation and recovery times were similar in patients sedated with ketamine-midazolam and ketamine-propofol ($p>0.05$) (Table I).

In both the ketamine-midazolam and ketamine-propofol groups, IOP values at the 1st minute of the procedure were statistically significantly lower than those of the pre-procedural period ($p<0.05$). Although there was a decrease in IOP values at all other times, except for the 3rd minute, no statistically significant difference was found ($p>0.05$) (Table II).

Table I. Distribution of some descriptive characteristics among study groups.

	KM (n = 30)	KP (n = 30)	*p*
Age (year)	43.37 ± 11.80	44.20 ± 11.08	0.888
Height (cm)	167.07 ± 8.32	166.67 ± 7.48	0.846
Body Weight (kg)	74.00 ± 13.88	73.73 ± 11.95	0.937
BMI (kg/m^2)	26.45 ± 4.33	26.48 ± 3.61	0.975
Sex			0.793
Male	18 (60.0)	17 (56.7)	
Female	12 (40.0)	13 (43.3)	
ASA			0.121
I	19 (63.3)	13 (43.3)	
II	11 (36.7)	17 (56.7)	
Colonoscopy Indication			
Hidden blood in stool (+)	5 (16.7)	5 (16.7)	
Iron deficiency anemia	6 (20.0)	5 (16.7)	
Abdominal pain/Constipation	7 (23.3)	8 (26.7)	0.933
Cancer screening	6 (20.0)	4 (13.2)	
Diarrhea	6 (20.0)	8 (26.7)	
Processing Time (min)	10.23 ± 3.90	9.77 ± 3.40	0.812
Cecum Time (min)	6.73 ± 2.02	7.00 ± 3.01	0.858
Sedation Time (min)	13.73 ± 4.42	12.27 ± 3.33	0.222
Recovery Time (min)	4.37 ± 2.63	3.50 ± 2.13	0.071

Table II. Distribution of mean blood pressure during colonoscopy procedures between the study groups and within each study group.

MAP (mmHg)	KM (n = 30) mean ± SD	KP (n = 30) mean ± SD	*p*
Preprocedural	104.83 ± 14.39	98.83 ± 13.42	0.100
1st min.	98.50 ± 1 5.24**	89.37 ± 8.79**	0.007
3rd min.	100.40 ± 15.70	101.20 ± 14.25	0.837
6th min.	104.47 ± 17.79	101.37 ± 11.35	0.425
9th min	99.52 ± 18.33	97.89 ± 9.72	0.724
Postprocedural	100.33 ± 18.26	95.10 ± 12.14	0.197
Recovery	92.60 ± 13.16**	92.07 ± 10.06*	0.861

SD: Standard deviation; MAP: Mean blood pressure; KM: Ketamine-Midazolam; KP: Ketamine-Propofol. *In comparison with the pre-process; $p < 0.05$; **In comparison with the pre-process; $p < 0.01$ #n = 21 in CM, n = 19 in KP.

The HR and SpO_2 values of the study groups at all time points showed similar characteristics (p>0.05). In both groups, the median sedation score was 3-4 during the procedure. There was no significant difference between the study groups in terms of sedation levels at any time point (p>0.05) (Figure 2).

There was a statistically significant difference between the pre-procedure IOP values of those sedated with ketamine-midazolam and the IOP values at the 1st minute of the procedure and at recovery (p<0.05), but there was no significant difference between the IOP values at the hepatic flexure level and at the time of cecum intubation (p>0.05). In patients sedated with ketamine-midazolam, IOP values at the first minute of the procedure and recovery were significantly lower than the pre-procedural IOP values (Table III). Likewise, in those sedated with ketamine-propofol, there was a statistically significant difference between the IOP value before the procedure and the IOP value at the 1st minute of the procedure (p<0.05), but there was no significant difference between the hepatic flexure level and the IOP values during cecum intubation, and at recovery (p>0.05).

In patients sedated with ketamine-propofol, the IOP value at the 1st minute of the procedure was significantly lower than the pre-procedural IOP value; no statistically significant difference was found between the IOP values of the study groups at any time points (p>0.05) (Table III, Figure 3).

The decrease between the IOP values of the patients before the procedure and at the 1st minute of the procedure was 1.53±0.77 mm Hg in the

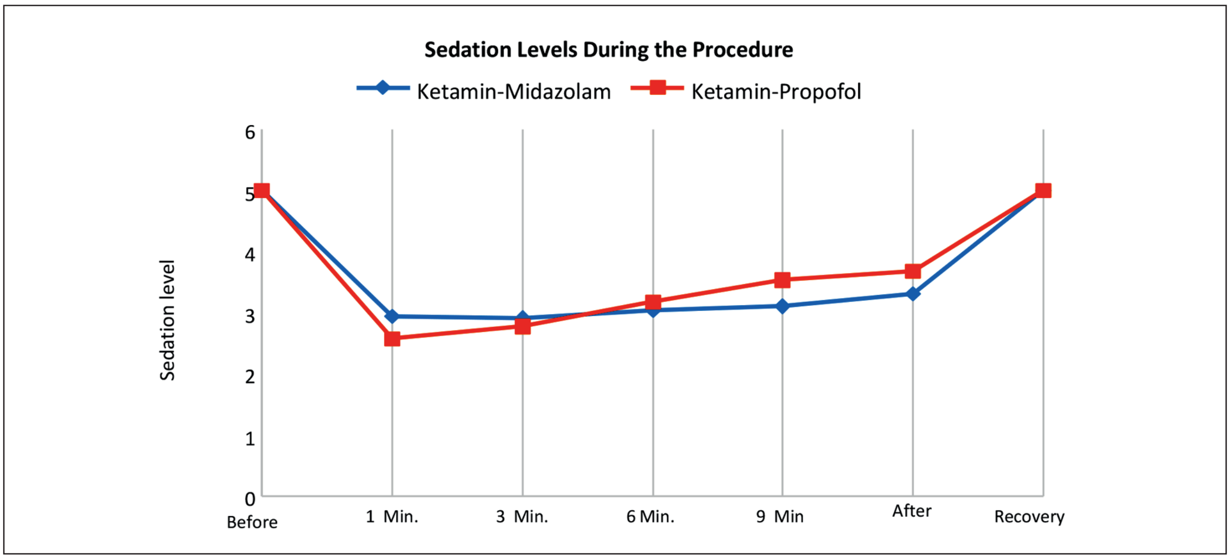

Figure 2. Distribution of sedation levels during the procedure by study groups.

Table III. Distribution of intraocular pressures during colonoscopy procedure between study groups and within each study group IOP (mmHg) KM (n = 30) KP (n = 30).

IOP (mmHg)	KM (n = 30) mean ± SD	KP (n = 30) mean ± SD	*p*
Pre-procedural	19.27 ± 3.57	20.10 ± 3.13	0.388
1st min.	17.73 ± 3.52*	17.93 ± 3.33**	0.822
Hepatic flexure	18.17 ± 4.10	18.47 ± 3.92	0.773
Cecum	18.20 ± 4.20	19.50 ± 4.22	0.237
Recovey	17.40 ± 3.78*	19.10 ± 3.92	0.052

SD: Standard deviation; IOP: Intraocular pressure; KM: Ketamine-Midazolam; KP: Ketamine-Propofol. *In comparison with the pre-processing; $p < 0.05$; **In comparison with the pre-processing; $p < 0.01$.

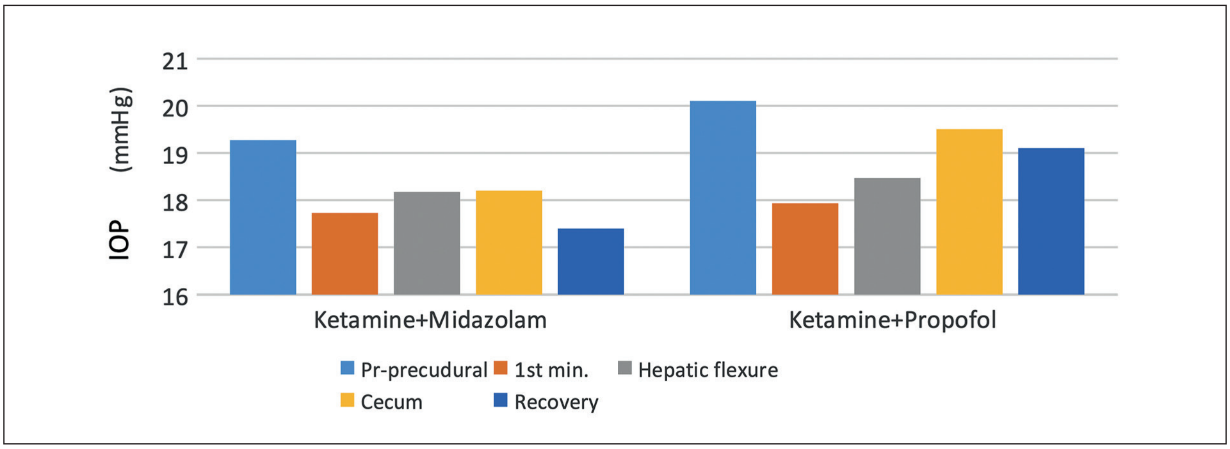

Figure 3. Distribution of intraocular pressure during the colonoscopy procedure.

ketamine-midazolam group and was 2.17±0.67 mm Hg in the ketamine-propofol group. There was no significant difference between the study groups in terms of the amount of IOP reduction in the 1st minute compared with the pre-procedure IOP values (p>0.05).

The visual analog scale (VAS) scores of the study groups during the procedure and at recovery were similar (p>0.05). There was no statistically significant difference between the satisfaction levels of the endoscopist and the patients between the groups (p>0.05).

As a result of the research, the ketamine-midazolam combination created a sufficient sedation level in 16 patients. In 46.7% (n=14) of the patients, insufficient sedation was accepted, and additional medication was needed because it caused the patient to feel pain and move. In the group of patients who were sedated with ketamine-propofol, adequate sedation depth was achieved in 26 patients, and additional drugs were used in only four patients (13.3%) (p<0.05) (Table IV). During the procedure, hypotension-bradycardia, hypertension-tachycardia, hypoxia, nausea-vom-

Table IV. Distribution of additional drug use, excessive and insufficient sedation conditions, and complications among the study groups.

	KM (n = 30) (%*)	KP (n = 30) (%*)	*p*
Additional Medication	14 (46.7)	4 (13.3)	**0.005**
Insufficient sedation	14 (46.7)	4 (13.3)	**0.005**
Hypotension/Bradycardia	2 (6.7)	1 (3.3)	0.998
Hypertension/Tachycardia	2 (6.7)	3 (10.0)	0.998
Hypoxia	5 (16.7)	8 (26.7)	0.347
Nausea-vomiting	1 (3.3)	0	0.998

*Column percent. KM: Ketamine-Midazolam; KP: Ketamine-Propofol.

iting, and the development of complications were similar ($p>0.05$) (Table IV). Excessive sedation, airway obstruction, or increased secretion was not observed in any patients.

Discussion

Non-operating room anesthesia has become more and more common. The selection of drugs to be used is very important to apply safe anesthesia. A short duration of action, rapid induction, early recovery, and minimal adverse effects are expected features of an anesthetic drug. However, because no agent fully meets these properties, various combinations are used.

Intraabdominal pressure, whose normal value is between 5-7 mmHg, rises to 12 mmHg with carbon dioxide infusion during colonoscopy procedures. Ece et al[9] reported that IOP values measured at 9-12-15 mmHg intraabdominal pressure created during laparoscopy were higher than in the control group. The differences were found to be significant. In our study, mean arterial pressure (MAP) and IOP were evaluated without measuring intraabdominal pressure.

The feeling of pain and discomfort during colonoscopy varies from person to person. During sedation, it is frequently encountered that different bolus applications are applied according to the clinician's initiative and anesthesia follow-up. Many sedative agents are used alone or in combination during procedures. The most commonly used agents are propofol, opioids, ketamine, and midazolam. However, combinations of opioids with midazolam and propofol can cause serious adverse effects, such as respiratory depression and bradycardia. It has been reported that ketamine should be used very cautiously in patients with uncontrolled cardiovascular problems, and even if there are other alternatives, ketamine should be avoided[10,11]. When ketamine is used together with other sedative agents, especially when applied with propofol, it causes less cardiovascular and respiratory depression and provides effective analgesia even at subanesthetic doses[12]. In many studies evaluating ketamine-propofol and ketamine-midazolam sedation, it was reported that no significant decrease was observed in the blood pressure and heart rate, hypotension, bradycardia, desaturation, or apnea of the patients, and it was reported that this effect was due to the opposing effects of the drugs on the autonomic nervous system. Badrinath et al[13] reported that tachycardia and hypertension due to ketamine did not occur in a propofol-ketamine combination. In a study by Sagir et al[14] on 100 patients, 0.5 mg/kg of ketamine was combined with propofol and midazolam, and hypertension and tachycardia were observed in only one patient in the ketamine-propofol group. Similarly, in our study, hypertension and tachycardia were not observed in any patients who were administered a bolus propofol-ketamine combination. Celik et al[15] reported that the combination of 1-1.5 mg/kg ketamine and 0.1 mg/kg midazolam caused hypertension and tachycardia in 15% of patients. In our study, a combination of ketamine and midazolam was used in one group. Tachycardia and hypertension were not observed in any patients in this group. We thought that this difference was due to the lower dose of ketamine that we used.

In a study performed with 0.5-1 mg/kg IV propofol and 0.05-0.1 mg/kg IV midazolam bolus doses, no statistically significant difference was observed between the two groups when comparing SBP[16]. In our study, although a decrease in blood pressure was observed in the 1st minute after induction in both groups, this decrease was at levels that did not require clinical intervention. Among the groups, SBP, DBP, and MAP values were found to be statistically significantly lower in the KP group at the 1st minute, compared with the KM group. We thought that this difference was probably due to the fact that 1 mg/kg propofol was more hypotensive than 0.05 mg/kg midazolam because the ketamine doses used were equal.

Sagir et al[14] reported that similar hemodynamic stability and sedation conditions were achieved in patients who underwent colonoscopy with midazolam-ketamine and propofol-ketamine combinations made with 0.5 mg/kg ketamine, unlike our study. However, the authors stated that the propofol-ketamine combination could be preferred in such interventions because it provided an earlier discharge time. Accordingly, we obtained similar hemodynamic parameters and sedation scores in both groups. We found recovery times were similar in both study groups.

In another study published in 2014, Aydogan et al[17] investigated the effects of ketamine-propofol mixture on IOP and hemodynamics in 50 patients aged over 65 years who would undergo elective urologic surgery under general anesthesia. A ketamine-propofol mixture (ketofol) and propofol 1.5 mg/kg prepared in a single syringe were administered as an IV bolus and a laryngeal mask was placed on the patients. As a result, it was suggested that ketofol induction provided a safe induction with minimal hemodynamic change and less IOP, even though there was a decrease in IOP in both groups. In the comparison of 1 mg midazolam and placebo in 55 pediatric patients with ophthalmic problems, there was no significant difference in baseline IOP in both groups. They stated that the addition of midazolam to ketamine might be beneficial in children undergoing ophthalmic surgery[18]. In our study, both drug combinations decreased the IOP compared with the baseline value, but no statistically significant difference was found between the two groups.

It has been reported that sedation must be given for both patient and procedure comfort in colonoscopy because it is a longer and more painful procedure than upper GIS endoscopy[19]. During this procedure, a moderate or deep level of sedation should be provided to maintain spontaneous ventilation along with analgesia and to allow the patient to tolerate the procedure. The OAA/S is a frequently used scale because it is practical in monitored anesthetic care. Nakagawsa et al[20] recommended that sedative drugs should be titrated to an OAA/S score of ≥3 and a bispectral index (BIS) value of >80 in order not to block protective reflexes and to provide cardiorespiratory stability during sedation in regional anesthesia. We did not use BIS monitoring in our study, and we aimed to provide 3-4 levels of sedation depth, in which patients were asleep but could respond to verbal stimuli according to the OAA/S score. Procedures could be performed under similar sedation levels in both study groups. However, even if the combination of 0.25 mg/kg ketamine + 0.05 mg/kg midazolam created the desired sedation level in the patient, we had to prescribe additional medication towards the end of the procedure. In both groups, no patient had a score of 1 with a deep sedation level.

In a study evaluating 70 patients administered 0.07 mg/kg midazolam + 2 mg/kg ketamine IV in emergency surgical interventions, apnea developed in three patients and laryngospasm developed in one patient[21]. During the procedure, no clinical interventions were required in any of the two groups, in which we provided routine nasal cannula oxygen support. Apnea and laryngospasm were not observed in any patients.

Dal et al[22] compared ketamine-midazolam and ketamine-propofol combinations for sedation at doses similar to our study during endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Although hemodynamic parameters were similar, the ketamine-midazolam group was found to be significantly superior in terms of bronchoscopist satisfaction. There was no significant difference between the groups in terms of patient satisfaction and adverse effects, and it was suggested that both combinations were effective and safe. In our study, we used similar doses, and similar patient and endoscopist satisfaction was reported in both groups. We used the same doses as the ketamine-midazolam group, but in our study, these doses were insufficient for colonoscopy. We thought that the pre-procedural anxiety levels of the patients who would undergo colonoscopy might affect this situation, but in both studies, the pre-procedural anxiety levels of the patients were not questioned.

Conclusions

As a result, both combinations can be used safely in adult patients who will undergo colonoscopy. However, due to the need for more additional drugs in the ketamine-midazolam group, we believe that the combination of ketamine and propofol in subanesthetic doses provides better sedation without disturbing the hemodynamics and is preferable. Although there are different opinions on the effect of using ketamine alone on IOP, we believe that the combined use of propofol or midazolam can be used safely without causing significant changes in IOP.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Funding
There were no funding recourses for this study.

Informed Consent
The authors declare that the patients included in the study signed informed consent forms to use their medical information in the studies.

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