A comparison of different proportions of a ketamine-propofol mixture administered in a single injection for patients undergoing colonoscopy

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Abstract

Introduction: In this study, we aimed to determine the appropriate proportion of ketamine-propofol (ketofol), which was prepared in two different proportions for colonoscopy procedures.
Material and methods: This is a prospective and randomized trial. Group 1 was administered a mixture of 100 mg ketamine and 200 mg propofol. Group 2 was administered 50 mg ketamine and 200 mg propofol. Additional doses of 0.5 mg/kg bolus propofol without ketamine were administered to both groups to stabilize the bispectral index at 70–80 and with a Ramsey sedation score of 3–4. The pulse rate, mean arterial pressure (MAP), peripheral oxygen saturation values, colonoscopy period, adverse events, recovery time, discharge time, additional propofol doses, total propofol doses, colonoscopist and patient satisfaction were recorded.
Results: In group 2, the 1 min MAP mean was significantly lower than the initial, 10, 15 and 20 min MAP means (p = 0.014, p = 0.002). The 20 min PR mean of group 2 was statistically significantly higher than group 1 (p = 0.045). The 15 min PR mean of group 2 was significantly lower than the initial and the 1 min PR means (p = 0.023, p = 0.006). The total propofol dose mean of group 2 was significantly higher than group 1 (p = 0.0001). The presence of adverse events in group 2 was significantly lower than that in group 1 (p = 0.0001). The mean colonoscopist satisfaction in group 2 was significantly lower than that in group 1 (p = 0.047).
Conclusions: In colonoscopy, a ketofol mixture prepared in the proportion 1 : 2 provides appropriate hemodynamic conditions and sufficient sedation.

Key words: colonoscopy, ketamine, propofol, ketofol.

Introduction

Colonoscopy, the gold standard in determining neoplastic changes and pathologies of the lower gastrointestinal system (GIS), is a painful process [1, 2]. Pain and anxiety extend the period of the operation and increase the possibility of complications. For this reason, sedo-analgesia is recommended [3]. The aim of sedo-analgesia in interventional endoscopic operations should be, together with a sufficient level of sedation, to reduce the pain and the anxiety, to keep the amnesia at a maximum level, and to provide stable hemodynamic and respiratory conditions [4, 5]. The ideal agent should achieve all these goals and have an effective beginning and ending. It should also exhibit equal perfor-

mance when administered via different routes, be able to be used safely in all age groups, and be cheap. At present, no single agent exhibits all these features [4]. Both ketamine and propofol are used for sedation and analgesia. Ketamine provides dissociative anesthesia and supplies excellent amnesia and analgesia. Together with muscle tonus, it protects airway reflections and continuous spontaneous respiration. Propofol has amnesic, antiemetic, and anticonvulsant properties. It induces a rapid response, and the recovery time is short [6]. However, as propofol does not have an analgesic impact, it is recommended for use with ketamine or with short-acting opioids in procedural sedation [7]. The combination of propofol and ketamine for procedural sedation increases the efficiency of the sedation and minimizes side effects. In addition, the cardiovascular effects of both drugs are reverse/opposite [4]. The negative effects produced by propofol can be prevented with the use of ketamine, resulting in an increase in mean arterial pressure (MAP) and cardiac indices [8]. Although there is a study comparing activities of ketamine-propofol (ketofol) sedations in different proportions in upper GIS endoscopy [9], there has been no study researching ketofol use in lower GIS endoscopy. In our study, we aimed to determine the appropriate proportion of ketamine-propofol (ketofol) prepared in different proportions for lower GIS endoscopy procedures.

Material and methods

After obtaining the approval of the ethics committee and the informed consent of the patients, a prospective, randomized study was undertaken of 80 outpatients, aged 18–65, ASA 1–2, scheduled to undergo elective colonoscopy in Sisli Etfal Training and Research Hospital. The study was completed in a 3-month period. The primary outcome of the study was to determine the appropriate ratio of ketamine-propofol prepared in two different proportions for the colonoscopy procedure in terms of hemodynamic and sedation conditions. The secondary outcome of the study was to compare adverse effects, colonoscopist and patient satisfaction. Prior to colonoscopy, the patients fasted for 8 h. All the patients were anesthetized by the same anesthetist and the colonoscopy procedure was conducted by the same colonoscopist. Patients who were pregnant or who had anticipated airway difficulties and those who had current active GIS bleeding, severe cardiac and respiratory insufficiencies, an increase in intracranial pressure, a history of allergy to sedative medication, alcohol and drug addiction, and psychiatric disorders were excluded from the study.

In all the patients, vascular access was achieved with an 18-gauge intravenous cannula, and fluid replacement was provided with a solution of 0.9% NaCl. To evaluate patient satisfaction, an oral scoring system on a scale of 1–10 was explained to the patients. For premedication, 1 mg midazolam was administered as standard to the patients. In the operation room, the values of peripheral oxygen saturation (SpO_2), the noninvasive MAP (mm Hg), and the pulse rate (PR; beat/min) were recorded. In the blood pressure follow-ups of the patients, a decrease of the initial value by more than 30% was considered as hypotension, while an increase by more than 30% was considered as hypertension. Decrease of the PR below 50 beat/min was considered as bradycardia, while an increase over 100 beat/min was considered as tachycardia. The bispectral index (BIS) was also monitored (Covidien Medical, Boulder, CO). With a nasal cannula, 3 l/min O_2 was given to the patients, who were assigned to the two groups according to their presentation at the hospital. The first group of patients (group 1) was administered 22 ml of ketofol prepared with 100 mg ketamine and 200 propofol. The mixture was carefully titrated, and standard induction was performed, with 1 mg/kg propofol and 0.5 mg/kg ketamine. The 0.5 mg/kg · h ketofol mixture was infused with an infusion pump. For the second group (group 2) a 21 ml mixture of 50 mg ketamine and 200 mg propofol was prepared. The mixture was carefully titrated, and standard induction was performed, with 1 mg/kg propofol and 0.25 mg/kg ketamine. The 0.5 mg/kg · h ketofol mixture was infused with an infusion pump. After the process of colonoscopy had started, additional bolus propofol doses of 0.5 mg/kg were applied to both groups, without adding ketamine and keeping the BIS at 70–80 and with a Ramsey sedation score (RSS) of 3–4. The PR and MAP values, SpO_2 values, RSS and BIS values of the patients were recorded 5 min after the beginning of the procedure and then at 1 min and 5 min intervals until the end of the operation. The duration from the induction to the end of the operation was accepted as the period of colonoscopy. Additional propofol doses administered and the total propofol dose were calculated. Adverse events that developed during the process such as hypersensitivity reactions, bradycardia, tachycardia, hypotension, hypertension, respiratory depression, desaturation, nausea, vomiting, diplopia, bleeding, and perforation were noted. Desaturation was defined as a decrease in the oxygen saturation below 85%. The duration from stopping all anesthetics to the time at which the patients were able to provide coherent answers to oral questions was accepted as the recovery time. After the operation was completed, patients with scores of 9 or above according to the Aldrete recovery score were discharged. The duration from the induction to the time at which the scores reached 9 or above according to

the Aldrete recovery score was accepted as the discharge time. Patient satisfaction was scored by patients orally on a scale of 1 to 10 (0 = not satisfied, 10 = very satisfied) after recovery. Colonoscopist satisfaction was evaluated with a 10 cm visual analog scale. The patients were questioned about their dreams in the follow-up period. Patients' relatives were informed about the complications that may occur due to ketamine and were warned that the patient should not leave the hospital alone.

Statistical analysis

The sample sizes were calculated with the assumption of a possible at least 30% difference in hemodynamic measurement between any two groups. Therefore 40 patients were allocated to each group in order to obtain an alpha error of 5% and statistical power of 80%.

In addition to the descriptive statistical methods (mean, standard deviation), one way/irreversible variant analysis was used in the repetitive measurements of the multiple groups. In the comparison of the sub-groups, the Newman-Keuls multiple comparison test was employed. In the comparison of the dual groups, the independent *t* test was used, and in the comparison of the qualitative data, the χ^2 test and Fisher's exact test were used. The statistical significance level was set at $p < 0.05$.

Results

There were no significant differences between the means of age ($p = 0.364$), weight ($p = 0.514$), colonoscopy period ($p = 0.835$), gender ($p = 0.823$), and distributions of the ASA score ($p = 0.370$) of the groups. There was also no statistically significant difference between the recovery time ($p = 0.433$) and the discharge time ($p = 0.321$) of the groups. The additional propofol dose mean of group 2 was statistically significantly higher than in group 1 ($p = 0.001$). The total propofol dose mean of group 2 was also statistically significantly higher than in group 1 ($p = 0.0001$). Statistically, the mean colonoscopist satisfaction in group 2 was significantly lower than that of group 1 ($p = 0.047$). The mean patient satisfaction did not differ between the groups ($p = 0.117$) (Table I).

There was also no statistically significant difference between the initial, 1, 5, 10, 15 and 20 min MAP means of the groups ($p > 0.05$). No statistically significant variation in the initial, 1, 5, 10, 15 and 20 min MAP means was detected in group 1 ($p = 0.548$).

There was a statistically significant change in these parameters in group 2 ($p = 0.001$). The 1 min MAP mean was statistically significantly lower than the 10, 15, and 20 min MAP means ($p = 0.014$, $p = 0.002$). The 5 min MAP mean was statistically significantly higher than the 20 min MAP mean ($p = 0.028$). No statistically significant difference was detected among the other groups ($p > 0.05$) (Table II).

Statistically, no significant difference was observed in the initial, 1, 5, 10, 15 and 20 min PR means of the groups ($p > 0.05$). There was also no statistically significant variation in the initial, 1, 5, 10, 15 and 20 min PR means in group 1 ($p = 0.093$). The 20 min PR mean in group 2 was statistically significantly higher than in group 1 ($p = 0.045$).

Table I. Mean age, weight, colonoscopy period, gender, ASA score, recovery time, discharge time, additional propofol dose, total propofol dose, colonoscopist and patient satisfaction of the groups

Parameter		Group 1 ($n = 40$)	Group 2 ($n = 40$)	Value of p
Age [years]		48.85 ±9.96	51.08 ±11.76	0.364
Weight [kg]		74.3 ±15.54	76.5 ±14.49	0.514
Colonoscopy period [min]		13.43 ±4.14	13.18 ±6.31	0.835
Gender	Female	21 (52.50%)	22 (55.00%)	0.823
	Male	19 (47.50%)	18 (45.00%)	
ASA score	1	21 (52.50%)	17 (42.50%)	0.370
	2	19 (47.50%)	23 (57.50%)	
Recovery time [min]		3.75 ±1.98	3.38 ±2.26	0.433
Discharge time [min]		34.73 ±8.13	33.03 ±7.05	0.321
Additional propofol dose [mg]		32.5 ±7.07	49.5 ±18.29	0.001*
Total propofol dose [mg]		82.48 ±18.08	108.63 ±33.33	0.0001*
Colonoscopist satisfaction		9.6 ±0.67	9.25 ±0.87	0.047*
Patient satisfaction		9.63 ±0.63	9.38 ±0.77	0.117

**p < 0.05 (mean ± SD). ASA – American Society of Anesthesiologists.*

Table II. MAP means of the groups

Variable	Group 1 (n = 40)	Group 2 (n = 40)	Value of p
Initial	92.55 ±13.68	97.8 ±21.03	0.190
1 min	86.1 ±14.99	84.43 ±19.23	0.665
5 min	90.23 ±15.13	90.75 ±18.44	0.890
10 min	93.53 ±14.82	97.24 ±18.48	0.372
15 min	91.92 ±14.34	92.31 ±15.69	0.946
20 min	90.33 ±12.5	85.71 ±9.9	0.546
Value of p	0.548	0.001*	

$p < 0.05$ (mean ± SD). MAP – mean arterial pressure.

Table III. PR means of the groups

Variable	Group 1 (n = 40)	Group 2 (n = 40)	Value of p
Initial	86.18 ±16.18	89.5 ±19.1	0.404
1 min	87.55 ±13.68	89.35 ±13.37	0.554
5 min	80.93 ±11.26	81.8 ±12.45	0.743
10 min	76.83 ±11.18	79.66 ±10.38	0.300
15 min	76 ±10.03	75.94 ±8.88	0.986
20 min	62.67 ±7.77	80.29 ±11.57	0.045*
Value of p	0.093	0.019*	

$p < 0.05$ (mean ± SD); PR – pulse rate.

Table IV. Peripheral oxygen saturation means of groups

Variable	Group 1 (n = 40)	Group 2 (n = 40)	Value of p
Initial	97.78 ±0.58	98 ±0.64	0.103
1 min	97.93 ±0.47	98.08 ±0.47	0.161
5 min	97.98 ±0.53	98.03 ±0.62	0.699
10 min	98.06 ±0.48	98.17 ±0.59	0.401
15 min	98.08 ±0.28	97.94 ±0.68	0.495
20 min	98.33 ±0.58	98.25 ±0.46	0.808
Value of p	0.921	0.279	

Table V. Ramsey sedation score means of groups

Variable	Group 1 (n = 40)	Group 2 (n = 40)	Value of p
1 min	4.83 ±0.45	4.98 ±0.16	0.049*
5 min	4.28 ±0.68	3.98 ±0.86	0.088
10 min	3.44 ±0.77	3.52 ±0.79	0.709
15 min	3.14 ±0.86	3.56 ±0.73	0.160
20 min	3.5 ±1.29	3.71 ±0.49	0.695
Value of p	0.028*	0.0001*	

$p < 0.05$.

Statistically significant variation was observed in the initial, 1, 5, 10, 15 and 20 min PR means in group 2 (p = 0.019). The 15 min PR mean was statistically significantly lower than the 1 min PR mean (p = 0.023, p = 0.006), but no statistically significant difference was observed among the other groups ($p > 0.05$) (Table III).

Statistically, no significant difference was observed between the initial, 1, 5, 10, 15 and 20 min SpO_2 means of the groups ($p > 0.05$). There was no statistically significant variation in the initial, 1, 5, 10, 15 and 20 min SpO_2 means of group 1 (p = 0.921) or group 2 (p = 0.279) (Table IV).

Statistically, there was no significant difference in the 1, 5, 10, 15 and 20 min RSS means of the groups ($p > 0.05$). There was a statistically significant difference among 1, 5, 10, 15 and 20 min RSS means of group 1 (p = 0.028). The 5 min RSS mean was significantly higher than the 15 min RSS mean (p = 0.035); there was no statistically significant difference among the other measurements ($p > 0.05$).

There was a statistically limited difference among the 1, 5, 10, 15 and 20 min RSS means of group 2 (p = 0.0001). The 1 min RSS means were significantly higher than the 10, 15 and 20 min RSS means (p = 0.015, p = 0.0001); the 10 min RSS mean was significantly lower than the 5 and 15 min RSS means (p = 0.047, p = 0.015), and there was no statistically significant difference among the other measurements ($p > 0.05$) (Table V).

Statistically, no significant difference was observed between the 1, 5, 10, 15 and 20 min BIS means of the groups ($p > 0.05$). Statistically significant variation was observed in the initial, 1, 5, 10, 15 and 20 min BIS means of group 1 (p = 0.0001). The initial BIS means were statistically significantly higher than the 1, 5, 10, 15 and 20 min BIS means (p = 0.026, p = 0.001). The 1 min BIS mean was statistically significantly lower than the 10, 15 and 20 min BIS means (p = 0.009, p = 0.001). There was no statistically significant difference among measurements performed at other times ($p > 0.05$).

The 15 min BIS mean of group 2 was statistically significantly lower than that of group 1 (p = 0.003). Statistically significant variation was observed between the initial, 1, 5, 10, 15 and 20 min BIS means of group 2 (p = 0.0001). The initial BIS mean was statistically significantly higher than the 1, 5, 15 and 20 min BIS means (p = 0.017, p = 0.0001), and the 1 min BIS mean was statistically significantly lower than the 5, 10, 15 and 20 min BIS means (p = 0.009, p = 0.0001). No statistically significant difference was observed among the other groups ($p > 0.05$) (Table VI).

Table VI. Bispectral index means of groups

Variable	Group 1 (n = 40)	Group 2 (n = 40)	Value of p
Initial	96.9 ±1.52	97.3 ±1.47	0.235
1 min	51.93 ±11.18	47.9 ±6.98	0.057
5 min	72.85 ±9.71	73.03 ±11.55	0.942
10 min	80.72 ±6.31	78.59 ±7.7	0.223
15 min	86.08 ±6.1	77.38 ±7.98	0.003*
20 min	75.43 ±4.86	75.43 ±4.86	0.999
Value of p	0.0001*	0.0001*	

*$p < 0.05$.

Statistically, no significant difference was observed in the distribution of dreaming reported by the groups (p = 0.478). The occurrence of adverse events in group 2, which was 1 (2.50%), was statistically significantly lower than in group 1, where it was 14 (35%) (p = 0.0001) (Table VII). The adverse events exhibited by the groups are listed in Table VIII.

Discussion

In urgent and elective cases and for painful procedural sedation, the use of ketofol in different combinations has been recommended for both adults and children [10–13]. In upper GIS endoscopy, one study showed that a ketofol mixture prepared in a 1 : 4 proportion provides optimal sedation and that it has explicit analgesic efficacy and a stabilizing impact in terms of hemodynamics, in addition to removing the need for opioids [9]. In our study, the patients in group 1 were hemodynamically stabilized with the mixture prepared in the proportion 1 : 2. In group 2, where we administered the mixture in the proportion 1 : 4, the 1 min MAP mean was lower than the initial, 10, 15 and 20 min MAP means due to the low proportion of ketamine. In this group, the 5 min MAP mean was higher than the 20 min MAP mean. This situation, again because of the low proportion of ketamine, was associated with the fact that the anesthetics rapidly became superficial in the patients and that additional propofol doses were

Table VII. Occurrence of dreaming and complications in groups

Variable		Group 1 (n = 40)		Group 2 (n = 40)		Value of p
Dreaming	Absent	25	62.50%	28	70.00%	0.478
	Present	15	37.50%	12	30.00%	
Adverse event	Absent	26	65.00%	39	97.50%	0.0001*
	Present	14	35.00%	1	2.50%	

*$p < 0.05$.

Table VIII. Frequency of adverse events in groups

Adverse events		Group 1 (n = 40)		Group 2 (n = 40)		Value of p
Nausea	Absent	39	97.50%	40	100.00%	0.999*
	Present	1	2.50%	0	0.00%	
Vomiting	Absent	38	95.00%	40	100.00%	0.494*
	Present	2	5.00%	0	0.00%	
Nausea, vomiting and diplopia	Absent	40	100.00%	39	97.50%	0.999*
	Present	0	0.00%	1	2.50%	
Vomiting and vertigo	Absent	39	97.50%	40	100.00%	0.999
	Present	1	2.50%	0	0.00%	
Diplopia	Absent	39	97.50%	40	100.00%	0.999
	Present	1	2.50%	0	0.00%	
Vertigo	Absent	33	82.50%	40	100.00%	0.011*
	Present	7	17.50%	0	0.00%	
Vertigo and diplopia	Absent	38	95.00%	40	100.00%	0.494
	Present	2	5.00%	0	0.00%	

*$p < 0.05$. Fisher's exact test.

needed. The 20 min PR mean of group 2 was remarkably higher than in group 1. Due to the additional propofol dose administered, the 15 min PR mean was significantly lower than the initial and the 1 min PR means. The additional propofol dose needed in group 2 was significantly higher than in group 1. Furthermore, while there was no difference between groups in terms of patient satisfaction in our study, the colonoscopist satisfaction was higher in group 1. We are of the opinion that this resulted from the better sedation conditions in group 1 despite lower application of additional propofol. These results lead us to the conclusion that ketofol prepared in the proportion 1 : 4 is not sufficient for colonoscopy.

Rapeport *et al.* [14] used ketofol safely and effectively in four high-risk cases and stated that this technique had advantages such as analgesia, airway protection, provision of spontaneous respiration, hemodynamic stability, and rapid recovery. In a study comparing propofol-fentanyl with ketofol, while the recovery time was similar, the discharge time in the ketofol group was longer [4]. This situation was linked with the fact that the patients experienced many side effects including nausea, vertigo, and visual complaints [4]. Another study compared propofol for procedural sedation in the emergency department with propofol-ketamine in terms of respiration depression and recovery time [15]. It found that subclinical respiratory depression developed at a higher rate in the propofol group than in the ketamine group. More frequent awakening agitation was also observed in the ketamine group compared with the propofol group. The time to the return of the basal mental status was also longer in the ketamine group than in the propofol group [15]. In another study that compared ketofol and propofol, the authors stated that although the group given ketofol experienced less explicit hemodynamic and respiratory problems, there was no difference between the two groups in terms of the need for active intervention, fluid-vasopressor support, supportive oxygen, or assisted ventilation [16]. They also stated that in terms of discharge time, ketofol did not show superiority over propofol. The study also reported that the patients administered ketamine at higher doses had more nausea, vomiting, and recovery reactions after the operation [16]. Phillips *et al.* [6] stated that ketofol offers a valuable combination in procedural sedation and that compared to propofol it results in lower hypotension, better sedation quality, and improved patient comfort. In a comparison of ketofol and propofol by Andolfatto *et al.* [17], the authors stated that respiratory side effects, induction time, efficacy, and sedation time were similar but that the depth of sedation was more consistent with ketofol. In our study, allergic reactions, bradycardia, tachycardia, hypotension, hypertension, desaturation, respiratory depression, and complications related to colonoscopy did not develop in any of the patients. However, in group 1, the rate of adverse events was much higher than in group 2. This was linked to the high proportion of ketamine. Dachs and Innes [18] suggested that the addition of midazolam as a premedication aid dramatically reduced undesirable side effects associated with ketamine such as unpleasant dreams and hallucinations. In our study, we did not observe psychomotor reactions in any of the patients. We attributed this finding to the midazolam premedication administered as standard before the procedure. We also observed no differences between the groups in terms of dreaming, recovery time, and discharge time.

Bispectarl Index Scale (BIS) is used to measure the depth of anesthesia [19]. It has been suggested that the BIS value should be kept at 70–80 in sedo-analgesia [20]. In our study, the BIS values after the induction were significantly low in both groups. We attributed this finding to the infusion of the standard dose of ketofol. We credited the low 15th min BIS value in group 2 to the administration of higher total propofol doses and additional propofol doses. Also, the 1 min RSS was lower in group 1. We are of the opinion that this resulted from the higher ketamine ratio.

In conclusion, in elective colonoscopy, a ketofol mixture prepared in the proportion 1 : 2 provides suitable hemodynamic conditions and sufficient sedation. Although the possibility of adverse events is higher with this proportion, there is no difference in terms of discharge time. Thus, we suggest that a ketofol mixture prepared in the proportion of 1 : 2 is suitable for elective colonoscopy.

Conflict of interest

The authors declare no conflict of interest.

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