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Ketamine versus alfentanil combined with propofol for sedation in colonoscopy procedures: A randomized prospective study

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Original Article

ABSTRACT

Background/Aims: Different drug combinations are used for sedation in colonoscopy procedures. A ketamine-propofol (ketofol) mixture provides effective sedation and has minimal adverse effects. Alfentanil also provides anesthesia for short surgical procedures by incremental injection as an adjunct. However, no study has investigated the use of ketofol compared with an opioid-propofol combination in colonoscopic procedures.

Materials and Methods: A total of 70 patients, ASA physical status I-II, scheduled to undergo elective colonoscopy, were enrolled in this prospective randomized study and allocated to two groups. After premedication, sedation induction was performed with 0.5 mg/kg ketamine +1 mg/kg propofol in Group KP, and 10 mg/kg alfentanil +1 mg/kg propofol in Group AP. Propofol was added when required. Demographic data, colonoscopy duration, recovery time, discharge time, mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation, Ramsey Sedation Scale values, colonoscopy patients' satisfaction scores, and complications were recorded.

Results: The need for additional propofol doses was significantly higher in Group AP than in Group KP. MAP at minute 1 and 5, Ramsey Sedation Scale at minute 5, and discharge time were significantly higher in Group KP than in Group AP. Additional propofol doses and total propofol dose were significantly lower in Group KP than in Group AP.

Conclusion: Ketofol provided better hemodynamic stability and quality of sedation compared with alfentanil-propofol combination in elective colonoscopy, and required fewer additional propofol; however, it prolonged discharge time. Both combinations can safely be used in colonoscopy sedation.

Keywords: Colonoscopy, sedation, alfentanil, ketamine, propofol

INTRODUCTION

Sedation is required to avoid discomfort during interventional radiological, endoscopic, and oncological procedures (1). Midazolam, propofol, and/or alfentanil or pethidine combinations, α-agonists, and neuroleptics are commonly used for sedation (2,3). The goals of procedural sedation are to provide appropriate levels of sedation, to reduce pain and anxiety, to maximize amnesia, to minimize adverse effects of drugs, and to provide stable cardiovascular and respiratory conditions. The ideal agent that achieves these goals should also have the same efficacy regardless of administration method, the possibility to be titrated, and a rapid onset and end of the clinical effects; it should also not be expensive. At present, no sole agent has all of these characteristics. For this reason, various doses of different drug combinations are used to achieve most of these desired effects (4,5).

The combination of ketamine and propofol (ketofol) induces a quality sedation, minimizes adverse effects, and provides a stable hemodynamic and respiratory profile in procedural sedation (4). Studies in the literature have investigated the use of ketofol during upper gastrointestinal endoscopy, but we were unable to find any study regarding the use of ketofol in colonoscopic procedures.

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Alfentanil is effective rapidly after injection in a time interval of 90 seconds, and is metabolized quickly in 30-60 minutes, which is an advantage in short procedures requiring sedation and rapid recovery for outpatient procedures (2).

In the present study, our aim was to compare a ketofol mixture with an alfentanil-propofol combination on sedation quality during colonoscopy.

MATERIALS AND METHODS

This prospective and randomized study was performed on 70 patients after approval by the Local Ethics Committee, and all patients' provided written informed consent Subjects were selected from a group of ASA physical status I-II patients, aged between 18-65 years, and who were scheduled for elective colonoscopy procedure. Researchers verified the status of each patient's minimal 8-hour fasting period and the absence of alcohol or sedative drug consumption 24 hours before the colonoscopy procedure. Sedation was administered to all patients by the same anesthesiologist. The exclusion criteria of this study was pregnancy, active gastrointestinal bleeding, known or predicted airway difficulty, alcohol or drug addiction, neuropsychiatric disease, severe heart or respiratory insufficiency, or history of allergy to sedatives.

After patients were admitted to the gastrointestinal endoscopy unit, an intravenous (IV) catheter size 18 gauge was placed into the right antecubital vein and 0.9% NaCl infusion was administered. Patients received 1 mg IV midazolam as premedication. The laterally positioned patients were monitored with noninvasive systemic blood pressure cuffs, 3-channel ECGs, and pulse oximetry. Supplemental oxygen flow was 4 L/min, administered by a nasal cannula. A computer program divided the patients randomly into two study groups: Sedation induction was performed with 0.5 mg/kg ketamine + 1 mg/kg propofol in Group KP (n=35), and 10 mg/kg alfentanil +1 mg/kg propofol in Group AP (n=35). During colonoscopy, the patients' Ramsey Sedation Scale (RSS) scores were maintained at 3-4 (Appendix 1) (6) with an additional 0.5 $mg.kg^{-1}$ bolus dose of propofol when required. Heart rate (HR), mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), and RSS scores were recorded before, at the beginning, and at every 5-minute interval throughout the colonoscopy procedure.
Colonoscopy duration included the overall time of the colonoscopy procedure. Recovery time was stipulated as the time from induction until RSS score progressed to 2, and additional administrated total propofol doses and complications were recorded. At the end of the procedure, patients were discharged when the Aldrete Score (Appendix 2) (6) was 9 or higher. Colonoscopist's and each patient's satisfaction were scored on a visual analog scale (VAS) from 1 to 10 and recorded.

Statistical analysis

In this study, statistical analyses were performed using Number Cruncher Statistical System (NCSS) 2007 Statistical Software (NCSS; Utah, USA) program. The obtained data, along with descriptive statistical methods (mean, standard deviation), were evaluated by an independent t-test for comparison of the two groups and a chi-square test was used for comparison of qualitative parameters. Results were considered statistically significant when p value was <0.05.

RESULTS

Demographic variables such as age, sex, weight, and ASA status were similar in both groups (Table 1).

Colonoscopy duration and complication rates were similar in both groups. Additional propofol requirement was significantly higher in Group AP than in Group KP (p=0.044). Additional propofol amount and total propofol consumption were significantly lower in Group KP than in Group AP (p=0.009, p=0.0001, respectively). Recovery time was similar in both groups. Discharge time was longer in Group KP than in Group AP (p=0.0001) (Table 2).

Mean arterial pressure at the 1st and 5th minutes was significantly higher in Group KP than in Group AP (p=0.0001, p=0.001, respectively), but no differences in MAP were noted between the two groups at all other times. Similar to Group AP, Group KP showed no significant differences in beginning MAP compared with all other times. No difference was observed in HR between the two groups at any time, and the beginning HR was also not different compared with other times. No significant differences were noted between the two groups in SpO_2 values. Both groups showed no difference when beginning SpO_2 was compared with SpO_2 at all other times. RSS values were similar in both groups. RSS score at the 5th minute was significantly higher in Group KP than in Group AP (p=0.006). No significant differences were seen in RSS scores between the first minute and at all other times in Group KP and Group AP (Table 3).

Colonoscopist's and each patient's satisfaction scores were similar in both groups (Figure 1).

DISCUSSION

Some studies suggest that the colonoscopy procedure can be performed without sedation. However, this procedure is invasive and painful, so comfortable performance of colonoscopy is important for both patient and colonoscopist (7).

Propofol and alfentanil have rapid onset and are short acting, making them useful agents for sedation (8,9). Alfentanil, a short-acting opioid, has been recommended for short procedures. However, when alfentanil is used as a sole agent, reports indicate a frequent occurrence of intra-operative and post-operative respiratory depression (10,11). Heiman et al. (12) suggested that the propofol-alfentanil combination is successful for pain management in the colonoscopy procedure. Other studies reported that the combination of propofol and opioid not only provides analgesia and amnesia, but also reduces the

incidence of nausea, vomiting, and respiratory depression (10). When propofol is used as the sole anesthetic agent for an invasive procedure, very high doses (14.9 mg/kg-h) are required for toleration of the procedure (8). The cardiovascular depressant effects of propofol, which are dose and concentration dependent, can also appear with the use of high-dose propofol (3,4).

Ketamine is often used for sedation and analgesia as a sole agent or adjuvant (13). It is a dissociative anesthetic, providing amnesia and analgesia, and maintains spontaneous respiration by protecting upper airway reflexes and muscle tone (4). Combining propofol with ketamine reduces the incidence of dose dependent adverse effects because lesser doses of both agents will be sufficient. Theoretically, the combination of these agents moderates the hemodynamic condition, because they have reverse effects to each other on the cardiovascular system (4). Ketofol has a minimal depressant effect on respiration and blood pressure and reduces the need for opiates. It also has significant analgesic and hemodynamic stabilizing effects. A ketofol mixture provides greater quality sedation than does ketamine or propofol as sole agents at the same doses (14,15). Nevertheless, one study that compared ketofol and propofol indicated that hemodynamic and respiratory problems were significantly reduced in a ketofol group than in a propofol group, but both groups were similar regarding the need for intravenous fluid or vasopressor agent administration and oxygen support or assist ventilation (16).

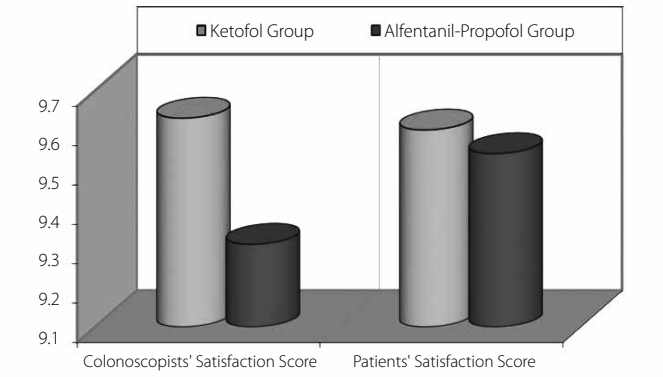

Figure 1. Colonoscopit's and patient's satisfaction scores in the ketamine-propofol (KP) and alfentanil-propofol (AP) groups.

In the current study, the mean additional propofol dose and mean total propofol dose were significantly lower in Group KP than in Group AP. The mean RSS value at the 5th minute was higher in Group KP than in Group AP. The mean MAP at the 1st

Table 1. Distributions of age, weight, sex, and ASA classification in the ketamine-propofol (KP) and alfentanil-propofol (AP) groups

		Group KP (n=35)		Group AP (n=35)		p
Age (years)		49±10.01		49.26±13.11		0.927
Weight (kg)		74.17±14.74		74.77±12.32		0.854
Sex	Female	21	(60%)	20	(57.1%)	
	Male	14	(40%)	15	(42.9%)	0.808
ASA	I	17	(48.6%)	13	(37.1%)	
	II	18	(51.4%)	22	(62.9%)	0.334

*p<0.05 is statistically significant, Mean±standard deviation (SD).
ASA: American Society of Anesthesia; KP: ketamine-propofol; AP: alfentanil-propofol

Table 2. Colonoscopy duration, additional propofol requirement, total propofol consumption, complication rate, recovery-discharge time in the ketamine-propofol (KP) and alfentanil-propofol (AP) groups

		Group KP (n=35)		Group AP (n=35)		p
Colonoscopy time (minutes)		13.69±4.03		13.43±4.24		0.795
Additional propofol requirement	Absent	27	(77.10%)	19	(54.3%)	
	Present	8	(22.90%)	16	(45.7%)	0.044*
Complication	Absent	26	(74.30%)	24	(68.6%)	
	Present	9	(25.70%)	11	(31.4%)	0.597
Additional Propofol (mL)		32.5±7.07		44.69±10.87		0.009*
Total Propofol (mL)		81.31±18.26		140.43±34.24		0.0001*
Recovery Time (minutes)		15.29±4.25		15.4±4.27		0.911
Discharge Time (minutes)		33.74±7.95		24.26±7.17		0.0001*

*p<0.05 is statistically significant, Mean±SD.
KP: ketamine-propofol; AP: alfentanil-propofol

Table 3. Mean arterial pressure (MAP), heart rate (HR), oxygen-saturation (SpO_2), Ramsey Sedation Scale (RSS) scores of ketamine-propofol (KP) and alfentanil-propofol (AP) groups

MAP	Group KP (n=35)	Group AP (n=35)	p
Beginning	92.63±14.07	95.83±19.09	0.427
First Minute	87.43±15.44	72.46±13.31	0.0001*
5th Minute	89.54±15.27	77.23±13.34	0.001*
10th Minute	92.48±14.69	83.45±21.1	0.053
15th Minute	90.7±8.21	82.23±16.33	0.086
20th Minute	90.33±12.5	85.75±15.52	0.340
p	0.548	0.193	
HR			
Beginning	84.09±15.13	90.57±13.85	0.066
First Minute	85.89±13.4	82.26±13.88	0.270
5th Minute	80.34±11.61	76.66±12.69	0.209
10th Minute	76.48±11.49	78.31±11.96	0.543
15th Minute	75.64±9.98	76.46±13.62	0.869
20th Minute	72.67±7.77	78.25±10.14	0.179
p	0.093	0.126	
SpO_2			
Beginning	97.49±0.82	97.91±0.98	0.055
First Minute	97.34±1.06	97.17±1.85	0.167
5th Minute	97.71±0.82	98.00±1.37	0.295
10th Minute	97.79±0.78	97.55±1.09	0.550
15th Minute	97.81±0.61	97.42±0.98	0.261
20th Minute	98.00±1.01	98.50±0.60	0.437
p	0.925	0.357	
RSS score			
First Minute	4.8±0.47	4.86±0.55	0.643
5th Minute	4.34±0.68	3.74±1.04	0.006*
10th Minute	3.48±0.8	3.28±1.1	0.390
15th Minute	3.25±0.87	3.31±1.03	0.881
20th Minute	3.5±1.29	3.25±1.26	0.791
p	0.065	0.125	

*p<0.05 is statistically significant, Mean ± SD.

MAP: mean arterial pressure; HR: heart rate; SpO_2: oxygen-saturation; RSS: Ramsey Sedation Scale; KP: ketamine-propofol; AP: alfentanil-propofol

and 5th minutes were significantly higher in Group KP than in Group AP. These data show that the ketofol combination provides sufficient and quality sedation and hemodynamic stability.

In a study by Loh et al. (16), ketofol and propofol administration resulted in similar discharge times. In a study comparing a propofol-fentanil combination with ketofol, respiratory depression incidence was five times higher in the ketofol group, but this difference was not considered statistically significant. Recovery times were similar in both groups but discharge time was longer for the ketofol group than for the propofol-fentanil group. This discharge time difference was explained by the presence of adverse effects including nausea, vertigo, and visual problems (4).

In the current study, mean recovery times were similar in both groups but mean discharge time was significantly longer for Group KP than for Group AP. No difference was noted between groups in complication incidence, but complication types were quite different. Complications in Group KP were vertigo in five cases, diplopia in one case, vomiting in two cases, and both vertigo and vomiting in one case. Complications in Group AP were vomiting in two cases and desaturation of oxygen in nine cases. Respiratory depression was not seen in any group. We considered that the long recovery time of Group KP's complications caused a longer discharge time in Group KP than in Group AP.

In previous studies, the use of a ketofol mixture in a single syringe was suggested as safe for use in an emergency unit and in orthopedic procedures for support of regional anesthesia (17-19). Willman et al. (20) reported that the use of ketofol was safe for painful procedures in an emergency unit. They obtained minimal adverse effects in their study, and the recovery from these adverse effects required no or minimal intervention or medication. Recovery time was short, and colonoscopist's and patients' satisfaction scores were high in their study. These satisfaction scores were similar to those for both of the groups in our study.

Ketofol mixture, prepared at a ratio of 1:2, provides better hemodynamic stability and better quality of sedation-analgesia than alfentanil-propofol in elective colonoscopy.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - H.Ş.T., M.A.; Design - H.Ş.T., M.A., O.Ü., C.T.I.; Supervision - S.O., M.E.A.; Resource - B.C.; Materials - O.Ü., C.T.I., B.C.; Data Collection&/or Processing - H.Ş.T., M.A., M.E.A.; Analysis&/or Interpretation - H.Ş.T., C.T.I., B.C., S.O., M.E.A.; Literature Search - M.A., O.Ü.; Writing - H.Ş.T., M.A., O.Ü., C.T.I., M.E.A.; Critical Reviews - S.O.

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REFERENCES

1. Mazanikov M, Poyhia R. Patient controlled sedation. Duodecim 2011; 127: 883-9.

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2. Sporea I, Popescu A, Sandesc D, Salha CA, Sirli R, Danila M. Sedation during colonoscopy. Rom J Gastroenterol 2005; 14: 195-8.
3. Dal H, Izdes S, Kesimci E, Kanbak O. Comparison of intermittant bolus versus target controlled infusion of propofol sedation for colonoscopy. Turkish J Anesth Rean 2011; 39: 134-42. **[CrossRef]**
4. Sanjay Arora. Combining ketamine and propofol ("ketofol") for emergency department procedural sedation and analgesia: A review. West J Emerg Med 2008; 9: 20-3.
5. Phillips W, Anderson A, Rosengreen M, Johnson J, Halpin J. Propofol versus propofol/ketamine for brief painful procedures in the emergency department: clinical and bispectral index scale comparison. J Pain Palliat Care Pharmacother 2010; 24: 349-55. **[CrossRef]**
6. Türk HŞ, Aydoğmuş M, Unsal O, Köksal HM, Açik ME, Oba S. Sedation-analgesia in elective colonoscopy: propofol-fentanyl versus propofol-alfentanil. Braz J Anesthesiol 2013; 63: 352-7. **[CrossRef]**
7. Runza M. Which type of sedation should be the target goal for use in colorectal endoscopic screening? Minerva Anestesiol 2009; 75: 673-4.
8. Fanti L, Agostoni M, Gemma M, et al. Sedation and monitoring for gastrointestinal endoscopy: A nationwide web survey in Italy. Dig Liver Dis 2011; 43: 726-30. **[CrossRef]**
9. Lee DW, Chan AC, Wong SK, Li AC, Sze TS, Chung SC. The safety, feasibility, and acceptability of patient-controlled sedation for colonoscopy: prospective study. Hong Kong Med J 2004; 10: 84-8.
10. Avramov MN, White PF. Use of alfentanil and propofol for out patient monitored anesthesia care: determining the optimal dosing regimen. Anesth Analg 1997; 85: 566-72. **[CrossRef]**
11. Usta B, Turkay C, Muslu B, et al. Patient-controlled analgesia and sedation with alfentanyl versus fentanyl for colonoscopy: A randomized double blind study. J Clin Gastroenterol 2011; 45: 72-5. **[CrossRef]**
12. Heiman DR, Tolliver BA, Weis FR, O'Brien BL, Di Palma JA. Patient-controlled anesthesia for colonoscopy using propofol: results of a pilot study. South Med J 1998; 91: 560-4. **[CrossRef]**
13. Bayat A, Ramaiah R, Bhananker SM. Analgesia and sedation for children undergoing burn wound care. Expert Rev Neurother 2010; 10: 1747-59. **[CrossRef]**
14. Mustafaeva MN, Mizikov VM, Kochneva ZV. Drug sedation during digestive tract endoscopy: current trends. Anesteziol Reanimatol 2009; 5: 32-8.
15. Nejati A, Moharari RS, Ashraf H, Labaf A, Golshani K. Ketamine/propofol versus midazolam/fentanyl for procedural sedation and analgesia in the emergency department: a randomized, prospective, double-blind trial. Acad Emerg Med 2011; 18: 800-6. **[CrossRef]**
16. Loh G, Dalen D. Low-dose ketamine in addition to propofol for procedural sedation and analgesia in the emergency department. Ann Pharmacother 2007; 41: 485-92. **[CrossRef]**
17. Andolfatto G, Willman E. A prospective case series of single-syringe ketamine-propofol (Ketofol) for emergency department procedural sedation and analgesia in adults. Acad Emerg Med 2011; 18: 237-45. **[CrossRef]**
18. Weatherall A, Venclovas R. Experience with a propofol-ketamine mixture for sedation during pediatric orthopedic surgery. Paediatr Anaesth 2010; 20: 1009-16. **[CrossRef]**
19. Rapeport DA, Martyr JW, Wang LP. The use of "ketofol" (ketamine-propofol admixture) infusion in conjunction with regional anesthesia. Anaesth Intensive Care 2009; 37: 121-3.
20. Willman EV, Andolfatto G. A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. Ann Emerg Med 2007; 49: 23-30. **[CrossRef]**

Appendix 1. Ramsay sedation scale

Definition	Score
Patient is anxious and agitated or restless, or both	1
Patient is cooperative, oriented, and tranquil	2
Patient responds to commands only	3
Patient exhibits brisk response to light glabellar tap or loud auditory stimulus	4
Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus	5
Patient exhibits no response	6

Appendix 2. Aldrete score

	Definition	Score
Activity	Able to move 4 extremities voluntarily or on command	2
	Able to move 2 extremities voluntarily or on command	1
	Able to move 0 extremities voluntarily or on command	0
Respiration	Able to deep breath and cough freely	2
	Dyspnea or limited breathing	1
	Apnea	0
Circulation	Blood Pressure ±20% of Preanesthetic level	2
	Blood Pressure ±20-50% of Preanesthetic level	1
	Blood Pressure ±50% of Preanesthetic level	0
Consciousness	Fully Awake	2
	Arousable on calling	1
	Not responding	0
O2 Saturation	Maintains >92% on room air	2
	Needs O_2 inhalation to maintain O_2 saturation >90%	1
	Saturation <90% even with supplemental oxygen	0