Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2021; 38(S1): 65-70
doi: 10.52142/omujecm.38.si.gastro.10

A comparison of propofol with ketofol for sedation quality and side effects in patients undergoing colonoscopy

Ender ÇAM[1,*], Deniz KARAKAYA[2], Sibel BARIŞ[3]

[1]Department of Anesthesiology and Reanimation, Gazi State Hospital, Samsun, Turkey
[2]Department of Anesthesiology and Reanimation, Faculty of Medicine, Ondokuz Mayis University, Samsun, Turkey
[3]Department of Anesthesiology and Reanimation, Faculty of Medicine, Ondokuz Mayis University, Samsun, Turkey

Received: 19.08.2020 • **Accepted/Published Online:** 02.01.2021 • **Final Version:** 18.03.2021

Abstract

Colonoscopy is an endoscopic method and ıt is better to perform this procedure under sedoanalgesia in order to eliminate patients' anxiety, the colic-like pain and discomfort that occur during the procedure. The aim of this study was to compare the effects of propofol and propofol+ketamine (ketofol) on sedation and side effects in patients undergoing colonoscopy. 50 patients with ASA I-II that are between the ages of 18-65. The patients in the propofol group and Ketofol group were given 0.1mL/kg of drug and/or combination of drugs. The vital parameters, injection pain, spontaneous time of opening eyes, the time of Modified Aldrete Score (MAS) ≥ 9 and the amount of medication used during the procedure and in the recovery, room were recorded. There was no significant difference between the two groups during the procedure and in the recovery room ($p<0.05$). It was shown that the ketamine reduces the amount of propofol by 50% and propofol induced injection pain. Ketofol had no positive effects on hemodynamic and respiratory parameters. We assert that the ratio of combinations will vary depending on the necessary sedation level and analgesic need of the procedure to be performed and depending on the frequency of the administration of additional doses. Although ketofol is being used in different procedures and different age groups in the recent years, there is still need for studies conducted with different drug dosages of this combination.

Keywords: colonoscopy, ketofol, hemodynamics, sedoanalgesia

1. Introduction

Outpatient procedures are generally performed on same-day anesthesia patients. It is better to perform this procedure under sedoanalgesia in order to eliminate patients' anxiety and colic-like pain and uncomfort that occur during the procedure (Seip et al., 2010). For this reason, short-acting drugs and drugs without any side-effects should be preferred. As there is not one drug that provide all these effects, the aim is to combine this with other drugs to increase its effects and reduce high dose induced side effects. When short-acting propofol that provides fast and full recovery is used in high dosage to provide the suitable conditions for the performance in order to avoid analgesic effect, it leads to complications such as hypotension, respiratory depression and loss of protective reflexes (Akcaboy et al., 2006). To reduce the complications at high dosages, several sedative and analgesics can be used either on their own or as a combination.

Ketamine is a different drug from other anesthetic agents as it has an analgesic characteristic while not having a depressant effect on the cardiovascular and respiratory systems. Its main effect is seen by separating the connection between talamus and the lymbic system. Thus, it provides "dissociative anesthesia." Using propofol and ketamine together, not only the hypotensive effect of propofol is prevented by sympathomimetic and analgesic effect of ketamine, but also inhibits the ketamine induced nausia, vomiting and psychotomimetic effects during recovery by the antiemetic and strong hypnotic effect of propofol. The combination of propofol and ketamine is called ketofol. These two drugs provide an ideal anesthetic approach with their synergistic effects.

Due to the fact that outpatient procedures are becoming common, anesthesia in outpatient procedures are becoming more important in order to improve the quality of the procedure and the patient comfort in procedures that cause pain and anxiety in patients. Outpatient anesthesia is needed in colonoscopy as well like in several other procedures. The colon is dilated with air during the procedure for a clear evaluation. As patients feel pain during dilation, this procedure becomes too difficult to tolerate for patients most of the time. In several ketofol conducted studies, ketofol is used in painful or invasive

* Correspondence: aesire@hotmail.com

procedures in emergency rooms in adults and children. However, there are few studies conducted on patients where semi-noninvasive procedures such as colonoscopy are performed. In this study, we aim to study the effects of ketofol on the quality of sedation and side effects in patients undergoing colonoscopy.

2. Materials and methods

After receiving an Ethical Review Board approval from Ondokuz Mayis University School of Medicine (OMU KAEK 2013/301), the study was conducted between January 2013 and February 2014 within the scope of outpatient anesthesia applications in the Gastroenterology Clinic in our hospital. All the patients were informed about the study prior to the colonoscopy and were asked to sign a consent form.

Fifty patients with ASA I-II that are between the ages of 18-65 undergoing an elective colonoscopy were included in this study. Patients who rejected to participate in the study, who is allergic to any of the drugs used in the study, patients with uncontrolled hypertension, severe renal, liver, cardiovascular and respiratory disorders, patients with epilepsy, patients with intracranial space-occupying lesion, pregnant patients, patients with severe neuropsychiatric disorders and patients with BMI>30 were not included in the study. A power analysis with a reference of 50% reduction of the total propofol dosage, was completed to determine the sample size of our study based on the study conducted by Mourad et al. (2004) on ketofol. The number of participants for each group was determined to be 25 with effect size of 99% and power of 99%.

2.1. Grouping

Randomization was completed by having patients draw closed envelopes that were prepared prior in accordance with the patient number in each group. The patients were distributed into two groups: Group P (Propofol) and Group K (Ketofol), of 25 randomly.

2.2. Procedure

The patients were asked not to eat for at least six hours. After taking patients into the procedure room, a 20-22 G intravenous cannula was inserted either from the dorsum of the hand or front arm and an infusion of 0.9% physiological saline solution was started with a speed of 1-2mL/kg/hour. Supplemental O_2 (4-6 L/minute) via a nasal cannula was administered during the procedure. A 0.02 mg/kg midazolam was given intravenously 15 minutes prior to the procedure to all patients. Colonoscopy and sedoanalgesia procedures were performed by the same gastroenterologist and anesthesiologist.

2.3. Preparation of drug syringes

Preparation of ketofol: 100 mg ketamine (2 ml from a 50 mg/mL ketamine) (Ketalar, Pfizer) and 100 mg propofol (10 mL from 1% Propofol lipuro) (Propofol Lipuro 1%, Fresenius Kabi) were drawn into a 20 mL syringe. The total volume was completed to 20 mL. Thus, a combination of 5 mg/mL propofol + 5 mg/mL ketamine was obtained (mix with a 1/1 ratio). This combination was given to patients in Group K. Preparation of Propofol: A 10 mg/mL propofol was prepared by drawing from a 1% propofol lipuro into a 20 mL syringe and given to patients in Group P. The study protocol was conducted as a double-blind manner. Patients were monitored for heart rate (HR), systolic, diastolic, and mean blood pressure (SBP, DBP and MBP respectively), respiratory rate (RR), and peripheral oxygen saturation (SpO_2) when they were at the colonoscopy table. Afterwards, patients were given the prepared drugs of 0.1 mL/kg intravenously. The colonoscopy procedure started after the reactions for verbal stimulations and the cornea reflex is lost. A ≥ 4 of sedation level was targeted according to the Ramsay Sedation Scale (RSS) during the procedure. When RSS was lower than 4, additional dosages of 0.05 mL/kg of the prepared drug were given. The pain during the injection was evaluated according to the “four-point injection pain scale” (0: no pain,1: light pain (only a response of having pain to the without any movement), 2: mild pain (a verbal response of pain with movement or expression pain spontaneously without being asked), 3: Severe pain (severe verbal response or behavioral response such as facial expressions or moving arm). A score of 2 or 3 was considered as having pain while a score of 0 or 1 was no pain.

Heart rate, SBP, DPB and, MBP, RR, and SpO2 were identified, and basal values were taken before the procedure. After the colonoscopy started, the values at 1, 5, 10, 15, 20, 30 minutes and at the end of the procedure were recorded. An MBP level of 20% more from the baseline value for one minute during the procedure was accepted as hypertension. In the case of hypertension, at first light anesthesia symptoms (opening eyes, moving) were evaluated. If the anesthesia is light, 0.05 mL/kg additional drug combination were given. If the hypertension continued, a 50-100 µg perlinganit was applied intravenously and the patient was monitored for another minute. An MBP level being 20% less than the baseline value was considered as hypotension. In the case of a hypotension, 5 mg of ephedrine was applied intravenously, and the patient was monitored for another minute. When needed, an additional dose of ephedrine was given. A HR of <45 beat/min was evaluated as bradycardia. In the case of a bradycardia, a 0.5 mg of atropine was applied intravenously. When the HR was >100 beat/min, light anesthesia symptoms were reconsidered, and a drug combination of 0.05 mL/kg was applied intravenously. When it was determined that the anesthesia is not light, a 5-10 mg esmolol was applied intravenously. The patient was monitored for one minute and an additional dosage of esmolol was repeated if needed.

The duration of anesthesia is identified as the time between the first propofol or ketofol dosage administration and the patient’s opening eyes spontaneously. The duration of colonoscopy is identified as the time between the insertion and removal of the colonoscope. And both durations were recorded as well as the total drug dosages.

After the colonoscopy procedure, spontaneous eye-opening

times, and the time for Modified Aldrete Scale (MAS) to become ≥ 9 were recorded. Satisfaction of the patient, the person who performed the colonoscopy and the anesthesiologist were evaluated on a scale of 1-10; 1: being not satisfied, and 10: very satisfied. The patients were given oxygen with a mask at the end of the procedure and were monitored for one hour in the recovery room equipped with emergency equipments. The HR, SBP, DBP and MBP, SpO2 and RR were recorded on the 5, 10, 20, 30 and 60 minutes after the procedure. The complications that occurred (hypertension, hypotension, bradycardia, bronchospasm, allergic rash, nausea-vomiting, coughing, dizziness, diplopia, agitation, desaturation, apnea, airway obstruction, laryngospasm, aspiration) were recorded.

The statistical analysis of the obtained data was completed with SPSS for Windows 15.0 statistical package program. As the data were evaluated, constant variables were stated as average ± standard deviation and the frequency data were stated as numerically (5). A "Shapiro-Wilk" test was completed in all statistical analysis to check normal distribution of measured variables. Categorical data were compared by Chi-square test. Differences between numeric variables were tested with Mann–Whitney U test. Friedman test was used in comparing the repeated measures within the group as there were parameters that did not fit the normal distribution in the HR, SBP, DBP and MBP values. A Spearman's Correlation test was conducted to determine the correlation between data. A p value of less than 0.05 was statistically significant.

3. Results

Study groups were similar in terms of demographic data, duration of colonoscopy and anesthesia (Table 1). When the injection pain during induction was compared, there was no pain in the patients given ketofol while there was pain in 19 patients who were given propofol ($p<0.05$). There was no significant difference between the groups in HR, SBP, DBP, MBP and RR during and after the procedure ($p>0.05$) (Figures 1 and 2). The SpO_2 level did not fall below 94% during and after the procedure in any of the patients.

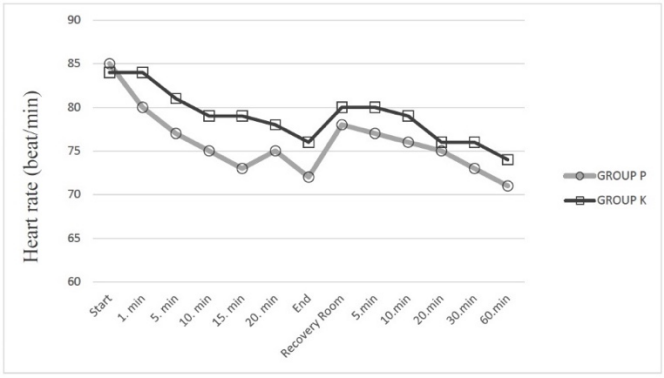

Fig. 1. Heart rates of the groups

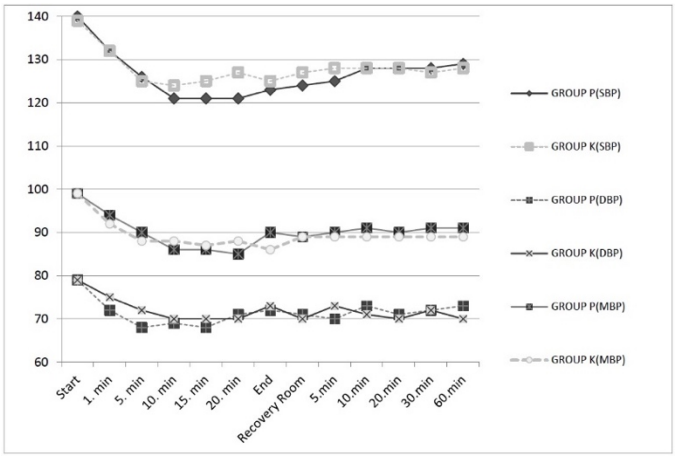

Fig. 2. Systolic, diastolic, and mean blood pressures of the groups

Table 1. Demographic data of groups, and duration of anesthesia and colonoscopy (mean±SD)

	Group P	Group K
Age (year)	49.9 ± 12.4	48.5 ± 12.7
Gender	20 (80%) / 5 (20%)	19 (76%) / 6 (24%)
Height (cm)	160.1 ± 6.9	164.4 ± 8.7
Weight (kg)	70.6 ± 15.2	74.6 ± 11.8
ASA (I/II) n	10 (40%) / 15 (60%)	13 (52%) / 12 (48%)
Duration of anesthesia (min)	24.7 ± 6.5	22.8 ± 5.7
Duration of colonoscopy (min)	22 ± 6.2	21 ± 5.5

In Group P 101.7±32.2 mg propofol was used while 50.55±11.4 mg propofol and 50.55±11.4 mg ketamine was used in Group K (Table 2). There was not a significant difference between the groups in spontaneous eye-opening times and the time for MAS being ≥ 9 ($p>0.05$) (Table 2).

Table 2. Administered drug amounts in Group P and Group K, and the times of spontaneous opening eyes and MAS ≥9 (mean±SD)

	Group P	Group K
Propofol Amount (mg)	101.7±32.2	50.5±11.4
Ketamine Amount (mg)	-	50.5±11.4
Time to reaching MAS ≥ 9 (min)	3.8±2.8	3.1±3.7
Spontaneous opening eye time (min)	3.2±2.0	2.3±2.8

No hypotension hypertension, bradycardia, tachycardia, bronchospasm, allergic rash, coughing, nausea-vomiting, agitation, desaturation, apnea, partial and full airway obstruction, apnea, or aspiration were seen in any patients in the recovery room. All the patients in both groups had dizziness in the early stages of monitoring in the recovery room, however, the dizziness regressed spontaneously within 30 minutes without a need for medical intervention.

There was not a significant difference between the groups in the satisfaction of the person that performed the colonoscopy, the patient, and the anesthesiologist ($p>0.05$) (Table 3).

Table 3. Satisfaction of patient, anesthesiologist, and the doctor performing colonoscopy

	Group P	Group K	p
Patient satisfaction	8.3±0.8	8.4±0.5	0.853
Anesthesiologist satisfaction	7.6±0.8	7.6±1.0	0.919
Satisfaction of the doctor performing colonoscopy	7.6±0.8	7.8±0.8	0.407

4. Discussion

Use of propofol and ketamine combination, called ketofol, for sedation in invasive procedures have become a popular approach in recent years. Ketofol is used frequently in outpatient procedures, particularly in the emergency room and for pediatric patients. Its sedation quality is good, it provides hemodynamic stability, minimizes the side effects of profol, therefore, it's emphasized that it can be uses in children and adults safely (Andolfatto and Willman, 2010; Shah et al., 2011; Willman and Andolfatto, 2007). The purpose in colonoscopy is to provide sedation along with analgesia. For this purpose, ketofol is used in different dosage and combination ratios (Akcaboy et al., 2006; Seip et al., 2010).

The analgesic effect of ketamine should also be mentioned. Ketamine in the ketofol combination is used at lower dosages than the dosages that would create anesthesia. Ketamine at the lower plasma level provides preemptive analgesic effect by inhibiting nociceptive central sensitization (Kwok et al., 2004). In the literature, comparative studies of propofol and ketofol do not address the injection pain of propofol. In our study, the patients who were induced with ketofol solution did not show any injection pain. Also, combining ketamine with propofol and the use at a subdissociative dosage reduce the need of anticholinergic premedication (Friedberg, 1993; Messenger et al., 2008). In our study, no hypersalivation that would require anticholinergic pre-medication was observed.

Although there are many studies supporting this fact, we did not see any significant effects of ketofol in sedation quality, hemodynamic stability, and side-effect profiles. Comparison of the use of propofol and ketamine together in invasive procedures to solely propofol use would theoretically suggest a cardiovascular stability, however, no benefit was shown in a systematic review (Slavik and Zed, 2007).

Ketamine is combined with propofol to reduce the side-effect incidence due to propofol. It is thought that combining propofol with low dosage of ketamine rather than high dose ketamine would provide a synergistic effect in sedation. Smischney et al. (2012) showed that ketofol prepared in a syringe with the ratio of 2:1 in the entubation of critical patients provide a better hemodynamic stability during the first 10 minutes after induction. Akın et al. (2005) and Frey et al. (1999) stated that ketofol reduces respiratory depression while increasing the sedation quality. Although there are several other studies supporting this statement, we did not see a benefit of ketamine addition to propofol in terms of sedation quality, hemodynamic stability, and side effect profiles in our study. Although it is thought that the use of propofol and ketamine together would provide cardiovascular stability compared to use of propofol only, this was not demonstrated in a systematic review(Slavik and Zed, 2007).

David and Shipp (2011) demonstrated that addition of ketamine at a subdissociative dosage to propofol does not reduce the respiratory depression rate and decreases the amount of propofol used while providing a better sedation level and satisfaction. Dereli et al. (2011) compared the effects of different sedation protocols in patients undergoing colonoscopy and showed that the addition of ketamine, fentanyl or remifentanil to propofol provided similar hemodynamic and sedation conditions while they did not find any significant difference in patient satisfaction. Khajavi et al. (2013) compared the ketofol and propofol+fentanil combination to provide conscious sedation and analgesia in colonoscopy and found that the patient satisfaction was higher in the ketofol group while they did not find any significant differences between the hemodynamic parameters, side-effects, and recovery times.

Aydogmus et al. (2015) showed that the addition of ketamine in different dosages to propofol in patients undergoing colonoscopy did not increase patient satisfaction. In this study, although there was a significant difference in the satisfaction of the person performing the colonoscopy in ketofol group, the necessity of ketamine addition into propofol is debatable.

Many studies emphasize on the hypotensive effect of propofol in ketofol which is reduced by ketamine, that ketamine's nausea-vomiting effect is reduced by propofol, and the differences of sedation quality, many randomized clinical studies support the opposite where they argue that it is not necessary to use ketamine with propofol, that there may be ketamine induced recovery agitations, and that using ketamine and propofol together is not necessary (Green et al., 2011). Effect of ketofol for providing a better hemodynamic stability compared to propofol is not very important and propofol induced hypotension is almost always temporary in healthy individuals and it constrains itself (Miner et al., 2015). In studies conducted by David and Shipp (2011) and Shah et al. (2011), procedural success and safety were mentioned and there were no significant difference between the two groups in respiratory side effects. As a result, the necessity of this combination is still questionable. Green et al. (2011) argue that ketamine and propofol can have a synergistic effect, however, this synergistic effect is not needed. They also state that ketofol's more positive effects compared to other agents that are used solely should be demonstrated before recommending ketofol. Considering the similarity of results for both group in the same review, it is difficult to explain the different results on doctor and nurse satisfaction and it is thought that there might be some bias. If the desired sedation is deep, then it can be provided very fast and safely by propofol only. If the desire

is dissociation, this can be achieved by ketamine fastly with dissociative dosages (Shah et al., 2011). Propofol is short-termed, and it would not create any problems even in long cases with repeated dosages. However, repeated dosages of ketofol can cause unpleasant pharmacokinetic effects due to ketamine's accumulative characteristic.

Although it is mentioned that ketofol provides a better hemodynamic stability and creates a better side-effect profile, there are no major complications or side-effect profile seen in studies conducted with only propofol. This may be due to the short duration of procedures, administration of low dose drugs, and the need for additional dose being less and therefore, not observing cumulative effects. Similarly in our study, no significant difference was found between patient and doctor satisfaction, and no significant clinical effect was found on the reduced propofol dosage due to ketamine addition. Similar values were obtained in terms of hemodynamics in both groups.

There are the studies showing the positive effects of propofol and ketamine combination on hemodynamics (Green et al., 2011; Mourad et al., 2004), there are also studies demonstrating that this combination does not have a clinical importance (Aouad et al., 2008; Badrinath et al., 2000; David and Shipp, 2011; Green et al., 2011; Loh and Dalen, 2007). Although the amount of propofol administered in the propofol group was twice as much the amount used in the ketofol group, there was no difference in hemodynamics. Additionally, although spontaneous eye-opening times of patients and time for sending the patients to the ward were shorter in the ketofol administered group, there was no statistical significance between groups. In other words, double dosage of propofol administration did not prolong the recovery time of patients.

Theoretically, ketofol may protect sedation efficacy while reduce the cardiovascular and respiratory adverse effects thought the dose reduction and because of their synergistic effects. The benefit of ketamine reducing the propofol dose has not been fully demonstrated. There is no significant difference in hemodynamic and respiratory parameters in both groups. This may be due to the small number of groups and patients in the groups. The combination of these drugs reduces their disadvantages and provide a better result. There are publications that support this as well as publications that support no clinical difference. No significant difference was seen in our study. Whether ketofol is useful is uncertain.

Sedation depth was titrated according to Ramsay Sedation Scale (RSS), respiratory and hemodynamic parameters (HR, SBP, DBP, SpO_2) verbal stimulations and cornea reflex was lost and not by using any special monitoring like bispectrl index (BİS) and End-tidal CO_2 monitoring.

Optimal dose and combination not yet found and the required dose probably depend on the planned sedation depth. It is recommended that the amount of ketamine in the mixture is as low as possible. Because the combination of subdissociative ketamine dose and propofol is seen with low side effects and high advantage in clinical applications. A low dose ketamine cause nausea, vomiting and hallucinogenic effects are less seen, as the analgesic effect it provides will be less, and it will not help us understand how much analgesic need is required for the procedure.

Overall, addition of ketamine into propofol with a 1:1 ratio only ameliorated the injection pain of propofol in adult patients who underwent colonoscopy. Additionally, it didn't affect the spontaneous eye-opening time and the time to reach a MAS ≥ 9. It didn't have have positive effect on the hemodynamic and respiratory parameters either. However, there were no side effects. There was no significant difference between the patient and doctor satisfaction. Although ketofol is being used in different procedures and different age groups in the recent years, there is still need for studies conducted with different drug dosages of this combination. We believe that the combination ratios would vary depending on the sedation level needed, analgesia, procedure times and the frequency of additional dosage.

Conflict of interest

None.

Acknowledgments

We thank patients for participating the study.

References

1. Akcaboy, Z.N., Akcaboy, E. Y.Albayrak, D.Altinoren, B.Dikmen, B.Gogus, N., 2006. Can remifentanil be a better choice than propofol for colonoscopy during monitored anesthesia care? Acta. Anaesthesiol. Scand. 50 (6), 736-741.

2. Akin, A., Esmaoglu A., Tosun Z., Gulcu N., Aydogan H., Boyaci A. Comparison of propofol with propofol-ketamine combination in pediatric patients undergoing auditory brainstem response testing. Int. J. Pediatr. Otorhinolaryngol. 2005. 69(11): p. 1541-5.

3. Andolfatto, G., Willman, E., 2010. A prospective case series of pediatric procedural sedation and analgesia in the emergency department using single-syringe ketamine-propofol combination (ketofol). Acad. Emerg. Med. 17(2), 194-201.

4. Andolfatto, G., E. Willman, 2011. A prospective case series of single-syringe ketamine-propofol (Ketofol) for emergency department procedural sedation and analgesia in adults. Acad. Emerg. Med. 18(3), 237-245.

5. Aouad, M.T., Moussa, A.R., Dagher, C.M., Muwakkit, S.A., Jabbour-Khoury, S.I., Zbeidy, R.A., Abboud, M.R., Kanazi, G.E., 2008. Addition of ketamine to propofol for initiation of procedural anesthesia in children reduces propofol consumption and preserves hemodynamic stability. Acta Anaesthesiol. Scand. 52(4), 561-565.

6. Aydogmus, M.T., Turk, H. S., Oba S., Gokalp, O., 2015. A comparison of different proportions of a ketamine-propofol mixture administered in a single injection for patients undergoing colonoscopy. Arch. Med. Sci. 11(3), 570-576.

7. Badrinath, S., Avramov, M.N., Shadrick, M., Witt, T. R., Ivankovich, A. D. The use of a ketamine-propofol combination during monitored anesthesia care. Anesth. Analg. 2000. 90(4), 858-862.

8. David, H. and Shipp., J. 2011. A randomized controlled trial of ketamine/propofol versus propofol alone for emergency department procedural sedation. Ann. Emerg. Med. 57(5): p. 435-41.

9. Dereli N, Babayiğit M, and Horasanı E., 2016. The comparison of the efficacy of different sedation protocols in colonoscopy. Gülhane Tıp Derg. 58: p. 3-147.

10. Frey K., Sukhani R., Pawlowski J., Pappas A.L., Mikat-Stevens M., Slogoff S. 1999. Propofol versus propofol-ketamine sedation for retrobulbar nerve block: comparison of sedation quality, intraocular pressure changes, and recovery profiles. Anesth. Analg. 89(2): p. 317-21.

11. Friedberg, B.L., 1993. Propofol-ketamine technique. Aesthetic. Plast. Surg. 17(4), 297-300.

12. Green, S.M., Andolfatto G., and Krauss B., 2011. Ketofol for procedural sedation? Pro and con. Ann. Emerg. Med. 57(5), 444-448.

13. Khajavi M., Emami A., Etezadi F., Safari, S.Sharifi A., Shariat Moharari R. 2013. Conscious Sedation and Analgesia in Colonoscopy: Ketamine/Propofol Combination has Superior Patient Satisfaction Versus Fentanyl/Propofol. Anesth. Pain. Med. 3(1), 208-213.

14. Kwok, R.F., Lim, J., Chan, M.T., Gin, T., Chiu, W.K. Preoperative ketamine improves postoperative analgesia after gynecologic laparoscopic surgery. Anesth. Analg. 2004. 98(4), 1044-1049.

15. Loh, G., Dalen, D., 2007. Low-dose ketamine in addition to propofol for procedural sedation and analgesia in the emergency department. Ann. Pharmacother. 41(3), 485-492.

16. Messenger, D.W., Murray H.E., Dungey P.E., Van Vlymen J., Sivilotti M. L. 2008. Subdissociative-dose ketamine versus fentanyl for analgesia during propofol procedural sedation: a randomized clinical trial. Acad. Emerg. Med. 15(10), 877-886.

17. Miner, J.R., Moore, J.C., Austad, E.J., Plummer, D., Hubbard, L., Gray, R.O. Randomized, double-blinded, clinical trial of propofol, 1:1 propofol/ketamine, and 4:1 propofol/ketamine for deep procedural sedation in the emergency department. Ann. Emerg. Med. 2015. 65(5)479-488 e2.

18. Mourad, M., El-Hamamsy, M., Anwar, M., 2004. Low dose ketamine reduces sedative doses of propofol during ambulatory transoesophageal echocardiography. Egypt. J. Anaesth. 20, 41–46.

19. Seip, B., Bretthauer, M., Dahler, S., 2010. Patient satisfaction with on-demand sedation for outpatient colonoscopy. Endoscopy. 42(8), 639-646.

20. Shah, A., Mosdossy, G., McLeod, S., Lehnhardt, K., Peddle, M., Rieder, M., 2011. A blinded, randomized controlled trial to evaluate ketamine/propofol versus ketamine alone for procedural sedation in children. Ann. Emerg. Med. 57(5), 425-433.

21. Slavik, V.C., Zed, P.J., 2007.Combination ketamine and propofol for procedural sedation and analgesia. Pharmacotherapy, 27(11): p. 1588-98.

22. Smischney, N.J.,Beach, M. L.Loftus, R. W.Dodds, T. M.Koff, M. Ketamine /propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent: a randomized, controlled trial. J. Trauma. Acute. Care. Surg. 2012. 73(1): p. 94-101.

23. Willman, E.V. and G. Andolfatto, 2007. A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. Ann. Emerg. Med. 49 (1), 23-30.