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Comparison of Patient Haemodynamics and Cost Analysis between Ketamine and Dexmedetomidine Used for Endoscopic Retrograde Cholangiopancreatography

Endoskopik Retrograd Kolanjio Pankreatografi Uygulamasında Ketamin ve Dexmedetomidin Kullanılan Hastaların Hemodinamik ve Maliyet Analizlerinin Karşılaştırılması

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ABSTRACT

Introduction: This study aimed to compare the ketamine-propofol and dexmedetomidine-propofol combinations used for endoscopic retrograde cholangiopancreatography (ERCP) performed under sedation. Primary outcomes were total propofol consumption, recovery and haemodynamic profiles of patients in each study group. Secondary outcomes were sedation-related complications and cost profiles of patients in each study group.

Methods: Patients with American Society of Anaesthesiologists class I-III, aged 18-80 years, who underwent ERCP under sedation, were included in the study. Patients were randomly divided into two groups, namely the ketamine group (group KP) and the dexmedetomidine group (group DP). Group KP received 1 mg/kg ketamine plus 1 mg/kg propofol. Group DP received a loading dose of 1 µg/kg of dexmedetomidine for 10 min and a maintenance dose of 0.5 µg/kg plus 1 mg/kg of propofol. Moreover, propofol (10-20 mg) was added to keep the Ramsay Sedation scale at ≥3. Cardiopulmonary side effects, nausea, vomiting, hiccups, straining or retching were recorded in all patients. The ERCP procedure duration, as well as the awakening and recovery times, were recorded. Doses and costs of the drugs used were recorded. Patients were discharged when their Modified Alderete score was 10.

Results: This study included 80 patients. The duration of ERCP in the groups KP and DP was 23.1±9.7 min and 24.4±15.2 min, respectively, and the duration of awakening was 6.0±3.2 min and 7.3±2.9 min, respectively. No statistically significant difference was noted. The recovery time was 18.6±10.6 min and 9.6±4.0 min in groups KP and DP, respectively, with a statistically significant difference noted. No statistically significant intergroup difference was noted regarding additional propofol doses; however, the total cost was

ÖZ

Amaç: Bu çalışmada derin sedasyon altında Endoskopik Retrograd Kolanjio Pankreatografi (ERCP) işleminde ketamin-propofol ve deksmedetomidin-propofol kombinasyonlarının karşılaştırılması amaçlandı. Birincil çıkarım; Her çalışma grubundaki hastaların toplam propofol tüketimi, derlenme ve hemodinamik profillerinin karşılaştırılması. İkincil çıkarım; Her çalışma grubundaki hastaların sedasyon ilişkili komplikasyonları ve maliyet profillerinin karşılaştırılması.

Yöntemler: Sedasyon altında ERCP yapılan, 18-80 yaş arası, ASA I-III olan hastalar çalışmaya dahil edildi. Tüm hastalara standart monitorizasyon yapıldı. Hastalar randomize olarak iki gruba ayrıldı. Ketamin grubuna (grup KP) 1 mg kg-1 ketamin+1mg kg-1 propofol uygulandı. Dexmedetomidin grubuna (grup DP) 1 µg kg-1 10 dakika yükleme ve 0.5 µg kg-1 idame +1mg kg-1 propofol uygulandı. Ramsay Sedasyon skalası ≥3 seviyesinde tutmak için propofol (10-20 mg) eklendi. Kardio-pulmoner yan etkiler, bulantı, kusma, hıçkırık, ıkınma öğürme vb. yan etkiler ve tedavisi tüm hastalarda kayıt edildi. ERCP işlem süresi, uyanma ve derlenme süreleri, kullanılan ilaç dozları ve maliyetleri kayıt edildi. Modified Alderad skoru 10 olunca tüm hastalar taburcu edildi.

Bulgular: Seksen hasta çalışmaya dahil edildi. ERCP işlem süresi grup KP ve grup DP'de sırasıyla 23,1±9,7, 24,4±15,2, uyanma süresi sırasıyla 6,0±3,2, 7,3±2,9 idi ve istatistiksel olarak fark yoktu. Derlenme süresi grup KP ve grup DP'de sırasıyla 18,6±10,6, 9,6±4,0 idi ve istatistiksel olarak anlamlı fark vardı. Ek propofol dozları karşılaştırıldığında gruplar arasında istatistiksel anlamlı farklılık yok iken maliyet açısından değerlendirildiğinde grup KP ve grup DP de toplam maliyet sırası ile 0,58±0,16, 3,03±0,60 $ idi ve istatistiksel olarak anlamlıydı.

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$0.58±0.16 and $3.03±0.60 in groups KP and DP, respectively.

Conclusion: Both ketamine-propofol and dexmedetomidine-propofol combinations provide safe and effective anaesthesia for ERCP performed under sedation. Even though the recovery time was significantly shorter in group DP, it had a significantly higher cost factor on analysis.

Keywords: Dexmedetomidine, ketamine, propofol, sedation

Sonuç: Sedasyon altında ERCP işlemi için hem ketamin-propofol hem de dexmedetomidin-propofol kombinasyonu güvenli ve etkin bir anestezi sağlamaktadır. Dexmedetomidin grubunda derlenme süresi anlamlı olarak kısa olmasına rağmen maliyet açısından değerlendirildiğinde ise anlamlı olarak yüksek olduğu gözlenmiştir.

Anahtar Kelimeler: Deksmedetomidin, ketamin, propofol, sedasyon

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive procedure that is widely used to treat several pancreaticobiliary diseases and performed under sedation. During the ERCP procedure, patients need to be under deep sedation, and anaesthesia must be provided without suppressing protective airway reflexes and preventing coughing and retching (1). The primary challenges during ERCP sedation are the protection of spontaneous breathing, airway sharing and lateral or semi-prone or prone positional changes (2). However, sedation can cause serious complications, such as respiratory depression and heart failure. Therefore, it is imperative to consider the sedative effects as well as safety (frequency of complications) of sedatives when choosing them. Notably, elderly patients are generally prone to sedation complications (3,4).

Propofol is a widely used sedative or hypnotic agent for ERCP sedation because of its pharmacological properties and rapid recovery profile. Despite its favourable profile, the lack of analgesic properties necessitates the use of large doses, especially during lengthy ERCP procedures, and this can cause adverse cardiorespiratory effects (5). Nevertheless, propofol requirement can be reduced by adding an adjuvant (6). Ketamine (NMDA antagonist) and dexmedetomidine (selective alpha-2 agonist) are sedatives with analgesic properties without clinically significant respiratory depressant effects (5,7).

Ketamine is a non-barbiturate derivative of phencyclidine that binds to sigma opioid receptors and N-methyl d-aspartate receptors. It provides dissociative anaesthesia, analgesia and amnesia. It has little or no respiratory and cardiovascular depressant effects (8). The antiemetic and anxiolytic properties of propofol counteract vomiting and unwanted reactions caused by ketamine, whereas ketamine counteracts the propofol-induced hypotension with its sympathomimetic action (9).

The combined use of ketamine and propofol provides successful sedation by reducing the total dose of each drug, thereby mitigating the toxicity caused by a single drug and leading to favourable recovery time profiles (10).

Dexmedetomidine is a selective alpha-2 agonist with sedative and analgesic properties that does not cause respiratory depression. However, as the only sedative agent for endoscopic procedures, it was noted to be ineffective compared with previous studies because it is neither a complete anaesthetic nor a complete analgesic (11). Nevertheless, propofol and dexmedetomidine combination is well tolerated with shorter recovery time, reduced movement and less need for airway interventions (6).

This study aimed to compare between ketamine-propofol and dexmedetomidine-propofol combinations for ERCP performed under deep sedation.

The primary outcomes were total propofol consumption, recovery and haemodynamic profiles of patients in each study group. The secondary outcomes were sedation-related complications and cost profiles of patients in each study group.

Methods

The study was performed with the approval of Necmettin Erbakan University Ethical Committee (ref no: 2019/2061) in concordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. This study prospectively reviewed the database and medical records of patients who underwent ERCP at the University between July 2019 and November 2019.

This study included patients who underwent ERCP under sedation, were aged between 18-80 years and whose physical status was classified according to the American Society of Anesthesiology (ASA) classification as I-III. Patients with known serious systemic diseases; severe cardiovascular, renal, liver, neurological and psychiatric diseases; long history of opioid and alcohol use; pregnancy or suspicion of pregnancy were excluded from the study.

Group Allocation

Group KP received 1 mg/kg ketamine (ketamin, Pfizer İstanbul, Turkey) plus 1 mg/kg propofol (Propofol, Fresenius, İstanbul, Turkey).

Group DP received dexmedetomidine bolus (1 µg/kg for 10 min) followed by dexmedetomidine infusion (0.5 µg/kg/h) (Precedex, Pfizer, Tokyo, Japan) plus 1 mg/kg propofol.

Propofol (10-20 mg) was added to maintain the Ramsay Sedation scale (RSS) at ≥3. Additional propofol doses were recorded.

Study Design

This study included 84 patients who underwent ERCP under sedation with either the combination ketamine-propofol or dexmedetomidine-propofol. Four patients were excluded from the final analysis (Figure 1).

The age, gender, weight and ASA scores of all 80 patients were recorded. All ERCP procedures were performed by the same experienced endoscopist using high-resolution video endoscopies (EC-530WL3, Fujinon, Fujifilm Corporation, Japan).

All patients were monitored per the ASA standards in the intervention room. Heart rate (HR), mean blood pressure (MBP) and peripheral

oxygen saturation (SpO_2) were measured and recorded (Petas KMA 800). Measurements were repeated every 5 min during the procedure. Intranasal oxygen (6 L/min) was administered to patients. After peripheral intravenous cannulation, 6 mL/kg/h normal saline infusion was initiated, and 0.03 mg/kg midazolam (1 mg/mL, 5 mL; Deva Holding, Istanbul, Turkey) was administered to all patients.

Systolic blood pressure under 90 mmHg was accepted as hypotension, and HR under 50 beats/min was accepted as bradycardia. Fluid infusion rate of patients who developed hypotension was increased threefold. An additional fluid infusion was continued for 10 min. Vasopressor (ephedrine) administration was planned in patients who had no response to liquid infusion. Intravenous atropine (0.01 mg/kg) was given to patients in the case of bradycardia. SpO_2 less than 90% was accepted as hypoxemia. When SpO_2 was determined to be less than 90% during the follow-up, a jaw thrust manoeuvre was performed. If SpO_2 persisted at less than 85% despite the jaw thrust manoeuvre, all infusions were stopped, and assisted ventilation was performed. It was planned to interrupt the procedure if SpO_2 remained less than 85% for more than 30 seconds.

Cardiopulmonary side effects (hypotension, bradycardia and hypoxemia), nausea, vomiting, hiccups, straining, retching and coughing, as well as their treatment were recorded in all patients. In addition, postoperative cognitive dysfunctions (agitation, hallucination and excitation) were recorded.

After the administration of drugs, a 60-second wait time was permitted before starting ERCP. Total procedure time was defined as the time between the initiation and completion of ERCP. Awake time was defined as the time from the end of ERCP until consciousness (0-6) score of ≥2 per the RSS, and the recovery time was defined as the time from the end of ERCP until a Modified Aldrete scoring (MAS) of 10 was achieved. After the procedure, all patients were transferred to the recovery room and vital findings, complications and MAS values were recorded. MAS, which is a 10-point scale, was used for assessing the recovery time (12). Patients were followed up until MAS of 10 and then discharged.

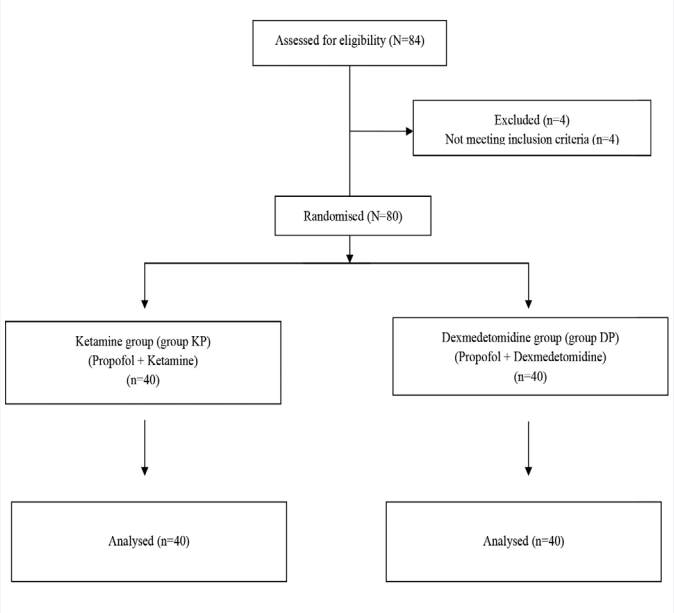

Figure 1. Flow diagram of the study

Outcome Measurements

Primary outcomes were total propofol consumption, recovery and haemodynamic profiles of patients in each study group.

Secondary outcomes were sedation-related complications and cost profiles of patients in each study group.

Statistical Analysis

Data were analysed using SPSS 20.00 software (Statistical Package for Social Sciences Inc, Chicago, IL). The continuous variables were expressed as mean ± standard deviation or number (%). The categorical variables were expressed as numbers and percentages (%). The normality of the data was tested using Kolmogorov-Smirnov. In the absence of normal distribution, the continuous variables were analysed using the Mann-Whitney U test. Intergroup comparison and analysis of categorical variables were performed using the chi-square test. A p value of <0.05 was considered statistically significant.

Results

This study included 80 patients who underwent ERCP under sedation. Of these, 56 were men (70%), and no intergroup differences were noted related to sex (p=0.329). The baseline characteristics of patients were the same in the two groups (Table 1).

Primary Outcomes: Propofol Consumption, Recovery and Haemodynamic Profile in Each Study Group

No statistically significant intergroup difference was observed regarding total propofol doses (p=0.059). In group KP, the ketamine consumption was 63.5±10.87 mg, and propofol consumption was 115.0±46.24 mg. In group DP, dexmedetomidine consumption was 96.5±20.7 mg, and propofol consumption was 100.3±13.6 mg. No statistically significant intergroup difference was observed related to regaining consciousness (p=0.075). Recovery time was longer in the group KP than in group DP

Table 1. Demographic and basal haemodynamic data of patients

	Group KP (n=40)	Group DP (n=40)	p
Age (years)	65.60±10.41	68.27±10.42	0.254
Male/Female	30/10	26/14	0.329
Weight (kg)	72.95±12.59	74.65±12.47	0.546
ASA n (%)			0.800
I	4 (10%)	3 (7.5%)	-
II	30 (75%)	29 (72.5%)	-
III	6 (15%)	8 (20%)	-
Basal MBP (mmHg)	105.9±12.5	107.1±8.9	0.601
Basal HR (beats/min)	89.5±17.3	82.9±14.2	0.068
Basal SpO_2 (%)	97.02±1.24	97.87±1.34	0.839

ASA: American Society of Anaesthesia score, MBP: mean blood pressure, HR: heart rate, SpO_2: peripheral oxygen saturation, DP: dexmedetomidine group, KP: ketamine group

(p<0.001). The mean total dose of sedatives administered during the procedure is presented in Table 2.

In both groups, the MAP and HR values were decreased compared with baseline values, and a significant intergroup difference was noted related to MAP and HR values (p<0.005) (Figure 2). No statistically significant intergroup difference was determined related to the RSS score (p>0.005).

Secondary Outcomes: Cost Profile and Complication in Each Study Group

Cost Profile

In group KP, ketamine cost was $0.21±0.03, and in group DP, dexmedetomidine cost was $2.70±0.58.

Total propofol cost in group KP was $0.37±0.02, and in group DP it was $0.32±0.01, with no statistically significant intergroup difference (p=0.058).

The total cost in groups KP and DP was $0.58±0.16 and $3.03±0.60, respectively. A statistically significant intergroup difference was observed (p<0.001).

Sedation-related Complications

No bradycardia, hypotension and hypoxemia were observed in any patients of groups KP and DP. Procedural complications in group KP were straining in six patients (15%), hiccups in two (5%), retching in two (5%) and coughing in two (5%). In group DP, the complications were desaturation in two patients (SpO_2= 92%) (5%), straining in two (5%), hiccups in two (5%), retching in three (7.5%) and coughing in three (7.5%) (p=0.069). Two patients (5%) developed nausea as a recovery complication in group KP (p=0.494). Postoperative cognitive dysfunction was not observed in either group.

Table 2. Sedative drug doses and procedure related times

Total dose, mean ± SD	Group KP (n=40)	Group DP (n=40)	p
Midazolam (mg)	1.36±0.26	1.27±0.21	0.085
Ketamine (mg)	63.5±10.87	-	-
Dexmedetomidine (µg)	-	96.5±20.7	-
Total propofol (mg)	115.0±46.24	100.3±13.6	0.059
Procedure related times			
Procedure time (min)	23.1±9.7	24.4±15.2	0.632
Awake time (min)	6.0±3.2	7.3±2.9	0.075
Recovery time (min)	18.6±10.6	9.6±4.0	p<0.001

Min: minute, SD: standard deviation

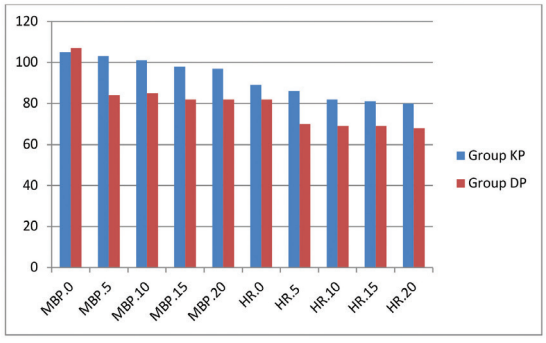

Figure 2. Haemodynamic data of groups

Group KP: ketamine group, Group DP: dexmedetomidine group

Discussion

ERCP is a lengthy and complex therapeutic procedure, requiring high-grade patient collaboration. Sedation and analgesia provide better tolerance and compliance to patients undergoing ERCP by reducing pain, discomfort and stress (1,13,14).

For procedural success, the anaesthetic technique should alleviate pain, anxiety and stress that may cause cardiorespiratory and haemodynamic instability, as well as allow spontaneous breathing of the patient without an airway device (15).

Propofol, a lipophilic drug, has rapid dispersion and elimination times, with no cumulative effect after infusion. Propofol has been evaluated in various regimens for ERCP and has been noted to provide superior sedation quality and shorter recovery time (14). It has been frequently used as a sedative agent for endoscopic procedures over the last two decades. However, propofol can cause deep sedation, as well as dangerous side effects necessitating cardiopulmonary support (2).

In our study, propofol was combined with other medications to reduce its dose and provide optimum sedation without compromising the recovery profile. Dexmedetomidine and ketamine were included in our study owing to their positive recovery profile characteristics, as well as safe anaesthetic effects. In both study groups, propofol was used as a fixed bolus dose, followed by a variable interval bolus.

Dexmedetomidine is a selective alpha-2 agonist with sedative and analgesic properties that does not cause respiratory depression. However, when used as the only sedative agent for endoscopic procedures, it was observed to be ineffective compared with previous studies, because of being neither a complete anaesthetic nor a complete analgesic (11). Therefore, we used it together with propofol. Ghodki PS et al. (16) observed a 62.5% reduction in the induction dose of propofol when co-administered with dexmedetomidine. It was observed that propofol consumption was significantly lower in the 1:4 ketamine-propofol (Ketofol) group compared with the fentanyl-propofol group in patients with obesity undergoing ERCP (2).

In a similar study, Mai W., Abdalla et al. (17) noted that total propofol consumption at the end of the procedure was low but not statistically significant in the dexmedetomidine-propofol group.

The total amount of propofol consumed was the primary endpoint of our study. Although the total dose of propofol consumed in the ketamine group was higher than the dexmedetomidine group, it was not statistically significant.

Ramkiran S. et al. (6) determined the discharge time from the recovery room to be 10±4.17 min in the ketamine group because of the use of low-dose ketamine. Studies using ketamine anaesthesia for interventional cardiology procedures have reported a longer recovery

time and haemodynamic instability in paediatric patients (18,19). A study that compared dexmedetomidine-ketamine with propofol-ketamine reported no haemodynamic or respiratory side effects, but a longer recovery time with the dexmedetomidine-ketamine combination (20). Another study that compared the ketamine group with the propofol group observed more frequent agitation during recovery and a longer time for recovery of the baseline mental state (21).

Mai W. Abdalla et al. (17) noted a shorter recovery time after ERCP with the dexmedetomidine-propofol combination compared with the ketamine-propofol combination.

The present study revealed that recovery time was significantly shorter in patients of group DP than of group KP. Nevertheless, no incidence of respiratory depression, need for respiratory support or loss of respiratory reflexes were observed in patients of both groups.

Another study that compared the effects of propofol and dexmedetomidine on cerebral oxygenation determined a statistically significant decrease in cerebral oxygenation between 5 and 10 min of the procedure. However, the authors concluded that this decrease was not clinically significant but could be harmful in clinically unstable patients (22). During the procedure, the HR and MAP values in the dexmedetomidine-propofol group were lower, which may be related to the effect of dexmedetomidine, which is a highly selective alpha-2 agonist. Notably, the average arterial pressure increases in the ketamine-propofol group because of increased diastolic pressure owing to the increased systemic vascular resistance (17).

Bajwa SJS et al. (23) compared the following drug combinations for total intravenous anaesthesia: propofol-ketamine (group I) and propofol-fentanyl (group II). The intraoperative HR and MAP values of group I were increased, whereas they were decreased after induction and intubation in group II, with a statistically significant intergroup difference noted. These results were concordant with the results of the ketamine-propofol group of our study.

Upon intergroup comparison of the haemodynamic profiles of patients, the dexmedetomidine group had a clinically insignificant, but statistically significant slow HR and low MAP compared with the other group. It was observed that the HR and MAP returned to baseline after the termination of anaesthesia.

Compared with group KP, a generally higher HR reduction was observed in group DP, as well as a transient decrease in SBP, DBP and MAP. Even though these findings were significantly different, no intervention was required. Both treatment strategies were determined to be adequate without a significant difference regarding the need for additional sedation.

Demiraran Y et al. (24) studied midazolam against dexmedetomidine for sedation during an upper endoscopy. In the midazolam group, one patient developed apnoea and two patients had desaturation (SPO_2 <90%), whereas the dexmedetomidine group had no deterioration in respiratory parameters (respiratory rate, desaturation). On the other hand, Bajwa SJR et al. (23) and Aydogan H et al. (25) reported no cases of respiratory failure in the ketamine-propofol group during upper GI endoscopy. A study by Hasanein and El-Sayed (26) reported agitation and irritability in 2% of patients receiving the ketamine-propofol combination, and the other group that received propofol-fentanyl did not have postoperative cognitive dysfunction.

In our study, two patients in the dexmedetomidine group desaturated, but saturation did not fall below 92%, and no hypoxia developed. Moreover, no hypoxia developed in the ketamine group either. Postoperative cognitive dysfunction was not observed in either study group. This difference could be because of the different types of patients with hyperbilirubinemia, increased liver enzymes and hepatic insufficiency, which may alter the pharmacokinetics and pharmacodynamic effects of ketamine.

The literature review did not reveal any cost calculation related to dexmedetomidine in non-operating room applications. Moreover, studies conducted on patients in intensive care revealed varying results.

Nevertheless, dexmedetomidine may be more cost-effective than other sedative agents in intensive care units (ICUs). Sedation with dexmedetomidine reduced ICU costs when compared with standard care. It was stated that cost savings were achieved by reducing the total ICU stay without prolonging hospital stay after intensive care (27). In another study, dexmedetomidine use was associated with increased total hospital cost, ICU stay and length of hospital stay compared with the use of propofol for sedation in critically ill patients.

In our study, compared with the ketamine group, the dexmedetomidine group exhibited a shorter recovery time but a higher cost.

Nonetheless, the present study had some potential limitations, such as small sample size. Therefore, more studies with larger samples are needed to test the efficacy and safety of the study drugs.

Another limitation was the inability to assess the depth of intraoperative anaesthesia and the incidence of intraoperative awareness because the BIS monitor could not be used. However, we believe that only a small intergroup difference could have existed related to the depth of anaesthesia during the study because of the homogeneity of patients and the similarity of the intervention performed.

In conclusion, dexmedetomidine-propofol and ketamine-propofol combinations are safe anaesthetic combinations that provide haemodynamic stability and low complication rates during the ERCP procedure. The combination of dexmedetomidine-propofol was superior to ketamine-propofol with short recovery time and low propofol consumption, albeit with a higher cost. Nevertheless, future randomised trials are required to confirm these findings.

Ethics Committee Approval: The study was performed with the approval of Necmettin Erbakan University Ethical Committee (ref no: 2019/2061) in concordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

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