Hemodynamic stability of ketamine/propofol admixture ketofol in patients undergoing endoscopic retrograde cholangiopancreatography

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Background and aim
Endoscopic retrograde cholangiopancreatography (ERCP) is a common procedure for diagnosis of many gastrointestinal tract disorders. Propofol is a commonly used agent, but we decrease its adverse effects by adding ketamine. We aimed in this study to compare propofol versus propofol–ketamine regarding hemodynamic stability, recovery, and complications in ERCP.

Patients and methods
A total of 90 American Society of Anesthesiology status II–III patients aged 18–60 years who underwent ERCP were randomly allocated by sealed envelope assignment into two groups of 45 patients each: group P received intravenous 2 mg/kg propofol and group KF received intravenous propofol–ketamine 3:1 mixture (%1 15 ml propofol + 1 ml 50 mg/ml ketamine + 4 ml saline in a 20 ml syringe, which resulted in 0.25 mg/ml ketamine and 0.75 mg/ml propofol) until Ramsay sedation scale increased to 3–4. For each patient, the following data were collected: heart rate, mean arterial blood pressure, oxygen saturation, procedure time, total drug dosage, recovery score, and patients' and the doctor's satisfaction score (clinical trial NCT02618668).

Results
The total dosage of propofol consumed was significantly higher in group P compared with group KF (283.78 ± 144.23 and 110.94 ± 51.75 mg, respectively). Recovery time was slightly longer in group P compared with group KF (20.67 ± 5.29 and 19.44 ± 4.16 min, respectively). There was a significance difference in patient satisfaction scores between group KF (1.16 ± 0.64) and group P (1.82 ± 0.83). There was a significance difference in surgeon satisfaction scores between group KF (1.11 ± 0.49) and group P (2.13 ± 0.97).

Conclusion
Propofol ketamine combination (ketofol) is associated with greater satisfaction scores and a shorter recovery than propofol and without important adverse effects in ERCP interventions.

Keywords:
endoscopic retrograde cholangiopancreatography, hemodynamic stability, ketofol, propofol

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Introduction

The question of 'why not two drugs instead of one?' remains to be answered. There is no perfect drug at present, so we will need to find the perfect combination to achieve the perfect sedation. Several factors are important in determining whether a sedative–analgesic combination is clinically acceptable. These include hemodynamic stability, effectiveness of the sedative–analgesic, the time required for surgery to start, recovery times, and the incidence of postoperative nausea and vomiting [1].

The ideal sedative–analgesic combination would provide a stable hemodynamic state, no respiratory depression, a rapid onset and recovery to baseline, and a low incidence of postoperative nausea and vomiting. Decreasing the incidence of postoperative nausea and vomiting is important because it significantly increases recovery time and is very upsetting to the patient. The ideal sedative–analgesic also will maintain a patient's hemodynamic status to as close to the presedation state as possible [2].

Endoscopic retrograde cholangiopancreatography (ERCP) is a common procedure for diagnosis of many gastrointestinal disorders. Comfort of the patient is of great importance for ERCP to be successfully completed [3]. There is significant interest in ketofol as an agent for procedural sedation and analgesia. A combination of ketamine and propofol can be used that can be mixed in the same syringe or administered independently in two separate syringes. Ketofol can be administered as boluses or as a continuous infusion for longer procedures [4].

This study was aimed at evaluating the effect of ketofol on hemodynamic stability, recovery time, and patient and doctor satisfaction scores during ERCP.

Patients and methods

Study design

This was a prospective double-blinded study that was carried out in Assiut University Hospital and El-Raghy Hospital during November 2015 to July 2017 on 90 patients undergoing ERCP. They were randomly allocated by sealed envelope into two groups of 45 patients each:

(1) Group KF received ketofol (1 ketamine: 3 propofol)
(2) Group P received 2 mg/kg of propofol.

Study population

Patients who were scheduled for ERCP were enrolled in the study after Institutional Ethics Committee approval and after written informed consent in this prospective, randomized study.

Inclusion criteria

Patients aged from 18 to 60 years, of both sexes, and with American Society of Anesthesiology status II and III were included in the study.

Exclusion criteria

The exclusion criteria for this study were as follows:

(1) Presence of liver and/or kidney failure, neuropsychiatric disorders, and morbid obesity
(2) History of substance abuse or dependence
(3) History of serious adverse effects related to anesthetics (e.g., allergic reactions), and a family history of reactions to the study drugs
(4) Pregnancy.

Methodology

This was a prospective double-blinded randomized study where patients were assigned to receive propofol or propofol/ketamine (3: 1 combination). After 8 h of fasting period before the procedure, peripheral intravenous access was established with a 20 G cannula, and 6–8 ml/kg/h crystalloid solution was started. No sedation was used before the procedure. All patients were monitored with ECG, noninvasive blood pressure (BP), and peripheral oxygen saturation. A volume of 2 l/min O_2 was administered to all of the patients with a nasal cannula. The hemodynamic parameters at the basal level and every 5 min till the end of procedure were recorded.

Patients were randomly allocated by sealed envelope assignment into two groups: group KF received ketamine–propofol 1: 3 mixture and group P received intravenous propofol. Group KF received intravenous propofol–ketamine 3:1 mixture (%1 15 ml propofol + 1 ml 50 mg/ml ketamine + 4 ml saline in a 20 ml syringe, which resulted in 0.25 mg/ml ketamine and 0.75 mg/ml propofol) until Ramsay sedation scale increased to 3–4 (Table 1). Supplementary study drug was added (intravenous 0.5–1 mg/ml) in case of need. Probable adverse effects such as nausea, vomiting, bradycardia (heart rate <50), hypotension (a systolic BP <90), respiratory depression (<8/min), and secretion increase were also recorded.

Treatment of complications

(1) The treatment for bradycardia was done with atropine 0.01 mg/kg
(2) The treatment for hypotension was done with ephedrine 6 mg/dose.

Data collection

Demographic data included age, sex, and weight.

Clinical data included as follows:

(1) Heart rate
(2) Mean arterial BP
(3) Oxygen saturation at the basal level and every 5 min till the end of procedure
(4) Procedure time
(5) Total drug dosage
(6) Recovery score (Table 2)
(7) Patients' and the doctor's satisfaction scores were recorded evaluating the overall score out of 4 (1 = perfect, 2 = good, 3 = moderate, and 4 = bad) (Table 3).

Statistical analysis

Statistical analysis was performed using SPSS for windows version 22.0 (SPSS Inc., Chicago, Illinois, USA). Distribution of continuous variables was analyzed with the one-sample Kolmogorov–Smirnov test, and all data were distributed normally. Comparisons among groups with respect to hemodynamic data and recovery parameters were evaluated using Student's *t*-test. Adverse effects among groups were evaluated using the χ^2-test. A two-tailed *P* value of 0.05 was considered to be statistically significant.

Discussion

Ketamine, an *N*-methyl-d-aspartate receptor antagonist, is also a significant anesthetic agent.

Table 1 Ramsay sedation scale

Sedation level	Description
1	Patient is anxious, agitated, or restless, or all
2	Patient is cooperative, oriented, and tranquil
3	Patient responds only to commands
4	Patient responds to light glabellar tap or loud auditory stimulus
5	Patient has a sluggish response to light glabellar tap or loud auditory stimulus
6	No response

Table 2 Recovery score

Variable evaluated	Score
Activity	
Able to move four extremities on command	2
Able to move two extremities on command	1
Unable to move any of the extremities on command	0
Breathing	
Able to breathe deeply and to cough freely	2
Dyspnea	1
Apnea	0
Circulation	
Systemic blood pressure ±20% of preanesthetic level	2
Systemic blood pressure 20-49% of preanesthetic level	1
Systemic blood pressure±50% of preanesthetic level	0
Consciousness	
Fully awake	2
Arousable on calling	1
No response	0
O_2 saturation	
Able to maintain O_2 saturation >92% on room air	2
Needs O_2 inhalation to maintain O_2 saturation >90%	1
O_2saturation <90% even with O_2 supplementation	0

Table 3 Patients' and the surgeons' satisfaction score in propofol and propofol-ketamine group

	Excellent	Good	Fairly well	Poor
Patient's satisfaction	1	2	3	4
Surgeon's satisfaction				

Cardiotoxicity, induction of psychotic episodes, and delayed recovery are the main disadvantages for ketamine. Combination of ketamine with various sedative agents to reduce these adverse effects therefore came into question, and benzodiazepines and propofol are widely used for this purpose.

The combination of propofol and ketamine has been efficiently used in separate syringes, as well as mixed in the same syringe, in a variety of settings, including coronary artery surgery in adults[5], interventional radiology [6], sedation for spinal anesthesia [7], and gynecological [8] and ophthalmological procedures [9].

The first study evaluating the effect of propofol–ketamine versus propofol in adult in Gastrointestinal endoscopy (GIE) was done by Harun *et al.* [10].

We have tested the hypothesis that propofol–ketamine mixture would have favorable effect (s) on hemodynamic parameters and recovery times compared with propofol alone in ERCP. We have shown that propofol–ketamine mixture (ketofol) has shorter recovery time compared with propofol alone; both groups have similar hemodynamic effects. Ketofol had more adverse effects such as secretions, but ketofol has more satisfaction scores than propofol.

In our study, ketofol maintained hemodynamic stability. The study by Hasanein and El-Sayed [11] agreed with or results that ketofol maintained hemodynamic stability, and another study done by Harun *et al.* [10] agreed also with our study that ketofol maintained hemodynamic stability.

In our study, total drug dose of propofol used in ketofol was smaller than used in propofol only. There was a highly significant difference in the total drug dosage of group P (283.78 ± 144.23) and group KF (110.94 ± 51.75). In the study by Hasanein and El-Sayed [11], the total dose of propofol needed to achieve a deep sedation level was lower in the ketofol group (57.71 ± 16.97) than in the fentanyl–propofol group (97.08 ± 23.31), which contributed to the lower incidence of propofol sedation-related adverse effects, and it agreed with us that in ketofol, we used small dose of propofol than used in propofol only. Moreover, other study was done by Harun *et al.* [10] that agreed with our finding.

In our study, ketofol had shorter recovery time compared with propofol only. Recovery time was shorter in group kf than group p in recovery room. The study by Harun *et al.* [10] agreed with us that ketofol had shorter recovery time. In the study by Hasanein and El-Sayed [11], the recovery time and time to discharge from the recovery room in the ketofol group were within the acceptable range (11.19 ± 2.59 and 13.28 ± 5.14, respectively), although they were slightly longer than that in group fentanyl–propofol (9.43 ± 1.23 and 12.58 ± 5.41, respectively). Slower clearance of ketamine in comparison with fentanyl was probably responsible for this [11].

Ketofol in our study had complications such as secretions, but in the study done by Harun *et al.* [10], ketofol had no complications; moreover, ketofol in our study had a shorter recovery time than that with propofol, as was seen in the study by Harun *et al.* [10].

Some studies established synergism between ketamine and propofol. Ketamine is known to be an analgesic in subdissociative doses, and when used in combination with propofol, it has been shown to diminish propofol expenditure and protect hemodynamic stability [12]. Additionally, it is assumed that the

sedative and antiemetic effects of propofol may offset the nauseant and psychomimetic effects of ketamine. Some physicians prefer ketamine and propofol in combination over either agent alone for reasons of this possible balance of effects.

In conclusion, the propofol–ketamine 3:1 mixture is associated with shorter mean recovery times and satisfaction scores than propofol alone, with similar hemodynamic stability without important adverse effects.

Conclusion

We can use combination of two drugs instead of one drug to avoid side effects , decrease recovery time and dose.

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Conflicts of interest

There are no conflicts of interest.

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