COMPARATIVE STUDY BETWEEN KETAMINE AND PROPOFOL COMBINATION VERSUS PROPOFOL ALONE FOR SEDATION OF PATIENTS UNDERGOING UPPER GASTROINTESTINAL TRACT ENDOSCOPY

By

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ABSTRACT

Background: Upper gastrointestinal (GI) endoscopy can cause pain and anxiety to the patients which in turn lead to hemodynamic instability and impairment in the patient tolerance. Consequently, adequate sedation and analgesia are required in such procedure to maintain the optimal conditions for patient's relief and recovery.

Objective: This work aimed to determine whether the use of ketofol instead of propofol resulted in fewer adverse respiratory events requiring physician intervention when used for procedural sedation and analgesia.

Patients and Methods: After approval of the Medical Ethical Committee at Al-Azhar University Hospitals, and after patient written consents, 60 patients of American Society of Anesthesiologists (ASA) physical status I or II, scheduled for elective upper GI endoscopy under sedation were enrolled in this randomized, controlled, prospective, double-blind, clinical trial study. Patients were randomly assigned into two equal groups:

 Group (I) received 0.5 mg /kg propofol i.v. Within a period of 30-40 seconds.

 Group (II) received 50mg ketamine plus 0.5 mg/kg propofol in 10 ml normal saline within a period of 30-40 seconds.

Results: The dose of propofol was equal in both groups. Hypoventilation was significantly lower in the group (II), compared to the group (I).

No significant difference was reported between both groups regarding hypoxia, heart rate, adverse effects, and systolic blood pressure, recorded after the procedure and 25-minute after the onset of procedure. Systolic blood pressure was significantly higher in the group (II), compared to the group (I), throughout the 20 minutes following propofol induction .

Conclusion: Combination of propofol and ketamine used for procedural sedation and analgesia in upper GI endoscopy had higher safety than the propofol alone. Respiratory and hemodynamic stability were more noted in the ketofol group than the propofol-only group .

Key words: Ketamine, Propofol, Deep sedation, upper GI endoscopy.

INTRODUCTION

Propofol is a commonly used anasthetic agent characterized by sedative, amnesic and anxiolytic effects, but no analgesic effect. It has an early-onset action with a single dose and a short half-life. So, it is characterized by rapid recovery *(Shah et al., 2011).*

Ketamine is a non-barbiturate anasthetic agent that binds to N-methyl D-Aspartate (NMDA) receptors, causing dissociative anesthesia. It has acceptable analgesic and sedative effects, with minimal cardiovascular risk *(Ozgul et al., 2013).*

This study was designed to determine whether the use of Ketofol, compared to propofol results in fewer adverse respiratory and hemodynamic events when used for procedural sedation and analgesia in upper GI endoscopy.

PATIENTS AND METHODS

After approval of the Medical Ethical Committee at Al-Azhar University Hospitals, and after patient written consents, 60 patients of American Society of Anesthesiologists (ASA) physical status I or II, scheduled for elective upper GI endoscopy under sedation were enrolled in this randomized, controlled, prospective, double-blind, clinical trial study from April 2019 to September 2019 after.

Preoperative preparation: Routine preoperative assessment was done for all patients on the day before operation including history, clinical examination and laboratory investigations .

Anesthetic technique: All patients were secured by peripheral intravenous line.

They received 4 ml/ kg/h Ringer Lactate solution, 2 liters of nasal O2 during the procedure, and 0.03 mg/kg midazolam IV as a premedication.

Group (I) received 0.5 mg/kg propofol i.v. In a period of 30-45 second. If patients did not achieve adequate sedation (Ramsey 4 on Ramsey sedation scale) after 2 min, another dose of 0.5 mg/kg propofol was applied every 2 min. The maximum dose of propofol was 2 mg/kg.

Group (II) received 50 mg ketamine plus 0.5 mg/kg propofol i.v. in 10 ml normal saline combination in a period of 30-45 second. If patients did not achieve adequate sedation (Ramsey 4 on Ramsey sedation scale) after 2 min., the same dose of this combination every 2 min. was given Pre defined maximum dose for ketamine-propofol was 2 mg/kg.

The Ramsay sedation scale was widely used for assessment of the depth of anathesia. The depth of sedation was maintained at the level 6 of Ramsay sedation scale throughout the procedure *(Dawson et al., 2010).*

Recovery from sedation was evaluated every 5 minutes, following end of the procedure, using the Modified Aldrete Score (MAS). The MAS was the standard post-anathetic recovery scoring system. MAS ≥9 was required before discharge from the recovery unit *(Valasareddy et al., 2018).*

Peripheral O2 saturation, respiratory rate (RR), blood pressure, heart rate (HR), ECG, and capnography were detected preoperatively and every five minutes during the procedure.

Sample size was calculated using STATA version 11 programs, setting the type -1 error (α) at 0.05 and the power (1-β) at 0.8. According to *Tutal et al. (2016)*, the percentage of respiratory distress among the propofol group was 19.1% compared to none among the ketofol group. Accordingly, 30 cases were required in each group.

Our primary outcome was the occurrence of respiratory events, such as hypoxia, (defined as $SPO_2 < 93\%$), and hypoventilation (defined as $RR < 8$ breath/min). The secondary outcomes included HR, BP, nausea, vomiting, aspiration, emergence delirium, and laryngospasm.

Statistical analysis:

Data were analyzed based on the t-test and the P-value, using the statistical software package SPSS for Window Version 20.0. Quantitative data were expressed as medians (ranges), means ± standard deviation (SD), whilst qualitative data were expressed as frequency and percentage. The Chi-square ($X2$) test was used to compare the incidence of two qualitative parameters. All data were statistically compared at the two-sided 5% level of significance. P-value <0.05 was considered significant.

RESULTS

Sixty patients were eligible for our procedure. They were randomized into either the ketofol group or the propofol-only group, 30 patients for each. No statistically significant difference was found between the the two groups, regarding the patients demographic characteristics (**Table 1**).

Table (1) : Demographic characteristics of the study groups

Groups / Demographic data	Group (I) (n=30)	Group (II) (n=30)	p-value
Age (years) Range Mean±SD	35-61 48.39±13.18	38-62 50.28±12.07	>0.05
Sex Male Female	17 (56.7%) 13 (43.3%)	14 (46.7%) 16 (53.3%)	>0.05
Height (cm) Range Mean±SD	155-172 171.28±9.29	153-176 170.26±11.36	>0.05
Weight (kg) Range Mean±SD	54-82 70.16±13.42	54-83 69.14±15.48	>0.05
ASA I II	13 (43.3%) 17 (56.7%)	12 (40.0%) 18 (60.0%)	>0.05

Hypoxia and hypoventilation were demonstrated and compared between both groups. Patients group I showed higher frequency of hypoxia, compared to the group II , 5 cases (16.7%) , 1 case (3.3%) respectively (P >0.05). Three cases (10.0%) in group II, and 13 cases (43.3%) in group I had hypoventilation, which was statistically significant **(Table 2)**.

Table (2): Comparison between groups regarding side effects and respiratory events

Groups Side effects	Group (I) (n=30)	Group (II) (n=30)	p-value
Hypoxia	5 (16.7%)	1 (3.3%)	0.05
Hypoventilation	13 (43.3%)	3 (10.0%)	<0.004**

Regarding oxygen saturation, our results showed a highly statistically significant difference between groups at 5, 10 and 20 minutes following induction. At 25 min, group II was not significantly different from group I **(Table 3)**.

Table (3): Comparison between groups according to SPO2

Groups SPO2 (mmHg)	Group (I) (n=30)	Group (II) (n=30)	p-value
Preoperative	97.38±2.32	97.88±1.61	>0.05
After 5 min	95.06±3.12	98.28±1.91	<0.001**
After 10 min	93.95±2.72	97.58±2.32	<0.001**
After 15 min	95.36±2.92	95.77±2.11	>0.05
After 20 min	95.87±2.62	97.78±1.51	0.001**
After 25 min	97.07±1.81	97.78±1.61	>0.05
Postoperative	98.48±1.71	98.79±2.52	>0.05

Our results showed that group II had higher cardiovascular stability than group I. Regarding the systolic blood pressure (SBP), there was a statistically significant difference between both groups at 5, 10, 15, and 20 minutes following induction. At 25 min, the II group was not significantly different from the group I **(Table 4)**.

Table (4): Comparison between groups according to SBP

Groups SBP (mmHg)	Group (I) (n=30)	Group (II) (n=30)	p-value
Preoperative Mean±SD	0 (0%) 133.95±14.80	0 (0%) 133.54±15.01	>0.05
After 5 min Mean±SD	5 (17%) 99.07±13.28	0 (0%) 128.88±13.18	<0.001**
After 10 min Mean±SD	10 (33%) 100.18±15.21	2 (7%) 126.85±15.41	<0.001**
After 15 min Mean±SD	6 (20%) 106.57±13.18	2 (7%) 127.87±13.08	0.003*
After 20 min Mean±SD	4 (13%) 111.64±12.17	0 (0%) 129.89±12.27	0.018*
After 25 min Mean±SD	0 (0%) 124.82±16.22	0 (0%) 126.85±16.43	>0.05
Postoperative Mean±SD	0 (0%) 126.65±14.20	0 (0%) 128.88±14.09	>0.05

As regared heart rate, there was no statistically significant difference between groups **(Table 5)**.

Table (5): Comparison between groups according to heart rate

Groups Heart rate (beat/min)	Group (I) (n=30)	Group (II) (n=30)	p-value
Preoperative	84.09±15.13	83.15±13.89	>0.05
After 5min.	80.34±11.62	81.34±12.69	>0.05
After 10min.	78.31±11.96	79.48±11.49	>0.05
After 15min.	77.88±11.25	77.11±11.09	>0.05
After 20 min.	76.46±13.62	79.64±9.98	>0.05
After 25min.	81.94± 4.93	81.03± 6.50	>0.05
Postoperative	78.01±9.95	82.50±8.61	>0.05

Regarding the side effects, group II showed no statistically significant difference, compared to group I in terms of nausea, vomiting, aspiration, emergence delirium and laryngeal spasm **(Table 6)**.

Table (6): Comparison between groups according to side effects.

Groups Side effects	Group (I) (n=30)	Group (II) (n=30)	p-value
Hypotension	9 (30.0%)	2 (6.7%)	<0.02*
N & V	1 (3.3%)	1 (3.3%)	0.05
Delirium	1 (3.3%)	2 (6.7%)	0.05
Laryngeal spasm	2 (6.7%)	3 (10.0%)	0.05
Aspiration	0 (0.0%)	0 (0.0%)	0.05

DISCUSSION

This study highlighted the safety of adding ketamine to propofol for procedural sedation and analgesia in upper GI endoscopy. Ketamine is N-methyl-D-aspartate receptor antagonist, which is primarily used as a hypnotic with analgesic effects. Indeed, it has minimal respiratory side effects, compared to other hypnotics like propofol. Importantly, it preserves the heart rate and the blood pressure, which is attributable to its protective sympathomimetic activity *(Peltoniemi et al., 2016)*. Nevertheless, high doses might cause hallucination, visual problems, nausea, vomiting and laryngospasm *(Tutal et al., 2016)*. Propofol is a commonly used sedative agent because of its short half-life, amnestic, anxiolytic, and antiemetic properties. Nevertheless, serious side effects may limit its spread such as respiratory depression, and hypotension. Hypotension is attributed to decreased cardiac output, and peripheral vascular resistance *(Tutal et al., 2016)*. Indeed, propofol is combined to ketamine, in an attempt to reduce these side effects. The combination of propofol and ketamine has been efficiently used, either separate or in the same syringe, in variety of settings, including coronary artery surgery in adults, interventional radiology, sedation for spinal anesthesia, gynecological and ophthalmological procedures *(Aydogan et al., 2013)*.

Hypoventilation was significantly more frequent in the propofol-only group, compared to the ketofol group (43.3% vs 10.0% respectively). Our results agreed with *Tandon et al. (2014)* who compared ketofol to propofol in upper GIT endoscopy and showed that airway assistance was used in 15% in the propofol group compared to 3% in the ketofol group. Nevertheless, the study done by *Ferguson et al. (2016)*, comparing the two drugs showed close results between the two groups. Hypoventilation was noted in 9% with ketofol and 4% with propofol, and respiratory interventions in 14% with ketofol and 16% with propofol. This discrepancy may be attributable to the different applied procedures and the confounding effect of opioids.

According to hypoxia, no statistically significant difference was found between both groups. This result agreed with *Ferguson et al. (2016)* with occurence of hypoxia in 8% of patients with propofol, and 6% of patients with ketofol. Aspiration did not occur is any patient with both groups.

Our study showed that using propofol alone led to significant decrease in blood pressure as hypotension occurred in 30% of the patients, but the addition of ketamine to propofol has aborted the hemodynamic instability that occurred with propofol alone as hypotension occurred in 6.7% of the patients with ketofol. Propofol decreases systemic vascular resistance, cardiac contractility, and the preload, which all cause a decrease in arterial blood pressure. Propofol also inhibits arterial baroreflex and hypotension induced tachycardia *(Stayer et al., 2010)*. There are some previous studies that reported propofol-ketamine combination is safe in means of hemodynamic stability in groups of

pediatrics, emergency room, and regional analgesia patients *(Tutal et al., 2016)*.

Smischney et al. (2012) compared ketamine-propofol and propofol in general anesthesia induction and reported lower myocardial depression and vasodilation in the ketamine-propofol group.

Providers have typically been reluctant to use ketamine in adults because of concern about emergence phenomena, with rates of 10% to 20% being quoted in the literature *(Ferguson et al., 2016)*. The rates of unpleasant emergence delirium in our study were lower suggesting that in this regimen, one of the adverse events most likely to deter providers from the use of ketamine is less likely to occur with ketofol than when ketamine is used as a single agent. A previous randomized controlled trial by *Perumal et al. (2015)* who used ketamine with and without midazolam for emergency department sedation in adults showed a similar reduction in emergence phenomena when midazolam was combined with ketamine in adults.

CONCLUSION

Ketofol was a good choice for safe and effective sedation and analgesia in patients undergoing upper GI endoscopy. It resulted in less adverse respiratory events and a better hemodynamic stability. The frequency of postoperative nausea, vomiting and delirium were comparable in both groups.

CONFLICTS OF INTEREST

There were no conflicts of interest regarding the present study.

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دراسة مقارنة بين عقاري الكيتامين والبروبوفول وعقار البروبوفول وحده كمهدئ لمرضي تنظير الجهاز الهضمي العلوي

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خلفيـة البحـث: يسبب منظـار الجهــاز العلـوي للجهــاز الهضـمي الألـم والقلـق للمرضي والـذي بـدوره يـؤدي إلـي عـدم إسـتقرار الوظـائف الحيويـة وتقلـل مـن درجـة تحمـل المـريض وبنـاء علـي ذلـك يلـزم إسـتخدام تسـكين وتخـدير كـافي لمثـل هـذ الإجـراء لتسـخير الظـروف المثاليـة لراحـة وشـفاء المرضي.

الهـدف مـن البحـث: تحديـد مـا إذا كـان إسـتخدام الكيتـامين والبروبوفـول بـدلا مـن البروبوفـول وحـده يـؤدي إلـي حـدوث عـدد أقـل مـن الآثـار الضـارة علـي التـنفس والتـي تتطلـب تـدخلات الأطبـاء عنـد إستخدامها للتخدير الإجرائي وتسكين الألم في منظار الجهاز الهضمي العلوي.

المرضـي وطـرق البحـث: بعـد موافقـة اللجنـة الأخلاقيـة بمستشـفيات جامعـة الأزهـر والحصـول علـي موافقـة خطيـة مـن المرضـي ، تـم اختيـار ٦٠مريضـا مصـنفين طبقـا للجمعيـة الأمريكيـة للتخـدير إلـي التصـنيف الأول والثـاني لإجـراء تنظير الجهـاز الهضـمي العلـوي إختياريـا تحـت تـأثير التخـدير، وتـم تقسيم المرضي عشوائيا إلي مجموعتين متساويتين.

النتـائج: حـدث نقـص فـي التهويـة أقـل بكثيـر فـي المجموعـة المشـتركة مقارنـة بمجموعـة البروبوفـول ، ولـم يحـدث فـرق معنـوي بـين المجمـوعتين فيمـا يتعلـق بـنقص الأكسـجين فـي الـدم ومعـدل ضـربات القلـب والآثـار الجانبيـة وضـغط الـدم الإنقباضـي التـي سـجلت بعـد الجراحـة وبعـد ٢٥دقيقـة مـن بـدء الجراحـة ، وكـان ضـغط الـدم الإنقباضـي أعلـي بكثيـر فـي المجموعـة المشـتركة عنهـا فـي مجموعـة البروبوفول وخلال٢٠ دقيقة بعد تحفيز البروبوفول.

الإسـتنتاج: كـان للجمـع بـين البروبوفـول والكيتـامين المسـتخدم للتخـدير الإجرائـي وتسـكين الألـم فـي منظـار الجهـاز الهضـمي العلـوي تـأثيرا أعلـي مـن البروبوفـول وحـده ، ولـوحظ إسـتقرار الجهـاز التنفسي والدورة الدموية في المجموعة المشتركة أكثر من مجموعة البروبوفول.