A comparative study between propofol–ketamine and propofol–fentanyl for sedation during pediatric diagnostic upper gastrointestinal endoscopy

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Background
The aim of this study was to compare propofol–ketamine (ketofol) with propofol–fentanyl in pediatric patients undergoing diagnostic upper gastrointestinal endoscopy.

Patients and methods
This was a prospective, randomized, double-blinded study to compare the effect of propofol–ketamine and propofol–fentanyl on oxygen saturation, heart rate (HR), and systolic blood pressure (SBP) when used for sedation in pediatric patients undergoing elective upper gastrointestinal endoscopy. Sixty ASA I–II patients, aged 6–12 years were included in the study. Oxygen saturation, HR, and SBP of all patients were recorded perioperatively, after induction, 5 min later, and at the end of the procedure. All patients received propofol 1.5 mg/kg, intravenous + either fentanyl 1 μg/kg, intravenous (propofol–fentanyl group) or ketamine 0.5 mg/kg, intravenous (propofol–ketamine group). The procedure started when the sedation score was 4–6. Additional propofol (1 mg/kg) was administered when needed in either group. Demographic data, operative data, and intraoperative and postoperative side effects (hypoxia, nausea and/or vomiting, increased oral secretions, and emergence reactions, or hallucinations) were recorded.

Results
There were no significant differences between both groups regarding the demographic and operative data (duration of the procedures, onset of anesthesia, number of patients needed additional dose (s), recovery time, discharge time, modified Ramsay sedation scale). The mean values of oxygen saturation, HR, and SBP were significantly lower ($P < 0.05$) in the propofol–fentanyl group than the propofol–ketamine group after induction, 5 min later, and at the end of the procedure. No significant difference regarding intraoperative and postoperative side effects between both groups ($P > 0.05$).

Conclusion
Propofol–ketamine 3: 1 mixture was associated with hemodynamic stability and better oxygen saturation without affecting the recovery and without significant side-effects.

Keywords:
fentanyl, ketamine, pediatrics, propofol, sedation, upper gastrointestinal tract endoscopy

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Introduction

Anesthesia practice in pediatric patients undergoing diagnostic upper gastrointestinal endoscopy (UGIE) is highly variable. There is no standard anesthetic technique for this procedure. Light sedation, deep sedation, and general anesthesia have been used [1].

Unlike adult patients, who receive conscious sedation, children usually require deep sedation or general anesthesia [2]. A combination of benzodiazepines with narcotics is the commonly administered intravenous (IV) sedation in children; however, the administration of propofol sedation by the anesthesiologist is gaining acceptance among pediatric gastroenterologists [3]. Optimum pediatric endoscopy requires proper patient preparation and amnesia as well as safe and effective control of anxiety, pain, and prompt patient recovery [4].

Propofol alone or combined with midazolam, or meperidine has been used successfully for sedation in pediatric UGIE [5]. Fentanyl has also been used alone or combined with other IV anesthetics [6,7]. Ketamine has been also used for both IV and intramuscular, alone or combined with midazolam and meperidine in pediatric UGIE [8–10].

Aim

The primary outcome of this study was to evaluate the effect of propofol–ketamine versus propofol–

fentanyl on the incidence of desaturation [oxygen saturation (SpO_2)<90%] in pediatric patients undergoing diagnostic UGIE. And the secondary outcome was the evaluation of the effects of the same drug combinations on the heart rate (HR) and systolic blood pressure (SBP).

Patients and methods

Study design

This was a randomized, double-blinded study. It was preregistered at ClinicalTrials.gov (ID: NCT03235609).

It was carried out in Assiut University Hospital, after approval by the local research ethics committee of Assiut Faculty of Medicine, Egypt. Informed consent was taken from the parents for each patient.

Sixty children, American Society of Anesthesiologists physical status I or II, aged 6–12 years, who were scheduled for elective UGIE were studied.

Excluded from the study were patients with known allergy to the study drugs: significant cardiac, hepatic, renal, or neurological disease; the presence of respiratory infection; hyperactive airways; and obesity (BMI 100–119% of the 95th percentile).

The patients were divided randomly (by a computer-generated program) into two equal groups (30 patients each). Group I (propofol–fentanyl): received 1.0 μg/kg fentanyl + 1.5 mg/kg propofol IV. Group II (propofol–ketamine): received ketofol (1 ketamine: 3 propofol) 0.5 mg/kg ketamine + 1.5 mg/kg propofol, IV.

All patients received propofol 1.5 mg/kg and lidocaine 1.5 mg/kg slowly IV + the study (blind) drug either fentanyl 1.0 μg/kg, IV (100 μg + 8.0 ml normal saline, each 1 ml contains 10 μg fentanyl) in the propofol–fentanyl group or ketamine 0.5 mg/kg (50 mg + 9.0 ml normal saline, each 1 ml contains 5 mg ketamine) in the propofol–ketamine group. Supplementary propofol in a dose of 1 mg, IV, was given when needed (movements, pain, or grimaces). All patients were fasted for 8 h before the procedure (except clear liquids 3 h). Peripheral intravenous access was established and 6–8 ml/kg/h crystalloid solution was started. No sedation was given before the procedure. All patients were monitored by ECG, noninvasive blood pressure (BP), SpO_2, and end-tidal CO_2 tension attached to one limb of the nasal cannula. Oxygen was administered to all the patients via a nasal cannula (3 l/min). Probable side effects such as nausea, vomiting, bradycardia (HR < 60), hypoxia (SpO_2 < 90%), hypotension (a SBP < 90), and increased secretions were recorded. Emergency equipment and drugs for resuscitation and anesthesia were available for every patient. The procedure started when the sedation score was 4–6.

Treatment of complications

(1) Desaturation (SpO_2 <90%) by airway manipulation (jaw thrust or chin lift) with supplementation of O_2 with bag mask ventilation or endotracheal tube.
(2) Bradycardia by atropine 0.01 mg/kg, IV.
(3) Hypotension by ephedrine 3 mg/dose, IV.

Data collection

Demographic data included age, sex, and weight. Clinical data included HR, SBP, and SpO_2.

All the above data were recorded before induction (base line), after induction, 5 min later, and at the end of the procedure. Operative data included duration of the procedure. Onset of sedation (from the start of sedation till the patient's readiness for starting the procedure). The number of patients who needed additional propofol doses, recovery time and sedation score (modified Ramsay sedation scale)[11] were recorded before starting and at the end of the procedure (Table 1). Adverse effects of any given drug were also considered.

Discharge criteria

(1) After the procedure, the patient can be discharged if the following criteria are met.
(2) Airway patent and stable unsupported.
(3) Oxygen saturation of more than 95% on room air.
(4) Hemodynamically stable.
(5) Hydration adequate, no bleeding, and urine output adequate.
(6) Returned to normal level of responsiveness and orientation for age and mental status.
(7) No nausea or vomiting.
(8) Pain controlled.

Statistical analysis

Sample size calculation was performed with online DSS research calculators. To detect a 15% reduction in the incidence of desaturation (SpO_2 <90%) we need to include 20 patients in each group with an α error of 0.05; this will give an actual power of 80%.

Statistical analysis

The data were analyzed using SPSS, version 17 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean ± SD, median (range), numbers, and percentage

as appropriate. Parametric data were analyzed using Student's *t*-test and nonparametric data were analyzed using the Mann–Whitney *U*-test, χ^2-test, and Fisher's exact test. A *P* value less than 0.05 was considered statistically significant.

Results

This prospective, double-blinded, controlled study was conducted on 60 pediatric patients (aged 6–12 years) undergoing UGIE.

Demographic and operative data of the studied groups

As shown in Table 2, demographic and operative data in both groups are comparable.

Hemodynamic data and oxygen saturation in the studied groups

The mean values of HR, SBP, and SpO_2 in the propofol–fentanyl group were significantly lower ($P < 0.05$) than the propofol–ketamine group after induction, 5 min later, and at the end of the procedure (Tables 3–5 and Fig. 1).

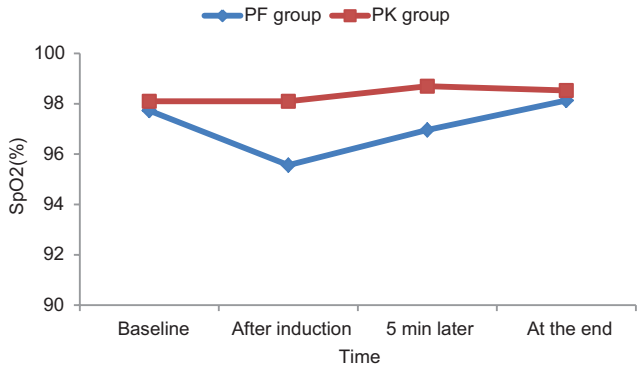
Intraoperative and postoperative side-effects in the studied groups

No significant difference regarding the intraoperative and postoperative side effects between both groups as shown in Table 6.

Discussion

Anesthesia practice in pediatric patients UGIE is highly variable [1]. Unlike adult patients, who receive conscious sedation, children usually require deep sedation or general anesthesia to ensure patient safety, comfort, and cooperation [2].

Figure 1



Oxygen saturation (SpO_2) changes in both groups.

Table 1 Modified Ramsay sedation scale

Score	Response
1	Awake and alert, minimal, or no cognitive impairment
2	Awake but tranquil, purposeful responses to verbal commands at a conversational level
3	Appears asleep, purposeful response to verbal commands at a conversational level
4	Appears asleep, purposeful responses to commands but at a louder than conversational level, requiring light glabellar tap, or both
5	Asleep, sluggish purposeful responses only to loud verbal commands, strong glabellar tap, or both
6	Asleep, sluggish purposeful responses only to painful stimuli
7	Asleep, reflex withdrawal to painful stimuli only

Table 2 Demographic and operative data of the studied groups

	PF group (*n*=30)	PK group (*n*=30)	*P*
Age (years)	9.27±2.13	8.90±2.35	0.53
Sex			
Male	13 (43.3)	15 (50)	0.39
Female	17 (56.7)	15 (50)	
Weight (kg)	24.70±3.69	24.03±5.05	0.56
Duration of procedure (min)	15.23±5.25	14.01±4.23	0.78
Onset of anesthesia (s)	19.83±5.33	19.01±4.62	0.52
Need for additional dose (s)	14 (50)	15 (46.6)	0.32
Recovery time (min)	2.66±0.80	2.30±0.59	0.54
Discharge time (min)	5.83±0.87	5.60±0.82	0.28
Modified Ramsay sedation scale			
After induction	6.0 (1.0)	6.0 (0.0)	0.86
At the end	3.0 (1.0)	2.5 (1.0)	0.46

Data were expressed as mean±SD, frequency (%), and median (IQR) for Ramsay sedation scale.IQR, interquartile range; PF, propofol-fentanyl; PK, propofol-ketamine.*P*>0.05, NS.

Table 3 Heart rate in both groups

Heart rate (beats/min)	PF group (*n*=30) (95% CI)	PK group (*n*=30) (95% CI)	*P*
At baseline	102.30±7.09 (99-105)	104.76±9.29 (101-108)	0.251
After induction	93.63±6.67 (91-96)	102.86±8.28 (99-106)	0.001*
5 min later	93.86±8.01 (91-97)	103.10±8.17 (100-106)	0.001*
At the end	95.76±8.45 (92-99)	100.63±8.27 (97-104)	0.025*

Values were expressed as mean±SD, 95% CI for mean.CI, confidence interval; PF, propofol-fentanyl; PK, propofol-ketamine.**P*<0.05, significant.

Table 4 Systolic blood pressure in both groups

SBP (mmHg)	PF group (*n*=30) (95% CI)	PK group (*n*=30) (95% CI)	*P*
At baseline	102.63±9.44 (99-106)	103.46±10.48 (99-107)	0.694
After induction	92.46±8.17 (89-95)	101.36±8.36 (98-104)	0.001*
5 min later	94.23±7.75 (91-97)	100.50±6.54 (98-102)	0.002*
At the end	95.20±7.31 (92-98)	99.10±7.88 (96-102)	0.030*

Values were expressed as mean±SD, 95% CI for mean.CI, confidence interval; PF, propofol-fentanyl; PK, propofol-ketamine; SBP, systolic blood pressure.**P*<0.05, significant.

Table 5 Oxygen saturation in both groups

Oxygen saturation (%)	PF group (*n*=30) (95% CI)	PK group (*n*=30) (95% CI)	*P*
At baseline	97.73±0.69 (97-98)	98.10±0.71 (98)	0.078
After induction	95.56±3.10 (94-97)	98.10±0.96 (97-98)	0.001*
5 min later	96.96±1.42 (96-97)	98.70±0.59 (98-99)	0.001*
At the end	98.13±0.82 (97-98)	98.53±0.77 (98-99)	0.012*

Values were expressed as mean±SD, 95% CI for mean.
CI, confidence interval; PF, propofol-fentanyl; PK, propofol-ketamine.*P<0.05, significant.

Table 6 Side-effects in both groups

Item	PF group (*n*=30)	PK group (*n*=30)	*P*
Hypoxia (transient)	3 (10)	0	0.083
Nausea and/or vomiting	2 (6.6)	1 (3.3)	0.326
Increased oral secretions	0	0	-
Emergence reactions or hallucinations	0	0	-

Data were expressed as *n* (%).PF, propofol-fentanyl; PK, propofol-ketamine.P>0.05, NS.

There are few studies, which evaluate the use of propofol during pediatric UGIE [5–7]. When used alone a relatively large dose of propofol is required to achieve adequate sedation. At times, such high doses may result in hypotension or respiratory depression [5,7].

The question of 'why not use one drug instead of two?' 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 the surgery to start, recovery times, and the incidence of postoperative nausea and vomiting [1].

There is no ideal anesthetic technique that can be applied in children UGIE. The goals of the anesthesiologist include sedation, adequate analgesia, and immobility, with minimal depression of cardiovascular function and respiratory drive [12].

There is significant interest in ketofol as an agent for procedural sedation and analgesia. A combination of ketamine and propofol (ketofol) 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 [3]. Fentanyl has also been used alone or combined with other IV anesthetics in the same setting [7–9].

In this prospective, randomized, double-blinded study, we compared the effect of propofol–ketamine versus propofol–fentanyl on the incidence of desaturation (SpO_2 < 90%) and hemodynamic stability (SBP and HR) in pediatric patients undergoing diagnostic UGIE. It was carried out on 60 (28 men and 32 women) pediatric patients aged 6–12 years; they were divided into two equal groups (30 patients each):

Group I (propofol–fentanyl): received 1.0 μg/kg fentanyl + 1.5 mg/kg propofol, IV.

Group II (propofol–ketamine): received ketofol (1 ketamine: 3 propofol) 0.5 mg/kg ketamine + 1.5 mg/kg propofol, IV.

In this study, however, the mean values of the hemodynamic data (HR and SBP) and SpO_2 were significantly lower in the propofol–fentanyl group than the propofol–ketamine group in all periods after induction. It is not clinically significant but statistically significant.

The sympathomimetic effects associated with ketamine administration may maintain the intraoperative BP and HR close to the baseline values [13].

Similar to our results on hemodynamics have been found by Tosun *et al.*[14] in their study on pediatric patients who were undergoing UGIE under either fentanyl–propofol or ketamine–propofol combination. Although they studied a wide range of age groups (1–16 years old) and gave more fentanyl (1.2 μg/kg) and more ketamine (1.2 mg/kg), they found that the ketamine–propofol combination resulted in stable hemodynamics.

In addition, Guit *et al.*[15] concluded that the combination of fentanyl with propofol resulted in depressed hemodynamics, but the combination of ketamine with propofol resulted in more stable hemodynamics.

Similarly, Akin *et al.*[12] concluded that when propofol is combined with low-dose ketamine (0.5 mg/kg), it preserves arterial BP better in pediatric patients undergoing cardiac catheterization.

Also, IV administration of low-dose ketamine (0.5 mg/kg) before induction and maintenance with propofol in pediatric patients (age: 9 days to 7 years) undergoing elective MRI preserves hemodynamics without changing the duration and the quality of recovery compared with propofol alone [16]. Erden *et al.*[17] stated that the addition of low-dose ketamine (0.5 mg/kg) to propofol–fentanyl combination decreased the risk of desaturation in pediatric patients during interventional radiology procedures.

In this study, the onset of sedation, recovery time, and/or discharge time had no significant changes between

both groups ($P > 0.05$). The number of patients needed additional dose (s) of sedation (propofol) was 14 (50%) in the propofol–fentanyl group, while in the propofol–ketamine group it was 15 (46.6%). Sedation was assessed after induction of anesthesia and at the end of the procedure using eight-point sedation scales (modified Ramsay sedation scale), and there was no significant difference in sedation score between both groups. Ketamine is reported to provide excellent sedation, analgesia, and amnesia with minimal cardiorespiratory effects [13]. The combination of propofol and ketamine has the potential to provide better sedation with less side effects than either drug alone [18]. Akin *et al.*[12] concluded that the combination of low-dose ketamine with propofol decreases the propofol dose and does not prolong the recovery period. Also, Tosun *et al.*[14] found no significant difference between propofol–fentanyl and propofol–ketamine in pediatric patients UGIE as regards sedation score, recovery time, and discharge time.

In this study, all episodes of hypoxemia, that is, $SpO_2 < 90\%$ (three in the propofol–fentanyl group after induction of sedation and no one in the propofol–ketamine group) were transient and no patient required bag/mask ventilation in either group and no serious complications were encountered in both groups.

This may be explained by the relatively long apnea time which may be produced by a combination of propofol and fentanyl[19] caused by respiratory depression [20].

The most frequently mentioned adverse effects related to ketamine is emergent delirium or hallucinations. This occurs more commonly if ketamine is used as the sole agent for sedation. In this study, no patients reported emergent delirium or hallucinations. It has been known that the combination of ketamine with propofol eliminates the side-effects of ketamine [15].

In this study, postoperative nausea and vomiting were seen in two cases in the propofol–fentanyl group and one case in the propofol–ketamine group. Also, Bahrami Gorji *et al.*[21] found that the frequency of nausea and vomiting in their study was more in the propofol–fentanyl group than in the propofol–ketamine group.

The main concerns regarding the addition of ketamine were increase in secretions, and delayed recovery and hallucinations. None of these occurred in this study using this low-dose of ketamine. This finding is supported by the literature. Guit *et al.*[15] reported that propofol could be effective in eliminating side effects of a low-dose of ketamine in humans. Similarly Tomatir *et al.*[16] found that the addition of a small dose of ketamine to propofol in pediatric sedation did not increase secretions, vomiting, or postoperative hallucination. As in the Tosun *et al.*[14] study a few cases in both groups required pharyngeal aspiration after removal of the endoscope, which was probably related to the procedure.

Conclusion

Ketofol (propofol–ketamine) 3: 1 mixture was associated with hemodynamic stability, better oxygen saturation without affecting the recovery, and without significant side effects. So, this mixture is a good option for pediatric patients undergoing diagnostic UGIE.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Michaud L. Francophone Pediatric Hepatology, Gastroenterology, and Nutrition Group. Sedation for diagnostic upper gastrointestinal endoscopy: a survey of the Francophone Pediatric hepatology, gastroenterology, and nutrition group. Endoscopy 2005; 37:167–170.

2 Wengrower D, Gozal D, Gozal Y, Meiri Ch, Golan I, Granot E, Goldin E. Complicated endoscopic pediatric procedures using deep sedation and general anesthesia are safe in the endoscopy suite. Scand J Gastroenterol 2004; 39:283–286.

3 Leffler TM. Propofol for sedation in the endoscopy setting: nursing considerations for patient care. Gastroenterol Nurs 2004; 27:176–180.

4 Tolia V, Peters JM, Gilger MA. Sedation for pediatric endoscopic procedures. J Pediatr Gastroenterol Nutr 2000; 30:477–485.

5 Khoshoo V, Thoppil D, Landry L, Brown S, Ross G. Propofol versus midazolam plus meperidine for sedation during ambulatory esophagogastroduodenoscopy. J Pediatr Gastroenterol Nutr 2003; 37:146–149.

6 Disma N, Astuto M, Rizzo G, Rosano G, Naso P, Aprile G, Bonanno G, Russo A. Propofol sedation with fentanyl or midazolam during oesophagogastroduodenoscopy in children. Eur J Anaesthesiol 2005; 22:848–852.

7 Ali S, Davidson DL, Gremse DA. Comparison of fentanyl versus meperidine for analgesia in pediatric gastrointestinal endoscopy. Dig Dis Sci 2004; 49:888–891.

8 Kirberg A, Sagredo R, Montalva G, Flores E. Ketamine for pediatric endoscopic procedures and as a sedation complement for adult patients. Gastrointest Endosc 2005; 61:501–502.

9 Law AK, Ng DK, Chan KK. Use of intramuscular ketamine for endoscopy sedation in children. Pediatr Int 2003; 45:180–185.

10 Gilger MA, Spearman RS, Dietrich CL, Spearman G, Wilsey MJJr, Zayat MN. Safety and effectiveness of ketamine as a sedative agent for pediatric GI endoscopy. Gastrointest Endosc 2004; 59:659–663.

11 Gill M, Green SM, Krauss B. A study of the bispectral index monitor during procedural sedation and analgesia in the emergency department. Ann Emerg Med 2003; 41:234–241.

12 Akin A, Esmaoglu A, Guler G, Demircioglu R, Narin N, Boyaci A. Propofol and propofol–ketamine in pediatric patients undergoing cardiac catheterization. Pediatr Cardiol 2005; 26:553–557.

13 Hwang J, Jeon Y, Park HP, Lim YJ, Oh YS. Comparison of alfentanil and ketamine in combination with propofol for patient-controlled sedation during fiberoptic bronchoscopy. Acta Anaesthesiol Scand 2005; 49:1334–1338.

14 Tosun Z, Aksu R, Guler G, Esmaoglu A, Akin A, Aslan D, Boyaci A. Propofol–ketamine vs propofol–fentanyl for sedation during pediatric upper gastrointestinal endoscopy. Paediatr Anaesth 2007; 17:983–988.

15 Guit JB, Koning HM, Coster ML, Niemeijer RP, Mackie DP. Ketamine as analgesic for total intravenous anaesthesia with propofol. Anaesthesia 1991; 46:24–27.

16 Tomatir E, Atalay H, Gurses E, Erbay H, Bozkurt P. Effects of low dose ketamine before induction on propofol anesthesia for pediatric magnetic resonance imaging. Paediatr Anaesth 2004; 14:845–850.

17 Erden IA, Pamuk AG, Akinci SB, Koseoglu A, Aypar U. Comparison of propofol-fentanyl with propofol–fentanyl–ketamine combination in pediatric patients undergoing interventional radiology procedures. Paediatr Anaesth 2009; 19:500–506.

18 Mortero RF, Clark LD, Tolan MM, Metz RJ, Tsueda K, Sheppard RA. The effects of small dose ketamine on propofol sedation: respiration, postoperative mood, perception, cognition, and pain. Anesth Analg 2001; 92:1465–1469.

19 Dwivedi MB, Puri A, Dwivedi S, Deol H. Role of opioids as coinduction agent with propofol and their effect on apnea time, recovery time, and sedation score. Int J Crit Illn Inj Sci 2018; 8:4–8.

20 Ebrahimi Dehkordi M, Razavi SS, Momenzadeh S. A comparison between sedative effect of propofol–fentanyl and propofol–midazolam combinations in microlaryngeal surgeries. Iran J Pharm Res 2012; 11:287–294.

21 Bahrami Gorji F, Amri P, Shokri J, Alereza H, Bijani A. Sedative and analgesic effects of propofol–fentanyl versus propofol–ketamine during endoscopic retrograde cholangiopancreatography: a double-blind randomized clinical trial. Anesth Pain Med 2016; 6:e39835.