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Research Article

Ketamine/propofol versus fentanyl/propofol for sedating obese patients undergoing endoscopic retrograde cholangiopancreatography (ERCP)

Riham Hasanein *, **Wael El-Sayed**

Faculty of medicine, Cairo University, Egypt

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KEYWORDS

Ketamine;
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Abstract *Objective:* This study was conducted to compare two techniques of sedation for obese patients undergoing ERCP, using either ketofol or fentanyl–propofol as regards propofol consumption, recovery time, patients' satisfaction, and sedation-related adverse events.
Materials and methods: Two hundred obese patients were randomly allocated to one of two groups; ketamine/propofol (ketofol) group KP ($n = 100$) or fentanyl/propofol group FP ($n = 100$). The level of sedation was adjusted to achieve a Ramsay Sedation Scale (RSS) score of 5.
Results: Total dose of propofol consumed was significantly higher in group FP compared with group KP (97.08 ± 23.31 mg and 57.71 ± 16.97) mg. Recovery time was slightly longer in group KP compared with group FP (11.19 ± 2.59 min and 9.43 ± 1.23 min, respectively), time needed to achieve Aldrete Recovery Scale Score of 9 was comparable in both groups, and sedation-related side effects as hypotension, bradycardia, apnea, and reduction of SpO_2 were more significant in the FP group.
In conclusion: Ketamine/propofol combination 1:4 provided better sedation quality than fentanyl/propofol combination with less side effects and can be safely used for sedating obese patients undergoing ERCP.

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a lengthy and potentially uncomfortable procedure that needs moderate to deep sedation or even general anesthesia to facilitate high success rate and avoid patient's discomfort [1,2]. Anesthetic management of ERCP can be challenging due to different factors; remote location, prone position, head of the patient is far away from the anesthetist, lengthy procedure, shared airway, and less familiar environment.

* Corresponding author.
E-mail address: rihamhasaneen@yahoo.com (R. Hasanein).
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Sedation for endoscopy in the obese patients is even more challenging; they have reduced total lung volume, reduced functional residual capacity (FRC), and reduced vital capacity. These decreases in lung volumes decrease exponentially with the increase in body mass index (BMI) [3]. Moreover, the ventilation/perfusion mismatches can occur more easily in these patients. In addition, obstructive sleep apnea is commonly detected during deep sleep in fatty adults [4].

There are three levels of the severity degree of obesity; overweight: BMI > 25, obese: BMI > 30, and morbidly obese: BMI > 35.

Propofol, a phenol derivative, is a short-acting intravenously administered sedative and hypnotic agent [5]. It has been used frequently over the past two decades as a sedative agent for endoscopic procedures [6]. However, propofol can cause deep sedation or even dangerous side effects that need cardiopulmonary support [7].

Ketamine, an NMDA receptor antagonist and has also been found to bind to opioid receptors and sigma receptors, leads to a condition called "dissociative anesthesia" [8]. It causes amnesia, analgesia and maintains spontaneous breathing [9,10]. But its use as a single sedative agent has been limited by its propensity to cause vivid and frightening emergent reactions [11], sympathomimetic effects, and vomiting when given in sedating doses [12].

A combination of ketamine and propofol in the same syringe (ketofol) for procedural sedation and analgesia (PSA) was proved to be safe and preserve sedation efficacy with minimizing their respective side effects. Ketamine and propofol given in combination have offered effective sedation for spinal anesthesia and for gynecologic, ophthalmologic, and cardiovascular procedures in all age groups [13].

This study was aimed to compare between two regimens of sedation; ketofol versus fentanyl/propofol in overweight and obese patients undergoing ERCP regarding recovery time, patients' satisfaction, and sedation-related adverse events. Morbidly obese patients are out of our scope, as preemptive endotracheal intubation may be appropriate for them prior to performing an ERCP.

2. Materials and methods

After obtaining ethical committee approval and written informed consent, a double-blind randomized study was done in Saad specialist hospital, Saudi Arabia; on 200 obese patients scheduled for ERCP during February 2009 to February 2011, aged from 18 to 70 years with BMI 25-35 and ASA physical status I, II, or III. Pregnant patients, morbidly obese patients, patients with chronic obstructive pulmonary disease, complicated airway, ASA physical classification IV–V, history of allergy or contraindications to the drugs used in the study, emergency need for ERCP, those whose informed consent could not be signed, and those with possible complex ERCP were excluded from this study. Patients were randomly allocated by the "sealed envelope technique" to one of two groups and received either of the following two regimens:

Ketofol group KP (n = 100).
Fentanyl/propofol group FP (n = 100).

Sealed envelope was broken when the patient was in the ERCP room. The study drugs were prepared by an assistant who was not involved in the clinical management of the study patients, and bolus drugs are given according to the lean body weight, while continuous infusion was adjusted according to the total body weight.

For ketofol (KP) group, a bolus dose of 10 ml normal saline followed by ketofol infusion (ketamine: propofol concentration 1:4) prepared in 50 ml syringe, by mixing 40 ml propofol 1% (10 mg/ml) with 2 ml ketamine (50 mg/ml) and 8 ml dextrose 5% (each ml contained 8 mg propofol and 2 mg ketamine).

In case of group FP, a bolus of fentanyl 1.5 μg/kg i.v., the volume of which was made to 10 ml followed by 40 ml propofol 1%, was mixed with 10 ml dextrose 5%, so that each milliliter contained 8 mg of propofol.

The anesthesiologist who gave the drugs and assessed the parameters was blinded to the randomization process and to the study drug identity but not to concentration of the drug in the syringes (mg/ml). Both bolus and maintenance doses will be given using syringe pump (B/Braun). Both the interventional drugs were given as an initial bolus dose of 0.5 mg/kg propofol IV (considering the syringes contained only propofol for simplicity). Then, infusion was started at the rate of 50 μg/kg/min. The level of sedation was assessed at 1–3 min intervals, and the infusion rate was adjusted accordingly to achieve a Ramsay Sedation Scale (RSS) score of 5 [14] (Table 1).

On arrival to the radiology suite, intravenous access was established, and (0.02–0.03) mg/kg midazolam and an infusion with lactated Ringer's solution were started. Routine monitoring included an electrocardiogram (ECG), noninvasive arterial blood pressure (NIBP), pulse oximetry (SpO_2), and end tidal carbon dioxide ($EtCO_2$) and respiratory rate (RR) measured through oxygen delivery nasal prongs. Supplemental oxygen was delivered at 3 l/min.

Any desaturation or apnea were recorded when the SpO_2 dropped to $<90\%$ or recorded cessation of respiration for 15 s or more, respectively, and were managed by supporting the airway and/or assisting ventilation. Hypotension was considered when the mean arterial pressure (MAP) decreased by $>20\%$ of the baseline MAP and managed by fluid bolus and/or vasopressors. Bradycardia was considered when heart rate was less than 55 beats/min and managed with atropine 20 mcg/kg i.v. Any movement of the patient was treated with increase in the study drug infusion rate. The study drug infusion was discontinued at the end of the procedure, and the total drug requirements were noted. The recovery time was considered as the time from discontinuation of infusion of the study drug till achievement of RSS score of 3 was recorded, and patients were transferred to the recovery room. The recovery nurse was blinded to the study medication received by the patients. The incidence of postoperative nausea and vomiting (PONV) or any other adverse events (e.g., hallucinations, agitation, or pain) were recorded and were managed accordingly. The patient's vital signs were assessed at 5 min intervals. Patients were discharged from the recovery room after attaining an Aldrete Recovery Scale Score of 9–10 (Table 2) [15]. Time taken to achieve this score was recorded.

Patient's satisfaction was assessed using a 100-mm visual analog scale (VAS) (0 = least satisfied, 100 = most satisfied). The patients rated their satisfaction by making a vertical mark on the 100-mm line. Only patients with score $\geqslant 75$ were considered satisfied. The exact question was "Are you satisfied with your sedation?"

Table 1 Ramsay Sedation Scale.

Sedation level	Description
1	Patient is anxious, agitated or restless, or both
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 The Modified Aldrete Scoring System [15].

Activity: able to move voluntarily or on command	
4 extremities	2
2 extremities	1
0 extremities	0
Respiration	
Able to deep breathe and cough freely	2
Dyspnea, shallow or limited breathing	1
Apneic	0
Circulation	
BP ± 20 mm of preanesthetic level	2
BP ± 20–50 mm of preanesthesia level	1
BP ± 50 mm of preanesthesia level	0
Consciousness	
Fully awake	2
Arousable on calling	1
Not responding	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_2 saturation < 90% even with O_2 supplementation	0

3. Statistical analysis

Data were statistically described in terms of mean ± standard deviation (±SD), or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student's *t*-test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Yates correction equation was used instead when the expected frequency is less than 5. *P* values less than 0.05 were considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

4. Results

Two hundred patients were enrolled in this study and completed it. There were no differences in the baseline characteristics of patients including gender, age, body mass index (BMI), procedure's duration, type of ERCP and ASA physical status classification (Table 3).

Total dose of propofol consumed was significantly higher in group FP compared with group KP (97.08 ± 23.31 mg and 57.71 ± 16.97) mg, respectively, $P < 0.01$). Recovery time was slightly longer in group KP compared with group FP (11.19 ± 2.59 min and 9.43 ± 1.23 min, respectively, $P < 0.01$). The time needed to achieve Aldrete Recovery Scale Score of 9 was comparable in both groups (13.28 ± 5.14 min and 12.58 ± 5.41 min, $P = 0.007$) in the KP and FP, respectively (Table 4).

Table 3 Patients' characteristics, procedure's duration and indications.

Variables	Group KP ($n = 100$)	Group FP ($n = 100$)	*P* value
Gender (male/female)	49/51	50/50	0.888
Age (years)[a]	57.67 ± 13.3	56.93 ± 11.9	0.679
BMI[a]	29.6 ± 3.53	28.9 ± 4.42	0.217
Procedure's duration (min)	31.61 ± 17.65	27.88 ± 14.38	0.099
ASA classification (%)			0.937
I	16	17	
II	61	62	
III	23	21	
Indication (%)			0.821
Cholethiasis	45	43	
Biliary stricture (tumor)	42	46	
Others	13	11	

[a] Data are given as mean ± SD.

Table 4 Mean dose of propofol and recovery times.

Variables	Group KP ($n = 100$)	Group FP ($n = 100$)	*P* value
Total dose of propofol (mg)	57.71 ± 16.97	97.08 ± 23.31	<0.01*
Recovery time (min)	11.19 ± 2.59	9.43 ± 1.23	<0.01*
Time to achieve Aldrete Score 9 (min)	13.28 ± 5.14	12.58 ± 5.41	0.349

Data are given as mean ± SD.
* *P* value < 0.05.

In this study, hypotension occurred in three patients (3%) in group KP compared with 12 (12%) in group FP, while hypertension was recorded only in two patients in group KP. Bradycardia was found in nine patients (9%) in group FP compared with one (1%) in group KP. Tachycardia occurred in three patients (3%) in group KP compared with one (1%) patient in FP group. Apnea occurred in two patients (2%) in group KP compared with 10 patients (10%) in group FP (Table 5).

Emergence reaction (agitation) occurred only in two patients (2%) in group KP and treated by i.v. midazolam 0.05 mg/kg. PONV occurred in three patients (3%) in group KP and in one patient (1%) in group FP, treated by i.v. ondansetron 0.1 mg/kg.

Patients' satisfaction was comparable in both groups; 90 patients in group KP had score ⩾75 versus 91 patients in the group FP. The satisfaction score in group KP was (90%) and in group FP was (91%) (Table 5).

5. Discussion

Overweight and obesity are increasingly common problems worldwide. Many of these patients are at high risk for the ERCP procedure and for sedation [3,4,16].

Table 5 Sedation-related side effects and patients satisfaction (n, %).

Variables	Group KP (n = 100)	Group FP (n = 100)	P value
Hypotension	3 (3%)	12(12%)	0.032*
Hypertension	2 (2%)	0	0.477
Bradycardia	1 (1%)	9 (9%)	0.023*
Tachycardia	3 (3%)	1 (1%)	0.614
Apnea	2 (2%)	10(10%)	0.037*
SpO_2 < 90%	0	7 (7%)	0.021*
Movement	4 (4%)	6 (6%)	0.746
Agitation	2 (2%)	0	0.477
PONV	3 (3%)	1(1%)	0.614
Patients' satisfaction	90 (90%)	91(91%)	1.000

* Statistically significant, P value < 0.05.

High BMI and conscious sedation were reported as risk factors for hypoxemia [17,18].

A multivariate analysis was carried out on variables which included BMI to determine its effect on hypoxemia, and they found a non-linear relation between incidence of hypoxemia and BMI. If BMI is 20 or less, odd ratio of hypoxemia kept nearly constant during GI endoscopy and did not change with BMI. But when BMI value is more than 20, the higher BMI value, the higher odd ratio of hypoxemia [19].

Our goal in this study was to provide an adequate level of sedation while minimizing pain and anxiety, minimizing the adverse drug-related events, controlling behavior, and maintaining a stable cardiovascular and respiratory status.

Continuous infusion technique was used in our study to maintain a steady state sedation level. The RSS score has been used to assess the level of sedation. Serious complications with propofol-based sedation as respiratory and cardiovascular side effects can occur and need to be rapidly recognized and appropriately managed.

In our study, higher incidence of hypotension, bradycardia, apnea, and desaturation has been observed in group fentanyl–propofol than in the ketofol group, and the ketamine–propofol combination is thought to act by antagonizing the side effects of each other.

In this study, 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.

In the present study, 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), although it was slightly longer than that of group fentanyl–propofol (9.43 ± 1.23) and (12.58 ± 5.41), respectively. Slower clearance of ketamine in comparison with fentanyl is probably responsible for this.

Although there is a higher incidence of emergence agitation and PONV in the ketofol group compared with the fentanyl–propofol group, this incidence rate is much lower than the usual incidence rate of ketamine alone. Emergence reactions and vomiting are significant adverse effects of ketamine usage, occurring more in adults than in children [20]. Emergence phenomena as high as 50% in adults have also been found by others [21].

The lower concentration of ketamine to propofol (1:4), counteraction of propofol, with its sedative and antiemetic effects, and the premedication with midazolam helped to reduce the overall incidence rates of these adverse events of ketamine.

Ketamine–propofol combinations in different ratios (1:1–1:5) have been used by many authors before [22–24]. All these combinations revealed hemodynamic stability. Increased discharge time was found when higher proportion of ketamine was used. Akin and colleagues found better maintenance of MAP without prolonging recovery in the ketamine–propofol (1:3) combination group than in the propofol monotherapy group [25].

The ratio of propofol to ketamine in preparing ketofol infusion is a challenge; Daabis et al. [13] compared the safety and efficacy of different concentrations of ketofol in procedural operations in children and concluded that propofol combined with ketamine (4:1) infusion for procedural operations resulted into adequate sedation and analgesia without hemodynamic and respiratory depression or psychotomimetic side effects and appears to be useful and can be safely used for procedural operations in the ambulatory setting.

Akin et al. [23] compared propofol (1.5 mg/kg) to propofol (1.5 mg/kg) and ketamine (0.5 mg/kg) in a ratio of 3:1 and reported no cases of desaturation with ketofol, but with propofol 4/30 had desaturation and 6/30 had apnea, blood pressure and heart rate were significantly lower with propofol than ketofol and reported that the addition of low dose ketamine to propofol reduced the risk of respiratory depression and the need for repeat medication administration.

5.1. In conclusion

Ketamine–propofol combination (1:4) provided better sedation quality than fentanyl/propofol combination, with less hemodynamic and respiratory depression and appears to be a safe and useful technique for sedating obese patients undergoing ERCP.

5.2. Limitations of this study

Wide range of age of the patients; drug requirements, recovery time, and side effects can be related to age. Further studies are needed in a larger group of obese patients with different concentration of ketamine:propofol combinations.

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