# Alfentanil versus ketamine combined with propofol for sedation during upper gastrointestinal system endoscopy in morbidly obese patients

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## ABSTRACT

**الأهداف:** مراقبة آثار كل من البروبوفول/alfentanil والبروبوفول/الكيتامين في التسكين أثناء تنظير الجهاز الهضمي العلوي في المرضى الذين يعانون البدانة المفرطة (UGSEMOP).

**الطريقة:** في دراسة استطلاعية مزدوجة التعمية وعشوائية سريرية، جرى اختيار 52 مريضاً لعمل UGSEMOP وجرى توزيعهم إما للمجموعة أ (n=26; 10 µg/kg intravenous [IV] alfentanil) أو المجموعة ك (n=26; 0.5 mg/kg IV ketamine). صُرف لكل مريض 0.7 mg/kg بروبوفول للتحريض و أُعطوا جرعة إضافية من البروبوفول IV عبر الوريد عند الضرورة. اجريت هذه الدراسة في مستشفى Sehitkamil State في مدينة غازي عنتاب، تركيا في الفترة الممتدة من يناير 2014 إلى 2015. اجمالي استهلاك البروبوفول، والوقت لتحديد Modified Aldrete Scores MAS بين 5 و10 باتباع الاجراءات، ومدى رضا الطبيب والمريض، وحالات من الآثار الجانبية، مثل ما سُجل من بطء معدل نبضات القلب وانخفاض ضغط الدم.

**النتائج:** كان كلاً من وقت بداية التسكين ومدته أقل بشكل ملحوظ في المجموعة أ واستغرق مرضى هذه المجموعة وقتاً أقل لتحقيق 5 من MAS. مجموع استهلاك البروبوفول كان أقل بشكل ملحوظ في المجموعة أ.

**الخاتمة:** قدمت كلاً من البروبوفول/alfentanil و البروبوفول/الكيتامين التنويم المغناطيسي والتسكين المناسب خلال UGSEMOP. مع ذلك، كان استهلاك البروبوفول أعلى بكثير باستخدام مزيج البروبوفول والكيتامين.

**Objectives:** To observe the effects of both propofol/alfentanil and propofol/ketamine on sedation during upper gastrointestinal system endoscopy in morbidly obese patients (UGSEMOP).

**Methods:** In a prospective, double-blinded, randomized clinical study, 52 patients scheduled for UGSEMOP were assigned to either group A (n=26; 10 µg/kg intravenous [IV] alfentanil) or group K (n=26; 0.5 mg/kg IV ketamine). Each patient was administered 0.7 mg/kg propofol for induction. If it was needed, the patients were administered an additional dose of IV propofol. This study was performed in Sehitkamil State Hospital, Gaziantep, Turkey, between January 2014-2015. Total propofol consumption, time to achieve Modified Aldrete Scores (MAS) of 5 and 10 following the procedure, physician and patient satisfaction scores, and instances of side effects, such as bradycardia and hypotension were recorded.

**Results:** Time to onset of sedation and duration of sedation were both significantly shorter in group A. Patients in group A also required less time to achieve an MAS of 5. Total propofol consumption was significantly lower in group A.

**Conclusion:** Both propofol/alfentanil and propofol/ketamine combinations provided appropriate hypnosis and analgesia during UGSEMOP. However, propofol consumption was significantly higher using the propofol/ketamine combination.


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Morbid obesity (MO) is a worldwide health problem, which causes additional health problems, such as sleep apnea and gastroesophageal reflux in patients.[1] Upper gastrointestinal system endoscopy is frequently performed in MO patients in order to minimize the complications of bariatric surgery or to identify MO-related health problems.[2] The inability to provide adequate pain control during UGSEMOP can lead to hemodynamic deterioration and esophageal rupture.[3] Provision of appropriate sedation and analgesia reduces stress to the patient and the incidence of complications.[3] Propofol is often used for sedation during UGSEMOP. Alfentanil is a synthetic opioid with a short half-life.[4,5] It theoretically reduces the frequency of apnea due to respiratory depression and reduces the inhibitory effect of propofol on blood pressure and heart rate.[6] Ketamine has amnesic and analgesic properties and therefore is well-suited for short procedures.[7,8] This prospective, randomized, double-blind study planned to compare propofol/alfentanil and propofol/ketamine combinations for use during UGSEMOP.

**Methods.** After obtaining approval from the appropriate ethics committee (Gaziantep University Medical Ethical Committee, Gaziantep, Turkey, a total of 52 patients were enrolled in the study. All patients provided informed consent. The patients had a body mass index (BMI) between 45 and 60 kg/m$^2$ and were scheduled for UGSEMOP. This study was conducted in accordance with the Declaration of Helsinki and was performed at Sehitkamil State Hospital, Gaziantep, Turkey) between January 2014-2015. The patients had an American Society of Anesthesiologists (ASA) physical status between II and III. Patients with pulmonary, hepatorenal, neuromuscular, or neuropsychiatric disorders were excluded from the study. In addition, candidates who did not provide written consent were excluded from the study.

Prior to the procedure, baseline data (electrocardiography, oxygen saturation [SpO2], non-invasive blood pressure) were obtained. Physiological saline (0.9% saline) was administered at 5 ml/kg/h. Each patient was randomly assigned to one of the 2 groups: group A (propofol/alfentanil) or Group K (propofol/ketamine). Each patient in group A was administered 10 μg/kg intravenous (IV) alfentanil (Rapifen® Johnson & Johnson, Istanbul, Turkey). Each patient in Group K was administered 0.5 mg/kg IV ketamine (Ketalar 500 mg® Pfizer, Istanbul, Turkey). Patients in both groups were then administered 0.7 mg/kg IV propofol (Propofol 1%® Fresenius Kabi, Istanbul, Turkey) 60 seconds after the first medication was administered. Physicians waited to start the procedure until the blink reflex was lost. During this wait time, oxygen was administered through a nasal cannula at a rate of 6 liters/minutes (min).

After the blink reflex was lost, the endoscopic procedure was initiated. During the procedure, whenever the heart rate increased above the base rate by 15% or exceeded 90 beats/min, additional propofol was administered at half the starting dose. Propofol was also administered if the systolic arterial pressure increased by more than 15% or movement of the body/extremities was observed. Heart rate and $SpO^2$ were measured continuously with heart rate, $SpO^2$, and blood pressure being recorded every 2 min.

Protocols were established to address the potential side effects of hypotension and bradycardia. Whenever the systolic blood pressure dropped to less than 30% of the starting value or measured less than 90 mmHg, 5-10 mg IV ephedrine was administered. Whenever the heart rate measured less than 50 beats/min, 0.5 mg atropine was administered.

The Modified Aldrete Score (MAS) was used to assess patient recovery. A Verbal Pain Scale (VPS) was used 5 and 10 minutes after the procedure to monitor pain. The scale was as follows: 0=no pain, 1=dull pain, 2=moderate pain, and 3=intense pain. Tramadol (Contramal® Abdi İbrahim, Istanbul, Turkey; 1 mg/kg) was intravenously administered to patients with intense pain. Two hours after the procedure, the patients were questioned regarding feelings of nausea and episodes of vomiting.

The total amount of propofol administered was recorded. In addition, the duration of the procedure, time elapsed before the patient opened his eyes (time for MAS to reach 5), recovery time (time for MAS to reach 10), and the total time elapsed since IV propofol was first administered were all recorded. Both the patients and the physicians were questioned regarding their satisfaction with the procedure. The scale was as follows: 0=not satisfied, 1=satisfied, and 2=very satisfied. Patient and physician satisfaction scores, MAS, VPS, and the patients' nausea/vomiting status were recorded by an independent anesthesiologist or surgical nurse. Recovery time was recorded as a first priority. Side effects, such as hypotension, bradycardia, and nausea/vomiting were recorded as secondary priorities.

A priori power analysis was performed to estimate the required sample size according to the duration of the procedure. The required sample size was determined to be 52; the power application was set at 90% and $\alpha$ at 0.05. Results were reported as median, mean and

standard deviation (SD), and number of patients. The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 15 was used in this study. Descriptive statistics included mean ± SD for numerical data, and numbers and percentages for categorical data. The Kolmogorov-Smirnov test was used as a normalization test. The Student t-test was used for comparing parametric changes, and the Mann-Whitney U test was used for comparing non-parametric changes. A value of $p<0.05$ was considered statistically significant.

**Table 1 -** Demographic status among 52 patients included in the study.

| Demographics | Group A | Group K | *P*-value† |
|---|---|---|---|
| Age (years)* | 33.5±9.8 | 36.7±8.7 | 0.2 |
| Male /Female | 6/20 | 6/20 | 1 |
| BMI* | 46.5±1.3 | 46.1±1.2 | 0.2 |
| ASA II/III | 14/12 | 14/12 | 1 |
| Duration of operation (minutes)* | 9±0.8 | 9±0.5 | 0.5 |

*Data mean ± SD or number of patient, †There are no sitatistically significant differences between the groups, *BMI - Body Mass Index, ASA - American Society of Anesthesiologists

**Table 2 -** Onset time of sedation, onset time of aldrete 5, onset time of aldrete 10, the duration of sedation and total propofol consumption

| Variates | Group A | Group K | *P*-value |
|---|---|---|---|
| The onset time of sedation (min) | 2.1±0.1 | 3.1±0.1 | 0.00* |
| The duration of sedation (min) | 10.9±0.9 | 12.5±1.2 | 0.00* |
| The onset time of aldrete 5 (min) | 7.5±0.7 | 8.3±0.7 | 0.00* |
| The onset time of aldrete 10 (min) | 9.8±0.4 | 9.3±0.8 | 0.06 |
| Total propofol consumption (mg) | 102.8±8.8 | 128.6±7.4 | 0.00* |

Data mean ± SD or median, min - minutes

**Table 3 -** Comparison of the satisfaction score and VPS of the groups

| Variates | Group A | Group K | *P*-value |
|---|---|---|---|
| The satisfaction score of patients of the groups (0/1/2) | 0/13/13 | 1/16/9 | 0.1 |
| The satisfaction score of doctor of the groups (0/1/2) | 0/12/14 | 0/17/9 | 0.2 |
| VPS minute 5 | 1.6±0.4 | 1.4±0.5 | 0.09 |
| VPS minute 10 | 1.4±0.5 | 1.6±0.4 | 0.09 |

Data mean ± SD or median, VPS - verbal pain scale

**Table 4 -** Incidence of adverse events.

| Variates | Group A (n:26) | Group K (n:26) | *P*-value |
|---|---|---|---|
| Hypotension | 5 | 1 | 0.08 |
| Bradycardia | 2 | 0 | 0.1 |
| Nausea | 3 | 8 | 0.09 |
| Vomiting | 0 | 2 | 0.15 |

**Results.** Demographic data and procedure times for each patient are presented in **Table 1** (age [years] $p=0.2$, male/female $p=1$, BMI $p=0.2$, ASA II/III $p=1$, procedure time [minutes] $p=0.5$). No statistically significant differences were found between the groups for these values ($p>0.05$). Sedation onset time, duration of sedation, total propofol consumption, and MAS are presented in **Table 2**. Sedation onset time and duration were both significantly shorter in group A [2.1 ± 0.1 min, 3.1 ± 0.1 min, $p=0.00$; 10.9 ± 0.9 min, 12.5 ± 1.2 min, $p=0.00$ ] $p<0.05$. Time required for MAS to reach 5 was significantly shorter in group A [7.5.3 ± 0.7 min, 8.3 ± 0.7 min, $p=0.00$)] $p<0.05$. Time required for MAS to reach 10 was shorter in group K but this was not statistically significant [9.8 ± 0.4 min, 9.3 ± 0.8 min, $p=0.06$] $p>0.05$. Total propofol consumption was significantly less in group A [102.8 ± 8.8 mg, 128.6 ± 7.4, $p=0.00$)] ($p<0.05$).

The patient and physician satisfaction scores as well as the VPS scores at 5 and 10 minutes are presented in **Table 3**. No statistically significant difference between the 2 groups was found for any of these values [patient satisfaction score $p=0.1$, physician satisfaction score $p=0.2$, VPS at 5 min $p=0.09$, VPS at 10 min $p=0.09$] $p>0.05$). The incidence of side effects, such as hypotension ($p=0.08$), bradycardia ($p=0.1$), nausea ($p=0.09$), and vomiting ($p=0.15$) are presented in **Table 4**. Hypotension and bradycardia were observed more often in group A, while nausea and vomiting were observed more often in group K. However, these differences were not statistically significant ($p>0.05$).

**Discussion.** Some studies[3,9] suggest that endoscopy can be performed without sedation but this is not recommended, as the procedure is very uncomfortable for patients.Both propofol and alfentanil have a rapid onset of action so are useful agents for sedation. However, when alfentanil is used alone, respiratory depression can be seen. Some studies[5,6,9] suggest that, when propofol is used with alfentanil, less respiratory depression is seen. Ketamine is a drug with both analgesic and anesthetic properties. The analgesic properties arise from the fact that it non-competitively antagonizes N-methyl-D-aspartate receptors, which play a critical role in the generation of pain sensation.[10-12] Epidural and intravenous administration of ketamine has been shown to reduce postoperative analgesic requirements by 35-40%.[13-16] Adding propofol to ketamine reduces the incidence of dose-dependent adverse effects on the cardiovascular and respiratory systems.[10,11]

In studies performed by Türk et al[8], propofol was combined with ketamine and alfentanil for sedation in colonoscopy procedures. Between the 2 protocols, it was observed that the combination of propofol and ketamine resulted in a longer time to onset of sedation and a longer duration of action. When comparing ketamine alone with fentanyl alone, it was observed that ketamine's time to onset of sedation and duration of action were longer.[9] Sahin et al,[18] found that the recovery time for propofol/ketamine was longer than that for propofol/alfentanil.

In this study, we observed that the time to onset of sedation and duration of sedation were significantly longer in group K. The time required for MAS to reach 5 was greater in group K. However, there was no statistically significant difference between the groups in terms of time required for MAS to reach 10. The reason for the differences observed may be the fact that ketamine is a more effective anesthetic medication compared with alfentanil. Ketamine increases systolic arterial blood pressure and heart rate due to sympathetic stimulation.[19] It has been suggested that when propofol is added to ketamine, it reduces these effects by sympathetic neutralization and hemodynamic stabilization.[19-22] In this study, we observed similar hemodynamic stabilization. Owing to the cardio-depressive effects of both propofol and alfentanil, the combination of these drugs results in hemodynamic instability.[18] In the current study, we observed that systolic arterial blood pressure and heart rate values were lower in group A; however, these differences were not statistically significant. Similar results were reported in studies performed by Sultan[23] and Eberi et al.[24] The reason for the lack of a statistically significant difference in this study may be that fact that low doses of propofol and alfentanil were used, which may result in improved hemodynamic stability.

Two studies performed by Ho et al,[17] revealed that the combinations of alfentanil and ketamine with propofol were both effective in providing sedation and analgesia. However, the studies revealed the depressive effects of alfentanil on the respiratory system. Both the dosage of the drugs and the methods of administration in those studies differed from what were used this study. This emphasizes the importance of both the drug itself and its dosage in safe sedation and analgesia.

Patient and physician satisfaction scores were found to be high in both groups. This is an indication that the drug combinations result in comfortable, high-quality procedures.[18-20] Our VPS scores suggest that postoperative pain is better controlled by drug combinations than by single agent protocols.

A limitation of this study was that all patients were all MO, and as a result, their ASA physical status was high. Therefore, the drug dosages were different from those that might otherwise be used. The lung capacity of MO patients is diminished so SpO2 needs to be observed closely during UGSEMOP. Further studies are required to evaluate drug dosages and monitoring of hemodynamic parameters.

In conclusion, this study suggests that propofol/alfentanil and propofol/ketamine are both safe options for sedation in UGSEMOP. Propofol/alfentanil provides a better quality of sedation and results in less total propofol consumption compared with propofol/ketamine during UGSEMOP.

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## Ethical Consent

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.