PROPOFOL-KETAMINE COMBINATION HAS SHORTER RECOVERY TIMES WITH SIMILAR HEMODYNAMICS COMPARED TO PROPOFOL ALONE IN UPPER GASTROINTESTINAL ENDOSCOPY IN ADULTS. A RANDOMIZED TRIAL

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[Combinazione di propofol ketamina riduce i tempi di recupero in tutta l'emodinamica ed è sovrapponibile a quella di propofol alone in endoscopia gastrointestinale superiore negli adulti. Uno studio randomizzato]

ABSTRACT

Background and aim: Gastrointestinal endoscopy (GIE) is a common procedure for many gastrointestinal disorders. Propofol is a widely used agent with rapid onset of action in GIE, however it may cause cardiovascular and respiratory depression in a dose dependent manner. These untoward effects may be reduced/eliminated with addition of ketamine. In this study, we aimed to compare propofol vs. propofol-ketamine combination in respect of hemodynamics and recovery times for upper GIE sedation.

Material and method: This prospective randomized study was performed on 100 patients who underwent upper GIE intervention. Patients were randomized to propofol (n:50) (P) or propofol-ketamine (n: 50) (PK) groups. All patients received study drugs till Ramsay sedation scale of patients titrated to 3-4. The heart rate, mean arterial blood pressure and peripheral O2 saturation were recorded. Total drug dosage, endoscopy time, spontaneous eye opening and response to verbal command time, patient and doctor satisfaction scores were also recorded.

Results: Demographic data, hemodynamic data and endoscopy time were found similar in the two groups (p>0.05 for all comparisons). Spontaneous eye opening and response to verbal commands time were shorter in PK group (p=0.03, p=0.01 respectively). Heart rate, mean arterial pressure, peripheral oxygen saturation were similar between groups in all time intervals (p>0.05 for all comparisons). Side effects including respiratory depression, bradycardia, hypotension, nausea, vomiting and secretion increase were found to be similar in both groups (p>0.05 for all comparisons). Patients’ and endoscopists’ satisfaction scores were also similar in both groups (p>0.05 for all comparisons).

Conclusion: Propofol ketamine combination is associated with a shorter mean recovery time than propofol, with similar hemodynamic stability and satisfaction scores, without any important side effects in GIE interventions.

Key words: Propofol, ketamine, endoscopy gastrointestinal.

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Introduction

Gastrointestinal endoscopy (GIE) is a common procedure for diagnosis in many gastrointestinal disorders. Comfort of the patient is of great importance for GIE to be successfully completed. A significant number of the patients can not tolerate the procedure due to lack of appropriate sedation(1). The aim of the sedation is to reduce the anxiety and increase the comfort of the patient and application success. Many agents such as benzodiazepines, opioids and sedative-hypnotic drugs are used in order to increase the effectiveness of the procedure(2,3,4) but there is no generally accepted sedation protocols for this invasive technique. Ideal sedation agent should have quick induction and recovery times with minimal side effects. There is no agent that completely fulfills these ideal sedative agent properties thus, different kinds of agents are being used in combination to provide ideal sedation(5,6).

Propofol is a widely used agent in GIE processes due to its rapid action onset and fast recovery time unfortunately it could be a possible cardiovascular and respiratory depressive in a dose dependent manner(7). It might be inadequate to quell patients in painful processes since it lacks of analgesic properties. Ketamin is an agent that provides sedation, analgesia and amnesia. Although, it
is recognized as an effective and reliable anesthetic agent, cardiotoxicity and induction of transitory psychotic episodes, together with delayed recovery and secretion increment are the main drawbacks for ketamine use\textsuperscript{8, 9}.

These untoward effects of both anesthetics agent may be reduced or completely be eliminated with their combination\textsuperscript{10, 11}. Ketamine mitigates propofol-induced hypotension, and propofol mitigates ketamine-induced vomiting and recovery agitation. The drugs display synergic and possibly smoother sedation, and the combination has the theoretical profit of decreasing the propofol dose\textsuperscript{11}.

We hypothesized that propofol-ketamine combination would have favorable effects on hemodynamic parameters and recovery times compared to propofol alone with negligible side effect in patients undergoing upper GIE. Accordingly, the current study was designed to evaluate the effect of propofol and propofol-ketamine (3:1 combination) in patients undergoing upper GIE.

Materials and methods

Study population

A hundred patients who were scheduled for upper GIE were enrolled to the study after Institutional Ethics Committee approval and after written informed consent in this prospective, randomized study. The study project was performed in accordance with the most recent version of the Helsinki Declaration.

Exclusion criteria

The exclusion criteria for this study were:

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

Anesthesia and upper GIE administration

The study population was randomly assigned to receive propofol or propofol/ketamine (3:1 combination) (Fig.1). After 8 hours of starvation period before the procedure, peripheral intravenous access established with a 20G cannula and 6-8mL/kg/h crystalloid solition was started. No implement of sedation was used before the procedure. All patients were monitored for electro cardiography (ECG), non-invasive blood pressure (BP) and peripheral oxygen saturation (SpO2). 2 L min-1 O2 was administrated to all of the patients with a nasal cannula. The basal and 1st, 5th, 10th, 15th minute hemodynamic parameters were recorded.

Patients were randomized to propofol (P) and propofol-ketamine (PK) group with closed envelope method. P group received iv %1 propofol and PK group received iv propofol-ketamine 3:1 mixture (%1 15 ml propofol + 1 ml 50mg/ml ketamine+ 4 ml SF in a 20-ml syringe which resulted in 0.25 mg.ml-1 ketamine and 0.75 mg.ml-1 propofol) until Ramsay Sedation Scale (RSS) increased to 3-4. Supplementary study drug was added (iv. 0.5-1 mg.kg-1) in case of need. Probable side effects such as nausea, vomiting, bradycardia, hypotension, respiratory depression, and secretion increase were also recorded.

Patients’ and the endoscopists’ satisfaction score were recorded evaluating the overall score out of 4 (1=perfect, 2= good, 3=moderate, 4=bad) (Table 1).

<table>
<thead>
<tr>
<th>Patient satisfaction</th>
<th>Excellent</th>
<th>Good</th>
<th>Fairly well</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopist’s evaluation</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 1: Patients’ and the endoscopists’ satisfaction score in propofol and propofol-ketamine group.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 11.5 (SPSS, Chicago, IL, 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 hemo-
dynamic data and recovery parameters were evaluated using student t test. Side effects among groups were evaluated using the Chi-square test. A two tailed p value of 0.05 was considered to be statistically significant.

The results were expressed as mean ± SD. Power calculations based on a pilot study with 12 patients to detect a significant difference in the spontaneous eye opening time (a = 0.05, power = 0.80) indicated that 48 patients were needed in each group. We decided to enroll 50 patients in each group.

**Results**

Demographic characteristics such as age, height, weight, gender, ASA and associated diseases are shown in Table 2. No significant difference was found between groups in regard to these characteristics (p>0.05).

![Fig. 2: Heart rate (HR) bpm beat per minute in propofol and propofol-ketamine group.](image)

**Table 2:** Demographic and clinical data of propofol and propofol-ketamine group.

<table>
<thead>
<tr>
<th></th>
<th>Group P (n = 50) Mean±SD</th>
<th>Group PK (n = 50) Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35.16±7.95</td>
<td>35.03±7.78</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.16±7.12</td>
<td>167.16±5.78</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.33±12.75</td>
<td>73.70±10.91</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>26/24</td>
<td>28/22</td>
</tr>
<tr>
<td>ASA I / II</td>
<td>16/34</td>
<td>18 /32</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>21</td>
<td>16</td>
</tr>
</tbody>
</table>

HR, MAP and SpO2 are summarized in Fig 2, Fig 3, Fig 4 respectively. There were no significant differences among groups in HR, MAP and SpO2 at basal, 1st, 5th, 10th and 15th minute values. (p>0.05, for all comparisons, Fig 2, Fig 3, Fig 4.)

![Fig. 3: Mean arterial pressure (MAP) in propofol and propofol-ketamine group.](image)

![Fig. 4: Peripheral oxygen saturation (SpO2) in propofol and propofol-ketamine group.](image)

Endoscopy time, spontaneous eye opening and obeying command time have been reported in Table 3. Endoscopy time were found to be similar in both groups, but spontaneous eye opening (10.3±3.6 min., 7.26±6.8 min.), and obeying command time were found to be statistically significant decreased in PK group (5.03 min.±1.6, 3.63±2.5 min.) (p=0.03, p=0.01 respectively).

<table>
<thead>
<tr>
<th></th>
<th>Group P (n = 50) Mean±SD</th>
<th>Group PK (n = 50) Mean±SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure time (s)</td>
<td>360.30±66.5</td>
<td>331.06±57.6</td>
<td>0.074</td>
</tr>
<tr>
<td>Obey commands (s)</td>
<td>5.03 ± 1.6</td>
<td>3.63±2.5</td>
<td>0.01*</td>
</tr>
<tr>
<td>Spontaneous open eyes (s)</td>
<td>10.30±3.6</td>
<td>7.26±6.8</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

**Table 3** Mean procedure time and recovery times of propofol and propofol-ketamine group.

Side effects are shown in Table 4. There were no significant difference among groups in regard to side effects (p>0.05 for all comparisons). Patients’ and endoscopists’ satisfaction scores have been reported in Table 5. There were no significant difference among groups in regard to satisfaction scores (p>0.05). Mean total drug dosages for P and PK groups were, respectively: 92 ± 10 mg propofol and 72 ± 12 mg propofol plus 24 ± 4 mg ketamine.
Discussion

With the present study, we have tested the hypothesis that propofol-ketamine mixture would have favorable effect(s) on hemodynamic parameters and recovery times compared to propofol alone in upper GIE anesthesia. We have shown that: (1) propofol-ketamine mixture have shorter recovery time compared to propofol alone, (2) both groups have similar hemodynamic effects, (3) similar side effect profile and (4) similar patients’ and endoscopists’ satisfaction scores.

Ideal drug for sedo-analgesy should have rapid action onset, rapid half-life and fast recovery time. However, there is no consensus on the best sedo-analgesy procedure (2). There were evidences that point out propofol is a secure and effective agent for GIE procedures (15). It has been shown that propofol provides enhanced degree of sedation with rapid action onset, faster discharging time, improved cooperation of the patient and a faster recovery time with increased application quality when compared with traditional procedures (16-18). On the other hand when administrated alone in GIE, without any combination propofol requires to be used in large amounts and might cause high degree of sedation (13). Previous studies have shown that use of propofol with other agents (meperidine, fentanyl, midazolam esc.) in GIE procedures results in reduction of complications with shorter recovery time and better patient cooperation and satisfaction (19,20) and it is concluded that combination of propofol with other agents might be preferred to propofol alone (21).

Ketamine, an NMDA receptor antagonist, is also a significant anesthetic agent. Cardiotoxicity and induction of psychotic episodes, and delayed recovery, are the main disadvantages for ketamine (8,9,22). Combination of ketamine with various sedative agents to reduce these side effects came into question and benzodiazepines and propofol are widely used for this purpose (23).

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 (24), interventional radiology (25), sedation for spinal anesthesia (26), gynecological (27) and ophthalmological procedures (28). Propofol-ketamine combination has also been effectively studied outside the operating room. When compared to a propofol–fentanyl combination, a combination of propofol–ketamine for deep sedation for burns dressings on the ward, was associated with fewer episodes of restlessness (29) and the 1:1 mixture in titrated bolus doses in the emergency department was proved to be an effective regimen (30). Furthermore, it was pointed-out that propofol-ketamine combination effectively produced deep sedation for prolonged pediatric orthopedic procedures (31). However, there is a limited number of studies concerning the use of propofol-ketamine in upper GIE anesthesia (32). Tosun et al. reported that there were no differences in propofol-ketamine and propofol-fentanyl group with respect to the endoscopist’s rating and recovery time in upper GIE of pediatric population (33). Our study was the first study evaluating the effect of propofol-ketamine combination vs. propofol in adult upper GIE.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Group P (n = 50)</th>
<th>Group PK (n = 50)</th>
<th>Chi-square, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting (n)</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Bradycardia (n)</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Hypotension (n)</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory depression (n)</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Secretion increase (n)</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 4: Side effects in propofol and propofol-ketamine group.

<table>
<thead>
<tr>
<th></th>
<th>Group P (n = 50)</th>
<th>Group PK (n = 50)</th>
<th>Chi-square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient satisfaction score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>33 (66%)</td>
<td>41 (82%)</td>
<td>NS</td>
</tr>
<tr>
<td>Good</td>
<td>17 (34%)</td>
<td>9 (18%)</td>
<td>NS</td>
</tr>
<tr>
<td>Endoscopist’s satisfaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>41 (82%)</td>
<td>46 (92%)</td>
<td>NS</td>
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<tr>
<td>Good</td>
<td>9 (18%)</td>
<td>4 (8%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 5: Patient and Endoscopist’s satisfaction score of propofol and propofol-ketamine group.
Some studies established synergism between ketamine and propofol. Ketamine is known to be an angesic in subdissociative doses, and when used in combination with propofol, it has been shown to diminish propofol expenditure and protect hemodynamic stability \(^{(33)}\). 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 contrast, the rational for combining ketamine and propofol in a permanent proportion would be questioned for reasons of the conflicting mechanisms of action of the two drugs and the dissimilarity in their durations of action \(^{(44)}\). Some authors argued that it is not realistic to administer two drugs and expect the sole adverse effects of each when monotherapy works just as well and presents only one set of potential adverse events.

In this study, hemodynamic data of the groups found to be similar and the mean recovery times of propofol-ketamine sedation were found to be shorter than propofol alone. These data suggest that the use of ketamine and propofol in combination might be beneficial for hemodynamic stability while lessening recovery time by reducing the total amount of propofol.

In conclusion, the propofol-ketamine 3:1 mixture is associated with shorter mean recovery times than propofol alone, with similar hemodynamic stability without any important side effects in upper GIE anesthesia.

References


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