**Abstract**

**Aim:** The purpose of this randomized double-blinded study is to compare the safety and efficacy of two different concentrations of ketofol on the intraoperative hemodynamics, respiration, bispectral index values and post-anesthesia recovery profiles in morbid obese patients undergoing upper GI endoscopy.

**Subjects and methods:** Patients were randomly allocated into two groups, group I (k/p 1/2), no = 50, and group II (k/p 1/4), no = 50, after receiving ethics committee approval and informed patient’s consent. Patients in group I received bolus dose of ketamine 0.5 mg/kg + propofol 1 mg/kg, and group II received ketamine 0.25 mg/kg + propofol 1 mg/kg, intravenously in separate syringes (dosed ketamine then propofol). Incremental doses, half the first dose of propofol (0.5 mg/kg) were given to get the desired depth of sedation, modified by aiming at bispectral index (BIS) values between 70–80, and when the sedation was considered as inadequate by the endoscopist. The baseline measurements were obtained just before the administration of the study drugs. The primary outcome was emergence reactions (recovery agitation or hallucination) following the procedure.

**Results:** There was no significant difference between group I (k/p 1/2) and group II (k/p 1/4) as regard to demographic data (age, gender and BMI) and procedure duration. Discharge time from postanesthesia care unit (PACU) was prolonged in group I (Mean±SD = 38.34±4.28) compared to group II (Mean±SD = 33.11±4.89), p = 0.0001. The number of patients requiring propofol top-up doses was 20 (40%) in group I compared to 35 (70%) in group II (the low-dose ketamine group), p = 0.004. There was a significant difference in the mean propofol top-up dose between the two groups (30±15 mg in group I and 41±13 mg in group II, p = 0.0002). No significant difference between both groups as regard to BIS values and VAS pain score.

**Conclusion:** The use of ketamine and propofol combination for upper GI endoscopy in morbid obese patients appears to be safe, effective and preserve the hemodynamic and respiratory parameters.

**Introduction**

Procedural sedation and analgesia refers to the technique of administering sedatives or dissociative agents with or without analgesics to induce an altered state of consciousness that allows the patient to tolerate painful or unpleasant procedures while preserving cardiorespiratory Function [1]. The aim of PSA is mainly to provide sedation, anxiolysis, analgesia and thereby enhances patient cooperation throughout the procedure. It is important to keep in mind that, the level of sedation can easily and quickly passed from conscious to deep sedation and result in loss of protective reflexes and in problems related to airway control [2]. Agents reported to achieve PSA includes midazolam, ketamine, propofol, fentanyl, remifentanil and dexmedetomidine [3]. The use of ketamine and propofol for procedural sedation and analgesia external to the surgical environment has grown in popularity [4]. Sedative drug selection and the dose depend on the patient’s emotional state, the intensity of pain during the examination, anticipated technical difficulties, surgeon’s experience and hospital-specific policy and procedures. An ideal sedation regimen would provide patient comfort, cooperation, hemodynamic stability, amnesia and maintenance of a patent airway with spontaneous ventilation [5]. Propofol has become a preferred sedative because it offers advantages over benzodiazepines in terms of lack of accumulation, quick onset, easy adjustment, and fast recovery after discontinuation. It has sedative and hypnotic effects that mediate the GABA receptor but has no analgesic action. Adverse effects associated with propofol included pain on injection, hypotension, bradycardia, respiratory depression,
Measurement that gives objective information about the depth
bispectral index (BIS). While clinical estimation of sedation
can be assessed clinically or with devices such as the
antagonized by the arousal effects of ketamine. The level of
and arousal and sedative effects of propofol may be partially
that small-dose ketamine increases thalamic sensory output
than either drug alone [14]. Mortero et al. 2001 [15], suggested
may minimize the need for supplemental opioid analgesics and
[13]. Furthermore, the combination of propofol and ketamine
kg [12], and minimal with ketamine doses less than 1 mg/kg
[11]. Respiratory problems are the most common adverse events
associated with propofol use. However, significant respiratory
depression is unlikely at propofol bolus doses less than 0.7 mg/
kg [12], and minimal with ketamine doses less than 1 mg/kg
[13]. Furthermore, the combination of propofol and ketamine
may minimize the need for supplemental opioid analgesics and
has the potential to provide better sedation with less toxicity
than either drug alone [14]. Mortero et al. 2001 [15], suggested
that small-dose ketamine increases thalamic sensory output
and arousal and sedative effects of propofol may be partially
antagonized by the arousal effects of ketamine. The level of
sedation can be assessed clinically or with devices such as the
bispectral index (BIS). While clinical estimation of sedation is
difficult, the BIS is a processed electroencephalographic
measurement that gives objective information about the depth
of sedation and anesthesia [16].

Aim of the Study

The purpose of this randomized double–blinded study was to
compare the safety and efficacy of two different concentrations
of ketofol on the intraoperative hemodynamic and respiratory
parameters, BIS values and post–anesthesia recovery profiles
in morbid obese patients undergoing upper GI endoscopy. The
study hypothesis is that the safety and efficacy of performing
sedation with ketofol concentration of (1:4) in morbid obese
patients is identical to ketofol concentration of (1:2) with the
advantage of less postoperative ketamine side effects.

Subjects and Methods

This study included 100 morbid obese adult subjects,
scheduled for upper GI endoscopy performed under topical
anesthesia with intravenous sedation, during the period from
October, 2015 to July, 2016. Patients selected were classified as
American Society of Anesthesiologists (ASA) physical status I
and II, aged from 18 to 50 years with a Glasgow Coma Scale
score 15. Patients were randomly allocated to two groups,
group I (k/p1/2), no = 50, and group II (k/p1/4), no = 50, after
receiving ethics committee approval and informed consent
from patients. All procedures were performed by the same
physician.

Exclusion criteria

ASA more than II, pregnant women, patients with drug
abuse or had allergy to egg, hypersensitivity to ketamine or
propofol, those who had severe bradycardia or any type of
atrioventricular block, heart failure or refused to participate in
the study.

In the operating room, patients were breathing
spontaneously. Nasal oxygen (3 L/min) was administered
and intravenous access was established. Standard monitoring
(Infinity Delta Monitor, Drager Medical System En, USA) was
used. Heart rate (HR) via ECG, non invasive mean arterial
pressure (MAP), pulse oximetry (SpO2), were attached. During
the procedure, the BIS Sensor (A–2000XP™, Aspect Medical
System) was used to assess the level of sedation. The BIS
values, hemodynamics and respiratory parameters (HR, MAP
and SpO2) were continuously monitored and recorded at the
baseline and then every 5 min thereafter during the procedure
and in the post anesthesia care unit (PACU). The baseline
measurements were obtained just before the administration
of the study drugs. Then, these parameters were compared
between the two groups at 5 time points; before induction
(at baseline), after induction of sedation (after induction), 5
minutes after induction (during procedure), after 15 minutes
from admission to post anesthesia care unit (at PACU), and
lastly post–procedure at 90 min after the original baseline
measurement where postoperative visit was undertaken (at 90
min). The primary outcome was emergence reactions following
the procedure. Secondary outcomes included hemodynamics,
respiratory profiles, sedation, analgesia, side effects,
supplemental propofol and patient as well as endoscopist
satisfaction.

All patients were premedicated with ondansetron 0.1 mg/kg,
and glycopyrrolate 4 mcg/kg intravenously before induction.
Midazolam 0.02 mg/kg was given as premedication. Fentanyl
0.5 mcg/kg was given IV to patients in both groups before the
start of endoscopy together with lidocaine local anesthetic
spray and ointment. The upper GI endoscope was commenced
after 30 seconds from injection of ketofol. Patients in the group
I received bolus dose of ketamine 0.5 mg/kg + propofol 1 mg/
kg (k/p 1/2), and group II received ketamine 0.25 mg/kg +
propofol 1 mg/kg (k/p 1/4) intravenously in separate syringes
(separate syringe strategy). Incremental doses, half the initial
dose of propofol (0.5 mg/kg) were given to get the desired
depth of sedation, modified by aiming at BIS values between
70–80 [17], and when the sedation was judged as inadequate by
the endoscopist. A ketamine and propofol dose was prepared by
an assistant who was not involved in the clinical management
of the study patients.

The patients in the PACU were assessed with the fast–
track score. Total score of 14, with minimal score of 12
would be required, with no score below 1 in any individual category
[18]. Each patient was informed about how to measure pain
intensity on a VAS pain score subjectively using a VAS ruler
0–10, with 0 representing “no pain” and 10 “the worst pain”
imaginable. During postoperative visit, satisfaction score

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was assessed and any adverse events were recorded as pain, nausea, vomiting, shivering, emergence reactions (agitation or hallucination), visual disturbances, myoclonus, seizure, rash, any hypoxic episode or apnea (desaturation was defined as a 10% decrease in peripheral oxygen saturation when compared to baseline, and apnea was defined as cessation of respiration for 15 seconds or more.), any episodes of hypotension (decrease in MAP > 30% of baseline) or bradycardia (decrease in HR > 30% of the initial rate or HR < 55/min). Surgeons and patients were asked to grade their overall satisfaction with sedation technique using a 3 point scale [poor (1), fair (2), and good (3)]. The patients were discharged home with Aldrete’s scores greater than 9 [19].

Statistical analysis

The collected data were statistically analyzed using SPSS version 16.0 (SPSS Inc., USA) for Windows (Microsoft Co., USA). Data were expressed as mean values ± SD or as number and percentages. Fisher’s exact, Student’s t and χ2 tests were used for comparison of the quantitative and qualitative values of the two groups. P < 0.05 was considered statistically significant.

Results

This randomized double-blind study was conducted during a 10-month period in which 100 morbid obese patients had PSA with ketofol. All patients underwent their planned upper GI endoscopy and received their allocated study drug.

The general characteristics of studied cases and operative data were represented in Table 1. This Table shows that, there was no significant difference between group I (k/p 1/2) and group II (k/p 1/4) as regard to demographic data (age, gender and BMI) and procedure duration. However, discharge time from PACU was prolonged in group I (Mean±SD = 38.34±4.28) compared to group II (Mean±SD = 33.11±4.89), p = 0.0001. The number of patients requiring propofol top–up doses was 20 (40%) in group I compared to 35 (70%) in group II (the difference in the mean propofol top-up dose between the two groups was statistically insignificant (p = 0.0002) as shown in Table 1. Heart rate increased after induction of sedation in both groups. The difference between the groups was statistically insignificant (p = 0.267). The change was least in group II (due to low ketamine dose), but no patient had severe tachycardia requiring treatment in both groups. There was a minimal decrease in MAP from baseline in both groups following the initial dose of ketofol. Heart rate and MAP decreased during procedure in group II compared to group I but this decrease is considered to be not quite statistically significant (p = 0.077 and 0.076 respectively). No significant differences in SpO2 between the two groups (Table 2, Figure 1-3). No cases needed manual ventilation or artificial airway. Overall, cardiovascular and respiratory adverse events were not significantly different between the two groups. These adverse events were transient and easily treated with no sequelae. There were no significant differences between both groups as regard to BIS values and VAS pain score (Table 3). Table (4) shows that there is no significant difference between the two groups regarding patient as well as surgeon satisfaction. Side effects are listed in (Table 5, Figure

Table 1: Demographic and operative data. Data expressed as Mean (±SD) or number (percent).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I</th>
<th>Group II</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (ys)</td>
<td>30.35±7.33</td>
<td>32.17±7.56</td>
<td>0.224(NS)</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>24/26</td>
<td>22/28</td>
<td>0.841(NS)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>39.44±2.34</td>
<td>38.78±3.23</td>
<td>0.244(NS)</td>
</tr>
<tr>
<td>Procedure duration (min)</td>
<td>19.38±13.13</td>
<td>20.11±5.62</td>
<td>0.204(NS)</td>
</tr>
<tr>
<td>Discharge time from PACU (min)</td>
<td>38.34±4.28</td>
<td>33.11±4.89</td>
<td>0.0001</td>
</tr>
<tr>
<td>Patients requiring top-up doses (No)</td>
<td>20 (40%)</td>
<td>35 (70%)</td>
<td>0.0046</td>
</tr>
<tr>
<td>Mean propofol top-up dose (mg)</td>
<td>30±15</td>
<td>41±13</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

BMI = Body Mass Index. PACU = Post Anesthesia Care Unit.

Table 2: Hemodynamic and respiratory parameters. Data expressed as Mean ±SD.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I Mean (±SD)</th>
<th>Group II Mean (±SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>At baseline 105.02± 5.70</td>
<td>103.96±6.21</td>
<td>0.376(NS)</td>
</tr>
<tr>
<td></td>
<td>At induction 98.00± 5.18</td>
<td>97.81±2.16</td>
<td>0.318(NS)</td>
</tr>
<tr>
<td></td>
<td>During procedure 73.04± 4.34</td>
<td>71.54±4.07</td>
<td>0.077*</td>
</tr>
<tr>
<td>MAP</td>
<td>At baseline 74.89±4.69</td>
<td>75.00±4.12</td>
<td>0.901(NS)</td>
</tr>
<tr>
<td></td>
<td>After induction 68.02±5.58</td>
<td>68.89±4.49</td>
<td>0.067(NS)</td>
</tr>
<tr>
<td></td>
<td>During procedure 70.00±2.39</td>
<td>71.58±5.32</td>
<td>0.076*</td>
</tr>
<tr>
<td>SpO2</td>
<td>At baseline 97.35±2.42</td>
<td>97.81±2.16</td>
<td>0.318(NS)</td>
</tr>
<tr>
<td></td>
<td>After induction 97.10±2.89</td>
<td>96.88±2.96</td>
<td>0.070(NS)</td>
</tr>
<tr>
<td></td>
<td>During procedure 97.76±2.12</td>
<td>97.58±2.32</td>
<td>0.686(NS)</td>
</tr>
<tr>
<td></td>
<td>At PACU 98.22±1.79</td>
<td>98.01±1.88</td>
<td>0.568(NS)</td>
</tr>
<tr>
<td></td>
<td>At 90 min 98.12±1.95</td>
<td>98.00±1.81</td>
<td>0.750(NS)</td>
</tr>
</tbody>
</table>


Figure 1: Heart rate before, during and after procedure. Data expressed as Mean ±SD.

Figure 2: Oximetry before, during and after procedure. Data expressed as Mean ±SD.

4. The most common side effect was visual disturbances. No difference in the occurrence of PONV between the two groups. Agitation on recovery, although not statistically significant (p value = 0.111); was more commonly reported with group I
(6 patients, two of them treated with midazolam 0.02 mg/kg intravenously with prompt resolution of the event) compared to the low-dose ketamine group (group II) in which only one patient developed recovery agitation and needs no treatment. Two patients (4%) in group I and no patient (0%) in group II experienced bad dreams and hallucinations. Side effects such as myoclonus, seizure and rash were not observed in any patient.

Discussion

Our study compared the safety and efficacy of two different ketofol (k/p 1/2 and k/p 1/4) concentrations given for upper GI endoscopy in morbid obese patients. It was intended to generate the hypothesis that the combination of ketamine and propofol was safe and effective for PSA in morbid obese patients. Our results demonstrated that the low-dose ketamine with propofol appear to be safe and effective, preserved the hemodynamic and respiratory parameters without prolonging recovery or increasing the incidence of adverse events. The most common side effect was visual disturbances. Agitation on recovery was less commonly reported with the low-dose ketamine group (group II).

Several studies had been published and demonstrated that the combination of ketamine and propofol for sedation is safe and effective. Consistent with our results, Ayatollahi et al. [20], conducted a study on 100 patients who underwent closed reduction of nose. The patients were divided into 2 groups of 50, and received either a combination of ketamine/propofol (1:1) or ketamine/propofol (1:3). There was a reduction in hallucination, vomiting, and recovery duration in the group that received lower concentration of ketamine.

Miner et al. [21], performed a randomized, double-blinded trial in which two hundred seventy-one adults in emergency...
The results conducted that ketofol was effective and safe for sedation in the endobronchial ultrasound-guided needle aspiration procedure. The comparator intravenous propofol doses ranged from 0.5 to 1 mg/kg, with propofol 0.75 mg/kg. The comparator intravenous propofol doses ranged from 0.5 to 1.5 mg/kg. The primary outcome was adequacy of sedation measured using the bispectral index scale. The propofol-ketamine group presented less of a difference in BIS between baseline and goal sedation. The authors recommended that adequate sedation with the combination of propofol and ketamine was completed without the need for deep sedation compared with the propofol alone. Safety outcomes revealed significantly less reduction in blood pressure in the propofol-ketamine group. Neither group experienced respiratory depression or a significant difference in length of sedation.

Phillips et al. [29], compared ketamine and propofol with propofol alone in 28 patients underwent procedural sedation in the emergency department. The intravenous ketamine doses ranged from 0.5 to 1 mg/kg, with propofol 0.75 mg/kg. The comparator intravenous propofol doses ranged from 0.5 to 1.5 mg/kg. The primary outcome was adequacy of sedation measured using the bispectral index scale. The propofol-ketamine group presented less of a difference in BIS between baseline and goal sedation. The authors recommended that adequate sedation with the combination of propofol and ketamine was completed without the need for deep sedation compared with the propofol alone. Safety outcomes revealed significantly less reduction in blood pressure in the propofol-ketamine group. Neither group experienced respiratory depression or a significant difference in length of sedation.

Akin et al. [30], published a trial on 60 patients between one month and 13 years of age undergoing cardiac catheterization who received sedation with propofol or propofol plus ketamine (3:1). They found a significant decrease in MAP in 11 patients in the propofol monotherapy group and three patients in the ketofol group. They concluded that the addition of low-dose ketamine to propofol preserved MAP and reduced the risk of respiratory depression, without prolonging recovery or increasing the incidence of adverse events.

The same authors, Akin and colleagues [31], in a trial of 40 adult patients undergoing endometrial biopsy, reported that the combination of propofol 1 mg/kg plus fentanyl 1 mcg/kg was compared to the combination of propofol plus ketamine 2:1. Time to recovery was similar. However time to discharge was longer in the ketofol group secondary to the increased presence of adverse events including nausea, vertigo, and

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visual disturbances. These authors concluded that although both regimens seem safe, ketofol 2:1 had more adverse events leading to a longer time until discharge and had a lower overall patient satisfaction.

Goh et al. [32], published a 90 patients having a laryngeal mask airway (LMA) placed received propofol with either ketofol 1:5, fentanyl 1 mcg/kg, or placebo normal saline. They found the ketofol group had a significantly higher systolic blood pressure than the other two groups. They concluded that ketofol provided equivalent LMA insertion conditions while maximizing hemodynamics and minimizing apnea.

Furuya et al. [33], suggested that the minimal change observed in arterial pressure may be dose related and also because sympathomimetic actions of ketamine were effective in counteracting the hemodynamic depression of propofol. The heart rate increased after induction in all the groups, but there was no occurrence of profound tachycardia in any group.

Badrinath et al. [34], published 100 female outpatients undergoing breast biopsy procedures under local anesthesia received an infusion of a solution containing propofol in combination with different doses of ketamine. The sedative infusion rate was varied to maintain a deep level of sedation and normal respiratory and hemodynamic functions. They reported that the concentration of ketamine/propofol 1:5 provides effective sedation and analgesia during monitored anesthesia care. The overall incidence of clinically significant psychotomimetic effects was small (8-16%), and occurred predominantly in the large dose ketamine group.

Friedberg [35], in a prospective study of 1,264 patients undergoing procedural sedation and analgesia for surgical procedures with ketamine and propofol, concluded that this combination was safe and effective.

Limitations

1. Our reliance on oxygen saturation instead of capnography may have led to underreporting of respiratory depression.

2. Although this study did not directly compare the study drugs with other known PSA regimens, we believe that the ketamine/propofol combination could be superior to opioids and benzodiazepines for PSA in morbid obese patients.

3. A larger sample volume might have changed those results that did not reach statistical significance.

Conclusion

Both concentrations of ketofol (1:2) and (1:4) are safe and useful techniques for procedural sedation and analgesia in morbid obese patients. The low-dose ketamine combination (1:4) minimizes the psychological side effects and shortens the time to discharge.

References


