PROPOFOL-KETAMINE COMBINATION HAS FA VORABLE IMPACT ON ORIENTATION TIMES AND PAIN SCORES COMPARED TO PROPOFOL IN DILATATION AND CURETTAGE. A RANDOMIZED TRIAL

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ABSTRACT

Background and aim: Dilatation and curettage (D&C) is a common procedure that generally causes considerable pain. Propofol is a widely used agent with rapid onset of action in D&C, 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. ketamine-propofol combination in respect of hemodynamics and recovery times for D&C sedation.

Material and method: This prospective randomized study was performed on 152 patients who underwent D&C procedure. Patients were randomized to propofol (n:76) (P) and propofol-ketamine (n: 76) (KP) groups. The heart rate, mean systolic and diastolic arterial blood pressures and peripheral oxygen saturation were recorded. Orientation time, patients’ and surgeons’ satisfaction scores were also recorded.

Results: Demographic data were found similar in two groups (p>0.05 for all comparisons). There were no significant differences in heart rate, systolic and diastolic arterial blood pressures were not statistically significant in all time intervals among groups (p>0.05, for all comparisons). Orientation time was statistically significant increased in Group P compared to Group KP (p<0.001). Aldrete score at 5th min was statistically decreased in Group P compared to Group KP and VAS scores at 5th and 10th min were statistically increased in Group P compared to Group KP (p<0.001 for both comparison). There were no significant difference among groups in regard to satisfaction scores (p>0.05).

Conclusion: Ketamine-propofol combination is associated with a shorter mean orientation time than propofol, with similar hemodynamic stability and satisfaction scores, without any important side effects in D&C procedure.

Key words: Dilatation and curettage, propofol, ketamine .

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Introduction

Dilatation and curettage (D&C) is a short-lasting procedure that generally causes significant pain due to cervical dilatation with dilators and tissue extraction. Comfort of the patient and avoidance of movement is of great significance during D&C to be effectively completed. Ideal sedation agent should have rapid induction and recovery times with minimum side effects. There is no agent that totally fulfills these ideal sedative agent properties thus, different kinds of agents are being used in combination to provide ideal sedation.

Propofol is a widely used agent in different sedation settings due to its rapid action onset and fast recovery time unfortunately it could be a possible cardiovascular and respiratory depressant in a dose dependent manner, also it might be insufficient in painful processes since it lacks of analgesic properties. Ketamine is an agent that provides sedation, analgesia and amnesia and it might be an appropriate option for short-lasting procedures. Cardiototoxicity and induction of transitory psychotic episodes, together with delayed recovery and secretion increment are the main drawbacks of ketamine.
These unpleasant effects of both anesthetic drugs may be reduced, or completely be eliminated, with their combination\cite{8,9}. Ketamine mitigates propofol-induced hypotension, and propofol mitigates ketamine-induced vomiting and recovery agitation.

We hypothesized that ketamine-propofol combination would have favorable effects on orientation times and pain scores compared to propofol alone with negligible side effects in patients undergoing D&C. Accordingly, the current study was designed to evaluate the effect of propofol alone versus propofol-ketamine (1:1 combination) sedation in patients undergoing D&C.

**Materials and methods**

**Study population**

A hundred and fifty two patients who were scheduled for D&C were enrolled in this prospective, randomized study after approval by Institutional Ethics Committee and after written informed consent was obtained (Fig.1). The study project was performed in accordance with the most recent version of the Helsinki Declaration.

**Exclusion criteria**

Exclusion criteria were\cite{10} Patients with pulmonary, hepatorenal, neuromuscular, and neuropsychiatric disease\cite{11} body mass index over 30 kg/m2,\cite{12} usage of sedative drugs or substance abuse\cite{13} emergency curettage for massive bleeding or hemodynamic instability.

**Anesthesia and D&C procedure**

Before anesthetic induction, standard monitoring including electrocardiogram, pulse oximetry, and noninvasive blood pressure monitoring was applied to all patients in the operating room. Lactated Ringer’s solution was infused at a rate of 5 ml/kg. Patients were randomly assigned to propofol (Group P) or ketamine-propofol group (Group KP) with sealed envelope technique. Patients were pre-oxygenated with 100% oxygen for 3 min, just before anesthesia induction. Both groups received 0.15 μg/kg/min remifentanil infusion. Propofol (10 mg/ml), or ketamine-propofol (1:1 mixture of ketamine 10 mg/ml and propofol 10 mg/ml mixed in a 20-ml syringe) was administered slowly (20 mg/10 s) until the patient no longer responded to her name being called loudly and showed loss of the eyelash reflex. Additional propofol or ketamine-propofol combination were given in 10-mg increments if the responsiveness to verbal command had not been lost within 60 s after drug administration in each group. The required total dose of propofol or ketofol was recorded.

During the D&C, an additional propofol or ketamine-propofol bolus of 10 mg was given if any of the following signs were detected: heart rate (HR) >15% above preoperative baseline or >90 beats/min; systolic arterial pressure (SAP) >15% above preoperative baseline; extremity or body movement. Administration was repeated after 1 min if necessary.

Blood pressure, HR, and oxygen saturation were recorded at baseline, 1st, 3rd, 5th, 10th, 15th min. Adverse events such as hypotension (mean arterial pressure <30% pre-induction baseline value, SAP <80 mmHg), or bradycardia (HR<50 beats/min) were also registered and were treated with IV ephedrine 5-10 mg or atropine 0.5 mg, respectively. A modified Aldrete scoring system was used to evaluate recovery of patients\cite{10} and a visual analog scale (VAS) was used to evaluate pain intensity, with 0 indicating absence of pain and 10 indicating the worst probable pain at 5 and 10 min postoperatively. Intravenous tenoxicam 20 mg was used as a rescue analgesic, but none of the patients needed it. Side effects including nausea and vomiting, respiratory depression and increase in secretion were recorded.

The total dose of propofol and ketamine-propofol combination were recorded, as well as duration of surgical procedure, and orientation time (from the end of procedure until able to recall name and date of birth). Patients’ and the endoscopists’ satisfaction score were recorded evaluating the overall score out of 4 (Table 1).
The primary endpoint was defined as orientation time, and the secondary endpoints were defined as VAS and Aldrete and satisfaction scores.

**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 hemodynamic data, recovery parameters, pain scores were evaluated using student t test. Side effects and satisfaction scores 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 20 patients to detect a significant difference in orientation time (alpha = 0.05, power = 0.80) indicated that 150 patients were needed.

**Results**

Demographic characteristics including age, height, weight, gender, ASA (American Society of Anesthesiologists) scores and associated diseases are shown in Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Group P (n = 76)</th>
<th>Group KP (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>37.03±8.09</td>
<td>36.6±7.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.81±6.8</td>
<td>170.26±5.49</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.1±12.45</td>
<td>78.72±10.58</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>ASA I/II</td>
<td>34 / 42</td>
<td>29 / 47</td>
</tr>
<tr>
<td>Procedure time (s)</td>
<td>477.15±67.1</td>
<td>463.42±73.78</td>
</tr>
</tbody>
</table>

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

There were no significant difference among groups (p>0.05, for all comparisons).

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

Orientation time, Aldrete scores at 5th, 10th min and VAS scores at 5th, 10th min are shown in Table 3. Orientation time was statistically significant increased in Group P compared to Group KP (3.12 ± 0.84 min vs. 2.31±0.62 min. respectively, p<0.00, Table 3). Aldrete score at 5th min was statistically decreased in Group P compared to Group KP (p<0.001, Table 3) and VAS scores at 5th and 10th min were statistically increased in Group P compared to Group KP (p<0.001 for both comparison, Table 3).

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). Surgeons’ and patients’ satisfaction scores were shown 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: 142± 24 mg propofol and 63± 25 mg propofol plus 63±25 mg ketamine.

<table>
<thead>
<tr>
<th></th>
<th>Group P (n = 76)</th>
<th>Group KP (n = 76)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation time(min)</td>
<td>3.12 ± 0.84</td>
<td>2.31±0.62</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aldrete 5th min</td>
<td>8(7-10)</td>
<td>9 (7-10)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aldrete 10th min</td>
<td>9(9-10)</td>
<td>9(8-10)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>VAS 5th min</td>
<td>5(4-7)</td>
<td>5(4-6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VAS 10th min</td>
<td>4(2-5)</td>
<td>3(3-5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Table 3: Mean orientation time and Aldrete and VAS scores of groups at 5th and 10th minutes.

Data are means ± SD, or median (range).

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

Side effects among groups were evaluated using the Chi-square test

n: number
NS: not significant

Table 5: Patient and Surgeon’s satisfaction score of propofol and ketamine-propofol group.

Satisfaction scores among groups were evaluated using the Chi-square test

n: number

Discussion

With the present study, we have tested the hypothesis that propofol-ketamine mixture would have favorable effect(s) on hemodynamic parameters and orientation times compared to propofol alone in D&C anesthesia.

We have shown that:
- ketamine-propofol mixture have shorter orientation time compared to propofol alone,
- ketamine-propofol mixture have decreased 5.min Aldrete and VAS scores and 10.min VAS scores,
- both groups have similar hemodynamic effects,
- similar side effect profile,
- similar patients’ and surgeons’ satisfaction scores.

Ideal drug for sedo-analgesy should have rapid onset and fast recovery time. However, there is still no consensus for best sedoanalgesic management for short-term procedures like D&C. Although there were studies focusing on the success of hysteroscope and curettage under local anesthesia, intravenous-based techniques are widely used for the patient who want to sleep during the procedure(11, 12). Propofol is one of the most accepted intravenous agents used for D&C due to its superior pharmacokinetic and pharmacodynamic properties. It was shown to provide good surgical condition and a low risk for cardiovascular complication in D&C(12). Different combinations like remifentanil/propofol(13), fentanyl/propofol(19), alfentanil/propofol or ketamine/propofol were shown to provide reliable and effective hypnosis and analgesia in D&C(3). Ketamine, an NMDA receptor antagonist, has been shown to decrease pain scores and reduce postoperative analgesic consumption by 35-40%(15) in different clinical settings. Cardiotoxicity and induction of psychotic episodes, and delayed recovery, are the main disadvantages for ketamine(6). 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(15). The combination of propofol and ketamine has been efficiently used in the same syringe, in a variety of settings, such as coronary artery surgery in adults(16), interventional radiology(15), and for sedation during endometrial biopsy(15). Propofol-ketamine combination has also been effectively studied outside the operating room in deep sedation for burns on the ward and for sedation in emergency
In this study, hemodynamic data, side effects, satisfaction scores found to be similar among groups and ketamine-propofol mixture found to have shorter orientation time with decreased pain scores. These data suggest that the use of ketamine and propofol combination might be beneficial for hemodynamic stability while decreasing orientation time and pain scores.

In conclusion, the propofol-ketamine 1:1 mixture is associated with shorter orientation times than propofol alone, with similar hemodynamic stability without any important side effects in D&C anesthesia.

References


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