Effects of the addition of low-dose ketamine to propofol-fentanyl anaesthesia during diagnostic gynaecological laparoscopy

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A B S T R A C T
Objectives: Diagnostic gynaecological laparoscopy (DGL) is a brief procedure, generally performed on an outpatient basis. Propofol-fentanyl is often used for anaesthesia in minor outpatient procedures because of its rapid onset, short duration of action and smooth patient awakening. However, propofol has various cardiovascular effects such as reduced arterial pressure, cardiac output and cardiac index. Ketamine is an intravenous anaesthetic and short-acting analgesic that can alleviate the haemodynamic effects of propofol due to its sympathomimetic activity. The aim of this placebo-controlled trial was to evaluate the effects of the addition of low-dose ketamine to propofol-fentanyl anaesthesia in DGL.

Study design: In this double-blind randomized trial, 60 healthy women undergoing gynaecological laparoscopy to investigate infertility were studied. Following injection of midazolam and fentanyl in all patients, the study group (n = 30) received ketamine 0.5 mg/kg and propofol 1–2.5 mg/kg, and the placebo group (n = 30) received saline 0.9% and propofol 1–2.5 mg/kg. Propofol was subsequently infused for the maintenance of anaesthesia.

Results: Patients in the study group had a significantly lower incidence of pain than patients in the placebo group during propofol injection (13% vs 87%, respectively; p < 0.0001). After induction of anaesthesia, 16 (53%) patients in the placebo group and three (10%) patients in the study group had a decreased heart rate (p < 0.001). The decrease in mean arterial pressure was greater in the placebo group compared with the study group (37% vs 7%, respectively; p < 0.001). During the procedure, the total mean ± standard deviation dose of propofol was 420 ± 65 mg in the placebo group and 330 ± 35 mg in the study group (p < 0.001). Pain scores for the first 3 h after the operation were significantly lower in the study group (p < 0.001).

Conclusion: Use of low-dose ketamine with propofol-fentanyl anaesthesia in patients undergoing DGL was associated with less pain during propofol injection, lower incidence of haemodynamic changes, lower total dose of propofol and improved postoperative analgesia.

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1. Introduction

Laparoscopy is one of the most common surgical procedures performed by gynaecologists, and is a safe method for the diagnosis of pelvic lesions, especially when investigating infertility [1,2]. Diagnostic laparoscopy is generally performed on an outpatient basis. The goals of effective ambulatory anaesthesia include rapid onset, effective intra-operative analgesia, cardiopulmonary stability, rapid awakening and recovery, and freedom from postoperative nausea/vomiting and pain [3,4].

Various methods have been used to provide anaesthesia for diagnostic gynaecological laparoscopy (DGL) [1,3]. Total intravenous anaesthesia with propofol-fentanyl has been used successfully and effectively [1,5]. Propofol is a non-barbiturate sedative hypnotic that has rapid onset, short duration of action and anemetic effects. It may cause pain at the site of injection, however, and the incidence of dose-dependent hypotension and respiratory depression is relatively high [6].

Ketamine is a phencyclidine derivative classified as a dissociation intravenous anaesthetic that has analgesic properties when used in subanaesthetic doses. In addition; it is a non-competitive N-methyl-D-aspartate receptor antagonist with opioid receptor activity. Therefore, ketamine is widely used as a pre-emptive analgesic for acute postoperative pain management [7–9]. However, it has cardiovascular stimulating properties and psychomimetic effects at high doses [10].

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It has been reported that ketamine administered in combination with propofol can achieve effective analgesia and preserve respiration [6,7,11–13]. The sympathomimetic actions of ketamine may also be effective in counteracting the haemodynamic effects of propofol [11,12].

Clinical reports have confirmed the analgesic effects of the ketamine/propofol combination for sedation in outpatient procedures such as tracheal intubation in the emergency department [11–14], and bone marrow aspiration and lumbar puncture [15], interventional radiology procedures [16] and burn dressing changes [17] in paediatric patients. To the authors’ knowledge, however, no studies have been undertaken regarding the use of ketamine and propofol in combination for anaesthesia in patients undergoing laparoscopic surgery. Tang et al. [18] reported that the ketamine/propofol combination provided adequate sedation and analgesia in patients undergoing DGL.

The aim of this study was to evaluate the effects of the addition of low-dose ketamine to propofol-fentanyl anaesthesia during DGL.

2. Methods

Following approval of the study by the Ethics Committee of Alzahra Hospital and receipt of informed consent from the patients, 60 women with American Society of Anesthesiologists’ physical status I or II, aged 20–40 years were enrolled in the study. Exclusion criteria were systemic or psychological disease, allergy to the study drugs and history of current analgesic drug therapy. All patients received midazolam 0.05 mg/kg and fentanyl 2 μg/kg intravenously prior to induction of anaesthesia. The patients were randomized into two equal groups using a computer-generated programme. Patients in the study group (n = 30) were anaesthetized with ketamine 0.5 mg/kg and propofol 1–2.5 mg/kg, and patients in the placebo group (n = 30) were anaesthetized with normal saline and propofol. A laryngeal mask airway was introduced, and anaesthesia was maintained with a continuous infusion of propofol and atracurium 0.2–0.3 mg/kg. The infusion rate of propofol was adjusted to maintain an adequate depth of anaesthesia (lack of somatic or autonomic response to painful stimulation), as indicated by clinical signs and haemodynamic changes.

Routine monitors included an automated blood pressure cuff, electrocardiogram, pulse oximetry and capnography. Ventilation was controlled, and minute ventilation was adjusted to maintain end-tidal CO₂ at 35 ± 5 mmHg. Two surgeons performed the laparoscopies, and two anaesthesiologists were responsible for monitoring anaesthesia and recording the variables. The surgeons, second anaesthesiologist and patients were blinded to the study. All study-related measurements were taken by the same anaesthesiologist who was not aware of the treatment allocation of the patients.

Five minutes before the end of the procedure, propofol infusion was discontinued. After obtaining a train-of-four ratio of 0.9, the residual muscle relaxant blockade was reversed, patients were extubated and then transferred to the post anaesthesia care unit (PACU). All patients received 10–15 ml/kg of crystalloid perioperatively for hydration. Postoperative analgesia was provided with intravenous tramadol (50–100 mg every 4–6 h) when pain scores were >4.

The anaesthetic variables recorded included induction and maintenance doses of propofol, duration of surgery and anaesthesia, local pain during propofol injection and haemodynamic status (baseline and then every 5 min until the end of anaesthesia). The recovery variables recorded included the interval from discontinuation of propofol until the patient opened her eyes, and pain scores on a visual analogue scale (VAS 0–10 cm; 0 = no pain, 10 = worst possible pain) in the PACU (at emergence) and over the first 24 h after surgery. First request for analgesia, total analgesic consumption and the presence of side effects (nausea/vomiting, hallucination) were determined over the first 24 h after surgery.

The sample size was based on a power calculation which showed that 60 patients (30 patients in each group) were required to achieve 90% power to detect the rescue dose of propofol (1.0 mg/kg) intra-operatively between patients treated with ketamine/propofol or placebo/propofol with α of 0.05. Statistical analyses were performed using Statistical Package for the Social Sciences Version 13.0 (SPSS Inc., Chicago, IL, USA). Student’s t-test was used to analyze group differences in patient demographics, and duration of surgery and anaesthesia. Chi-squared analysis and Fisher’s exact test, when appropriate, were used to compare the incidence of variables. A p-value <0.05 was considered to indicate significance. All data are presented as mean ± standard deviation or n (%).

3. Results

The patients in the two groups were comparable with respect to age, height, weight, and duration of surgery and anaesthesia (Table 1).

Table 2 shows that the incidence of local pain during propofol injection was significantly lower in the study group compared with the placebo group (13% vs 87%; p < 0.0001). During the induction of anaesthesia, 16 (53%) patients in the placebo group and 10 (10%) patients in the study group experienced a decrease in heart rate (p < 0.001). Mean arterial blood pressure decreased by 7% in the study group and 3% in the placebo group (p < 0.01). Haemodynamic changes during anaesthesia are shown in Fig. 1. The mean total dose of propofol was significantly lower in the study group compared with the placebo group (330 ± 35 mg vs 420 ± 65; p < 0.001). The interval from discontinuation of propofol to eye opening was not significantly different between the two groups (p = 0.64).

Table 2 also shows postoperative variables in the two groups. All patients in the placebo group and 27% of patients in the study group reported a pain score >4 in the PACU (p < 0.001). Time to first request for analgesia was significantly different between the two groups (17.0 ± 8.5 min vs 165.0 ± 28 min; p < 0.0001). Pain scores (VAS) for the first 24 h following surgery are shown in Fig. 2. The incidence of nausea was not significantly different between the two groups. Hallucination was not reported by any patients in either of the groups.

4. Comments

The combination of ketamine and propofol has been used with great success in anaesthesiology for many years, but its use in ambulatory anaesthesia is fairly recent. Both propofol and ketamine have a rapid onset, and are safe and effective for sedation and analgesia in minimally invasive procedures [11–17]. At subanaesthetic doses, ketamine provides analgesia and adequate operating conditions [11–18]. An additional advantage of ketamine is the maintenance of postoperative analgesia when it is used before the first surgical incision (pre-emptive analgesia).

Table 1: Patient characteristics and duration of operation and anaesthesia in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Study group (n = 30)</th>
<th>Placebo group (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.7 ± 3.4</td>
<td>34.3 ± 5.4</td>
<td>0.86</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.8 ± 8.2</td>
<td>66.7 ± 0.8</td>
<td>0.79</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.0 ± 6.2</td>
<td>158.4 ± 7.2</td>
<td>0.58</td>
</tr>
<tr>
<td>Duration of operation (min)</td>
<td>32.5 ± 8.7</td>
<td>35.3 ± 35</td>
<td>0.74</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>45.5 ± 7.8</td>
<td>40.3 ± 5.6</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation.
Table 2
Peri-operative variables in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Study group (n = 30)</th>
<th>Placebo group (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local pain during propofol injection (%)</td>
<td>4 (13)</td>
<td>26 (87)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Decrease in heart rate (%)</td>
<td>3 (10)</td>
<td>16 (53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Decrease in mean arterial pressure (%)</td>
<td>2 (7)</td>
<td>11 (37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory depression (%)</td>
<td>1 (3)</td>
<td>16 (53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean total dose of propofol (mg)</td>
<td>330 ± 35</td>
<td>420 ± 65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intake from propofol discontinuation to eye opening (min)</td>
<td>5.4 ± 2.3</td>
<td>4.8 ± 1.6</td>
<td>0.64</td>
</tr>
<tr>
<td>PACU discharge time (min)</td>
<td>82 ± 18</td>
<td>73 ± 22</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Incidence of pain score ≥4:
- 1h in PACU: 8 (27) vs 30 (100), p < 0.0001
- 3h after surgery: 18 (60) vs 6 (20), p < 0.001
- 6h after surgery: 0 vs 0
- 12h after surgery: 0 vs 0
- 24h after surgery: 0 vs 0
- Time to first request for analgesia (min): 17.0 ± 8.5 vs 165.0 ± 28.0, p < 0.0001
- Total dose of tramadol (mg): 35.0 ± 15.0 vs 95.0 ± 25, p < 0.001

Side effects:
- Nausea: 5 (17) vs 2 (7), p = 0.22
- Hallucination: 0 vs 0

PACU, postanaesthesia care unit.
Data are n (%) or mean ± standard deviation.

[19–21]. As observed by Hashemi et al. [15], the combination of propofol and ketamine (‘ketofol’) provides effective sedation and analgesia for bone marrow aspiration in children. Ketamine preserves heart rate, blood pressure and cardiac output through its sympathomimetic effects. Administration of low-dose ketamine (<1.0 mg/kg) with propofol has favourable haemodynamic effects [22].

Local pain due to propofol injection is a common side effect (28–90% in adults). In this study, the frequency of injection site pain was low in the study group (13%). This may have been due to a peripheral local anaesthetic action of ketamine, which attenuated the afferent pain pathway, rather than a central analgesic effect [23,24]. The total dose of propofol was lower in the study group compared with the placebo group. This may have been due to the additive effect of ketamine (N-methyl-D-aspartate receptor antagonist) and propofol (γ- amino butyric acid agonist) [18]. Propofol induces a decrease in arterial blood pressure after induction of anaesthesia. This is due to a decrease in systemic vascular resistance and the direct myocardial depression effects of propofol. The decrease in cardiac output, may be via its action on sympathetic drive to the heart [22]. Administration of ketamine prior to propofol has the advantage of producing a non-significant decrease in arterial pressure compared to the pre-operative level. These findings were similar to those of Saadawy I. et al. [23].

Patients who received ketamine were pain-free for longer in the immediate postoperative period, with a mean difference of 148 min in the time to first request for analgesia between the two groups. Both groups were exposed to the same surgical trauma, and prolonged analgesia in the study group must have been due to a pre-emptive analgesic effect of ketamine [19–21,25,26]. Patients undergoing DGL experience limited tissue injury during the intra-operative period. However, tissue trauma during surgery modifies. The induction and maintenance of such central sensitization may be dependent on the activation of NMDA receptors. Pre-operative administration of a small dose of ketamine (an NMDA receptor antagonist) can block central sensitization and may improve postoperative analgesia [19,21–26].

![Fig. 1](image1.png)

**Fig. 1.** (A) Changes in heart rate before and after injection of study solutions. (B) Changes in mean arterial pressure before and after injection of study solutions. Base, baseline before the injection of study solutions; T5, 5 min after injection of study solutions; T15, 15 min after injection of study solutions; T30, 30 min after injection of study solutions. *p < 0.05 at T5 and T15.

![Fig. 2](image2.png)

**Fig. 2.** Change in pain scores (visual analogue scale [VAS] scores) with time in both groups. *p < 0.05 in the postanaesthesia care unit and up to 3 h after surgery.
No cases of hallucination were reported in this study because doses of ketamine \(< 1\) mg/kg are not associated with psychomimetic effects [22,26].

A limitation of this study was that doses of ketamine \(> 0.5\) mg/kg were not investigated. Larger doses would have led to sedation and thus biased the results, and may have induced psychomimetic effects.

5. Conclusion

The results of this study suggest that the addition of low-dose ketamine to propofol-fentanyl anaesthesia in patients undergoing DGL decreases the incidence of local pain during propofol injection, decreases the total dose of propofol intra-operatively and improves the postoperative pain variables in the PACU and up to 3 h after surgery.

Considering the low number of studies undertaken in this area, it is recommended that: (1) broad studies should be undertaken on operative laparoscopy to evaluate the effects of this combination; (2) the beneficial effects of this combination should be studied in different operations; and (3) in minor operations, this combination can be a method conventional painkillers for postoperative pain.

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References