Comparison of propofol/ketamine versus propofol/alfentanil for dilatation and curettage

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Summary

Background and Objectives: The use of propofol with an analgesic agent is probably the principal technique for the induction of anesthesia for dilatation and curettage (D&C) at the present time. We designed a randomized, double-blind study to compare the clinical efficacy of ketamine and alfentanil when combined with propofol for short-lasting anesthesia during D&C. *Methods:* The study included 60 patients scheduled for D&C. Either alfentanil 10 μg/kg^{-1} IV (Group A) or ketamine 0.5 mg/kg^{-1} IV (Group K) were given to each patient with propofol 0.7 mg/kg^{-1} IV for anesthesia induction. Surgeon and patient satisfaction, Aldrete score, Verbal Pain Scale rating, total propofol dose, orientation time, and adverse events such as bradycardia, hypotension, nausea, and vomiting were evaluated. *Results:* In Group A orientation time was significantly shorter and propofol consumption significantly lower than in Group K. *Conclusions:* Both alfentanil/propofol and ketamine/propofol combinations provide reliable and effective hypnosis and analgesia; however, the ketamine/propofol combination leads to higher consumption of propofol and results in a longer orientation time than the alfentanil/propofol combination.

Key words: Alfentanil; Ketamine; Propofol; Dilatation curettage; Analgesia; Orientation time.

Introduction

Dilatation and curettage (D&C) is a short-lasting procedure that generally causes considerable pain due to cervical dilatation performed usually by Hegar dilators and tissue extraction. Prevention of movement responses to pain during D&C is important. The use of propofol with an analgesic agent is probably the principal technique for induction of anesthesia for D&C at the present time. Alfentanil is a synthetic opioid with a rapid onset and short elimination half-life used for short-time procedures [1, 2]. Theoretically, alfentanil may increase the incidence and duration of apnea due to respiratory depressant effects, and may enhance the depressant effects of propofol on blood pressure and heart rate [3].

Ketamine has intrinsic analgesic and amnestic properties, and thus may be a suitable choice for short-lasting procedures [4-6]. However, it has the potential for undesirable side-effects that include unpleasant emergence hallucinations and emesis [7, 8]. To our knowledge, no anesthesia studies have been done in which alfentanil or ketamine are added to propofol for D&C. We designed a randomized, double-blind study to compare the clinical efficacy of ketamine versus alfentanil when combined with propofol for short-lasting anesthesia during D&C.

Patients and Method

The study was approved by the ethics committee of our institution, and each patient included provided informed written consent. The study included 60 patients between the ages of 18 and 60 who were scheduled for D&C procedures for evaluation of abnormal uterine bleeding. Their physical status, as rated by the American Society of Anesthesiologists (ASA) criteria, ranged from I to II. Patients with pulmonary, hepatorenal, neuromuscular, and neuropsychiatric disease, body mass index over 30 kg/m^2, regular use of sedative medication or substance abuse, and patients undergoing emergency curettage for massive bleeding or hemodynamic instability were excluded from the study. Patients unable or refusing to give informed consent were also excluded.

Before anesthetic induction, standard monitoring was applied (electrocardiogram, pulse oximetry, and noninvasive blood pressure monitoring) to all patients in the operating room. Lactated Ringer's solution was infused at a rate of 5 ml/kg. Each patient included was then randomly assigned to receive either a combination of propofol/alfentanil (Group A) or propofol/ketamine (Group K) for anesthesia. Patients were preoxygenated with 100% oxygen for 3 min, just before anesthesia induction.

Alfentanil (Rapifen, Janssen-Cilag, Germany) 10 μg/kg^{-1} IV was given to each patient in Group A, and ketamine (Ketalar 500 mg flc, Phizer, Luleburgaz, Turkey) 0.5 mg/kg^{-1} IV to each patient in Group K, followed 60 sec later in both groups for anesthesia induction applied with propofol (propofol 1% Fresenius, Fresenius Kabi, Australia) 0.7 mg/kg IV. If the eyelid reflex failed to disappear with this medication, an additional half of the induction dose of propofol was administered. After loss of consciousness, ventilation was assisted manually via a face mask as necessary with a fresh gas flow of 6 l/min (3 l/min N_20, 3 l/min oxygen). N20 was discontinued when the gynecologist declared the D&C procedure completed.

During the D&C, an additional propofol bolus of half the induction dose 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 2 min intervals.

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Adverse events such as hypotension (mean arterial pressure < 30% pre-induction baseline value, SAP < 80 mmHg), or bradycardia (HR < 50 beats/min^{-1}) 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 [9] and a verbal pain scale (VPS) used to evaluate pain intensity, with scores of 0-3 (0: no pain; 1: light pain; 2: moderate pain; 3: severe pain) at 5 and 10 min postoperatively. Tramadol 1 mg/kg IV was administered to patients with a score > 1. Two hours later, all patients were questioned about the occurrence of nausea or vomiting.

The total dose of propofol was recorded, as well as duration of surgical procedure, duration of anesthesia (from first propofol injection to open eyes), and orientation time (from N20 discontinuation until able to recall name and date of birth). After the operation, surgeons were questioned about their subjective evaluation of surgical working conditions during the D&C, and patients were questioned at discharge about their anesthetic experience (0: not satisfied; 1: satisfied; 2: extremely satisfied). Surgeon and patient satisfaction scores, Aldrete scores, VPS, nausea, and vomiting were recorded by independent anesthesiologists or nurse anesthetists blinded to the study groups. The primary endpoint was defined as orientation time, and the secondary endpoint was defined as adverse events such as hypotension, bradycardia, nausea, and vomiting.

Statistical analysis

After the power analysis (priority analysis) according to orientation time, we found the total sample size to be 58, power 0.95, and effect size 0.9 (alpha = 0.05, actual power = 0.95, delta = 3.3). Results are expressed as the median (range), mean ± SD, and patient number. A normalization test was done using the Kolmogorov-Smirnov Z-test for parametric data. The independent Student's t-test was used to compare parametric variables and the Mann-Whitney U test for non-parametric variables; a p value < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS 10.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA).

Results

Data regarding demographics, duration of surgery, and anesthesia of patients in the two groups are summarized in Table 1. There were no statistically significant demographic differences between the two groups. Duration of surgery and duration of anesthesia were also similar between the two groups (Table 1).

Postoperative evaluation data are shown in Table 2. Orientation time was significantly shorter in Group A than Group K (4.6 ± 1.2 min vs 7.1 ± 1.1 min [$p < 0.001$], respectively). In addition, propofol consumption was significantly lower in Group A than Group K (86.7 ± 36.5 mg vs 142.6 ± 42.4 mg [$p < 0.001$], respectively).

There were no statistically significant differences between groups regarding surgeon satisfaction, patient satisfaction, VPS, and Aldrete score. Similarly, no statistically significant differences were found between the groups in terms of adverse events (hypotension, bradycardia, nausea, and vomiting) (Table 3).

Table 1. — *Patient characteristics of the groups*.

	Group A (n = 30)	Group K (n = 30)	p value
Age (years)	38.7 ± 11.5	43.2 ± 10.6	0.46
Weight (kg)	68.4 ± 9.8	74.3 ± 11.2	0.38
ASA physical status I/II	12/18	10/20	0.59
Duration of surgery (min)	5.9 ± 0.9	6.3 ±0.9	0.22
Duration of anesthesia (min)	7.7 ± 0.8	8.1 ± 0.9	0.32

Data are means ± SD, or number of patients.
There were no statistically significant differences between the groups.

Table 2. — *Postoperative evaluation data*.

	Group A (n = 30)	Group K (n = 30)	p value
Orientation time (min)	4.6 ± 1.2	7.1 ± 1.1	0.001
Propofol consumption (mg)	86.7 ± 36.5	142.6 ± 42.4	0.001
Surgeon satisfaction (0/1/2)	0/16/14	0/19/11	0.60
Patient satisfaction (0/1/2)	0/15/15	1/18/11	0.30
VPS 5th min	0 (0-2)	0 (0-2)	0.94
VPS 10th min	0 (0-2)	0 (0-2)	0.56
Aldrete score 5th min	9 (7-10)	8 (7-10)	0.28
Aldrete score 10th min	10 (9-10)	9 (8-10)	0.07

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

Table 3. — *Incidence of adverse events*.

	Group A (n = 30)	Group K (n = 30)	p value
Hypotension	5	1	0.08
Bradycardia	3	0	0.07
Nausea	1	4	0.17
Vomiting	0	2	0.15

Data are number of patients.

Discussion

This study shows that both anesthesia protocols were effective and reliable for D&C. There were significant differences only in propofol consumption and orientation time between groups. Propofol consumption was greater in the ketamine group than in the alfentanil group, depending on the vital signs and movement of patients in this study. It may be that use of a low ketamine dose caused patients in the ketamine group to feel more pain compared with the alfentanil group [10]. In fact, ketamine is known to have both analgesic and anesthetic properties. The analgesic effect of ketamine is explained by its noncompetitive antagonism at the N-methyl-D-aspartate (NMDA) receptor, which plays a significant role in the pathogenesis of pain perception [11, 12]. Ketamine administered intravenously or epidurally in a low-dose manner has been shown to decrease pain scores and reduce postoperative analgesic consumption by 35-40% [13-16]. According to the results of this study, alfentanil was a more effective analgesic than ketamine during the intraoperative period. We believe that the propofol/alfentanil combination provided more effective analgesia and anesthesia than the propofol/ketamine combination. Perhaps the need for propofol is associated with the synergistic effect between these two drugs and propofol.

Both the propofol/ketamine combination [17, 18] and the propofol/alfentanil combination [19-22] interact additively to produce hypnosis and immobility and suppress

responses to both noxious and non-noxious stimulation. These reports show that the synergistic effect of the drug combinations is more important than their individual effects. We propose that the alfentanil/propofol combination provides more effective hypnosis and immobility than the ketamine/propofol combination.

In this study, although there was no statistically significant difference between groups in terms of Aldrete recovery score, the orientation time was longer in the ketamine group than in the alfentanil group. This may seem contradictory, but we suspect that the extended orientation time is associated with the stronger amnestic effect of ketamine and the use of higher doses of propofol in the ketamine group. St. Pierre *et al*. [23] reported an extended recovery time for propofol/ketamine compared with a propofol/alfentanil combination.

Ketamine produces sympathetic stimulation which leads to increased SAP and HR [24]. When administered with propofol to induce anesthesia, even in subanesthetic doses, it may produce hemodynamic stability by neutralizing the sympatholytic activity of propofol [24-26]. This study expected the finding that a ketamine/propofol combination would provide a stable hemodynamic course because of previous studies [21, 24, 27, 28]. Due to the cardio-depressant activity of both propofol and alfentanil, their combination caused more hemodynamic instability than the ketamine/propofol combination. Similar results were reported by Fruya *et al*. [25], and Salihoglu *et al*. [29] who showed that SAP and HR were significantly lower in an alfentanil group compared with a ketamine group. With the alfentanil/propofol combination, decreased SAP and HR do occur, but there was no statistical difference between groups in bradycardia and hypotension as defined in this study. In addition, alfentanil was used in a low dose with propofol and the propofol was administered gradually according to need. We consider that this method of alfentanil use provided a reliable hemodynamic effect.

Begec *et al*. [30] and Chiaretti *et al*. [31] investigated these two drug combinations and found both protocols effective to obtain good sedation and analgesia. However, alfentanil caused respiratory depression in both studies. These two studies used different methods and twice the alfentanil dose compared with our study. We can infer that both the type and dose of agent used is important for safe anesthesia and analgesia during short procedures.

Besides the depressive cardiac and respiratory effects of opioids, the most frequently mentioned adverse effect related to ketamine is emergent delirium or hallucinations. This occurs more commonly if ketamine is used as the sole agent for sedation. In the present study, no patients reported emergent delirium or hallucinations. The combination of propofol/ketamine has been known to eliminate the side-effects of ketamine [24]. The combination of either alfentanil [32] or ketamine [26] with propofol reduces the levels of both the hypnotic and anesthetic dose of propofol.

Patient satisfaction, surgeon satisfaction and Aldrete recovery scores indicated that comfortable and reliable anesthesia was achieved in both groups. The VPS showed that both study drugs provided effective and equal postoperative analgesia.

We note several limitations of this study. First, we compared the hemodynamic data between groups only in terms of bradycardia and hypotension. Second, N_2O is an agent with analgesic properties, and we did not take its use into account when evaluating data for either group. Although the present study has clinical importance, our findings could be considered preliminary data and our results, especially the lower frequency of adverse effects, should be confirmed by larger studies with more adequate power. In addition, further studies should be designed to determine the optimal drug and dose for D&C.

In conclusion, the results of this study suggest that both alfentanil and ketamine in combination with propofol provide reliable and effective hypnosis and analgesia, but that the ketamine/propofol combination results in higher consumption of propofol and longer orientation time than alfentanil/propofol.

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