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ORIGINAL ARTICLE

# Intravenous ketamine compared with diclofenac suppository in suppressing acute postoperative pain in women undergoing gynecologic laparoscopy

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**Abstract**
*Purpose* We aimed to compare the analgesic effects of low-dose intravenous ketamine with the effects of diclofenac suppositories in acute postoperative pain management in women undergoing gynecologic laparoscopic surgery under general anesthesia.
*Methods* In a double-blind, randomized clinical trial, 80 patients were selected and entered the study. After the induction of general anesthesia, one group received 0.15 mg/kg intravenous ketamine and the other group received a 100-mg rectal diclofenac suppository. The two groups were compared regarding acute pain scores, postoperative morphine requirements, and untoward complications.
*Results* Pain scores and morphine requirements were lower in the rectal diclofenac suppository group at the 1st, 3rd, and 6th postoperative hours. Higher incidences of postoperative nausea and vomiting (PONV), delusions, and oral secretions were observed in the ketamine group.
*Conclusions* Diclofenac 100-mg suppositories were more effective in suppressing acute pain than 0.15 mg/kg intravenous ketamine in women undergoing elective gynecologic laparoscopy, with fewer untoward complications.

**Keywords** Acute pain · Diclofenac · Gynecology · Ketamine · Laparoscopy

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## Introduction

Acute postoperative pain is one of the most untoward effects of surgical procedures, including laparoscopic surgeries, mandating treatment [1, 2]. Opioid derivatives are among the first-line drugs used for acute pain treatment; however, their complications are their drawbacks [1]. Non-opioid agents have been used to compensate for this problem, to decrease postoperative pain severity, and to decrease the chance of the occurrence of complications related to opioids [3–5]. Besides, multimodal analgesic regimens decrease pain severity and increase the quality of analgesic strategies; a combination of analgesics is the cornerstone of these protocols [6].

Intravenous ketamine is a nonspecific antagonist of the *N*-methyl-D-aspartate (NMDA) receptor [6–9], which plays a key role in the processing and transmission of pain. Ketamine has a relatively rapid onset and fast recovery [7–11]. There are some studies that have questioned its anesthetic effects [12, 13], especially when used as IV patient-controlled analgesia (PCA) [5]; however, there are other studies with different results [14–17]. One of the nonsteroidal anti-inflammatory drugs (NSAIDs) used for acute pain management is diclofenac, in suppository form, and other steroids have been studied for the same purpose [18].

This study compared the analgesic effects of low-dose intravenous ketamine and diclofenac suppositories on acute postoperative pain in women undergoing gynecologic laparoscopic surgery under general anesthesia.

## Patients, materials, and methods

The study proposal and its protocol were reviewed and approved by the Institutional Ethics Committee,

Department of Research Affairs, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

In a double-blind, randomized clinical trial, among all the patients admitted to the gynecology operating room of Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, in a 12-month period, 80 patients were selected and entered the study after inclusion and exclusion criteria were applied. All these patients provided informed written consent to participate in the study. Inclusion criteria were women undergoing elective laparoscopic surgery (lasting less than 1 h), age 18–45 years, and American Society of Anesthesiologists classification 1 or 2 (i.e., ASA I or II). Exclusion criteria were: patient refusal to enter or continue the study; current or previous history of drug abuse or illicitly used controlled drugs or substances; and a history of gastrointestinal (GI) disorders, renal disorders, asthma, or central nervous system disease causing increased intracranial pressure.

For sample size determination, according to a previous study that was done in a similar geographical population [19] and using a power analysis, considering $\alpha = 0.05$ and $\beta = 0.2$, a sample size of 80 was calculated; the patients were then randomly assigned to 2 groups (the ketamine group and the diclofenac group), according to a computer table of random numbers.

One of the authors (a constant colleague) visited each patient the night before the surgery and informed them of the details of the study. In this visit, the patients were also trained regarding the method of postoperative pain assessment using a 100-mm visual analog scale (VAS).

A dose of 0.1 mg/kg intramuscular morphine was used as a premedication dose 1 h before each patient was transferred to the operation room.

One of the authors was responsible for anesthetizing all the patients in the operating room (in both groups). She did not have any contribution to the data collection process in the postoperative period; also, she did not have any kind of contribution to the process of blinding or the process of patient allocation to the study groups.

At the same time, the author who cared for the patients in the postoperative period and assessed the postoperative outcomes was blinded regarding the specific group each patient belonged to.

To keep the patients uninformed regarding their study group, the following protocol was used for them: all received 4–6 L/min oxygen through a mask; electrocardiography monitoring, pulse oximetry, and non-invasive blood pressure and heart rate monitoring were initiated, and all received 0.05 mg/kg of intravenous midazolam; then 1.5 μg/kg fentanyl, 5 mg/kg sodium thiopental, and 0.5 mg/kg atracurium besylate were administered over 3–5 min through a peripheral intravenous catheter. After appropriate muscle relaxation and tracheal intubation were achieved, the patients in the ketamine group received 0.15 mg/kg intravenous ketamine (Ketamine Hydrochloride®, 50 mg/mL; RotexMedica, Trittau, Germany) in a single bolus dose, and the patients in the diclofenac suppository group received a 100-mg diclofenac rectal suppository (Diclofenac Sodium 100 mg Suppository®, Aburaihan Pharmaceutical, Tehran, Iran). Anesthesia maintenance was done using 1 % isoflurane, and muscle relaxation was maintained with incremental 5-mg intravenous doses of atracurium besylate if respiratory movements were present. At the end of the surgery, the patients were reversed using 0.07 mg/kg of neostigmine plus 0.02 mg/kg of atropine; then, after full awakening and full muscle force recovery, they were extubated.

If any procedure lasted more than 1 h, the patient would be withdrawn from the study and would receive her standard care.

After termination of the operation and patient arousal, the patients were reversed using a combination of neostigmine plus atropine (as noted above); then, after extubation, they were transferred to the post-anesthesia care unit and then they were transferred to the ward after meeting transfer criteria. For postoperative supplementary analgesia the following protocol was used (Fig. 1):

1. The patients were checked at the 1st, 3rd, 6th, and 12th hours after the operation regarding VAS; this procedure was done by one of the authors according to a predetermined protocol.
2. Then, if a VAS pain score of more than 30 (maximum of 100) was reported by any of the patients in the postoperative period, a dose of 0.1 mg/kg intravenous morphine sulfate was administered by the author who had performed step 1; she administered the first morphine dose immediately. Then she waited to check the analgesic response of the patient; if the first morphine dose was not enough for pain control, she would administer the next incremental doses of morphine, which could be increased up to 0.2 mg/kg.
3. Which could be extended to 0.2 mg/kg after a VAS score more than 30;
4. One of the the authors (an anesthesiologist) checked the pain scores at the specified intervals after the operation and administered morphine according to the determined protocol;
5. Nasal oxygen prongs and a mask were always available before morphine administration and the patients were monitored with pulse oximetry.

Pain scores, total morphine consumption, the time interval between post-anesthesia care unit entry and patient request for analgesics, the incidence of patient requests for administration of postoperative analgesics, and also the duration of the surgery from incision to skin closure were

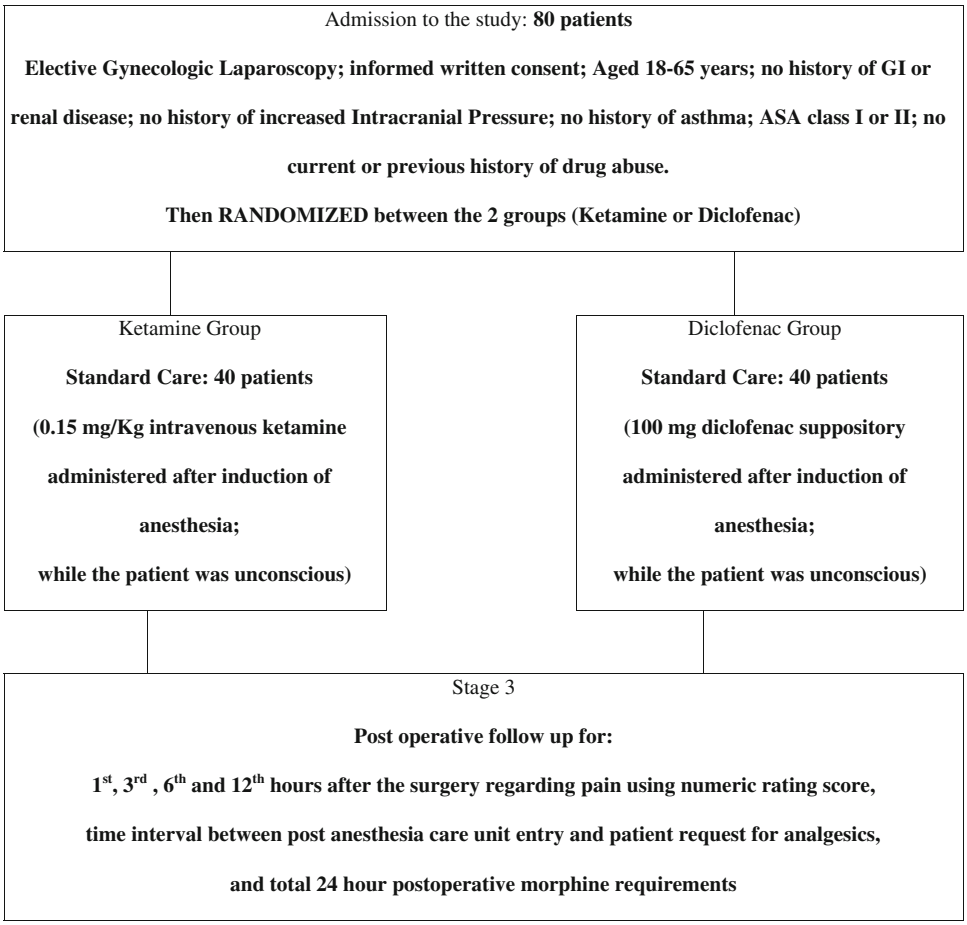


**Fig. 1** Study flowchart. *ASA* American Society of Anesthesiologists, *GI* gastrointestinal

documented (Fig. 1). Also, if any patient showed the possibility of nausea and vomiting, she was treated using a spectrum of anti-emetics, and the related data were recorded.

Throughout the study, the patients' personal data were kept fully confidential.

Data entry and analysis was performed with SPSS software (version 11.5; SPSS Inc, Chicago, IL). For data analysis, Student's *t*-test and the $\chi^2$ test were used. Data findings were expressed as means ± SEM and a *P* value of $<0.05$ was considered as statistically significant.

## Results

The two groups had no differences in baseline variables (Table 1). Pain reported by the diclofenac group at the 1st, 3rd, and 6th hours after the termination of anesthesia was significantly less than that in the ketamine group (Table 2). This difference was not statistically significant at 12 h after the termination of anesthesia.

The total morphine requirement for diclofenac group patients was 1.3 ± 0.2 mg/kg and for ketamine group patients, it was 3.3 ± 0.8 mg/kg (*P* value for *t*-test = 0.015).

**Table 1** Age, body weight, and duration of surgery in the two groups

| Variable | Ketamine | Diclofenac | *P* value |
|---|---|---|---|
| Age (years) | 28.3 (7.6) | 29.4 (8.1) | >0.05 (for *t*-test) |
| Body weight (kg) | 62.7 (5.6) | 61.6 (6.1) | >0.05 (for *t*-test) |
| Duration of surgery[a] | 42 (11) | 44 (9) | >0.05 (for *t*-test) |

Data are presented as means ± SEM; total 80 cases

[a] Duration of surgery in minutes

**Table 2** Pain scores in the two groups (maximum visual analog scale [VAS] score of 100)

| Assessment time (h after end of surgery) | Diclofenac | Ketamine | *P* value (for *t*-test) |
|---|---|---|---|
| 1 | 1.5 (0.3) | 2.3 (0.5) | <0.002 |
| 3 | 1.1 (0.2) | 2.1 (0.4) | <0.001 |
| 6 | 1 (0.3) | 1.6 (0.7) | <0.02 |
| 12 | 1.2 (0.6) | 1.5 (0.9) | >0.05 |

Data are presented as means ± SEM

Also, the time interval between post- anesthesia care unit entry and patient request for analgesics was 72 ± 32 min in the diclofenac group and for ketamine group patients, it was

**Table 3** Incidence of postoperative complications in the two groups

| Complication | Diclofenac ($n = 40$) | Ketamine ($n = 40$) | $P$ value* |
|---|---|---|---|
| Nausea[a] | 6 (16.7 %) | 20 (50 %) | 0.005 |
| Vomiting[a] | 2 (5 %) | 14 (35 %) | 0.03 |
| Secretions[b] | 0 | 8 (20 %) | 0.006 |
| Delusions[a] | 0 | 6 (15 %) | 0.026 |

* $P$ value for $\chi^2$ test

[a] Not all of these patients needed pharmacologic treatment

[b] Oral secretions

68 ± 25 min ($P$ value for $t$-test = 0.695). The incidence of patient requests for administration of postoperative analgesics (i.e., the first 24-h need for supplemental morphine) was less in the diclofenac group than in the ketamine group; 18 of 40 patients (45 %) in the diclofenac group compared with 30 of 40 patients (75 %) in the ketamine group ($P$ value for $\chi^2 = 0.01$).

Regarding the postoperative complications of the two analgesic methods, the incidences of postoperative nausea and vomiting, oral secretions, and postoperative delusions were higher in the ketamine group than in the diclofenac group (Table 3).

## Discussion

The results of this study demonstrated that in women undergoing elective gynecologic laparoscopy (less than 1-h surgery) under general anesthesia, the severity of acute postoperative pain was lower in the patients receiving a 100-mg diclofenac suppository than that in the women who had received 0.15 mg/kg intravenous ketamine. Also, the diclofenac group had lower postoperative morphine requirements than the ketamine group and experienced fewer postoperative complications, including postoperative nausea and vomiting, delusions, and oral secretions.

Studies regarding acute pain have recommended the use of multimodal therapeutic regimens, in order to enhance the efficacy of analgesic regimens while decreasing the untoward side-effects [1, 5]. Accordingly, in our study we compared two different analgesic agents combined with morphine, in order to find a more effective analgesic combination for acute pain.

In another study, it was demonstrated that gabapentin, dexamethasone, and ketamine combined with paracetamol and ketorolac decreased the postoperative acute pain scores but did not decrease morphine consumption [11].

Also, different studies have demonstrated the role of NSAIDs in reducing acute pain [19–22]; but none of these studies has compared the analgesic effects of these drugs in the form of suppositories with the analgesic effects of intravenous ketamine; especially considering the untoward complications related to ketamine. However, the use of analgesic suppositories for the treatment of acute pain and administered while the patient is unconscious (i.e., during anesthesia) is a common part of multimodal analgesia, especially in children [23–26] and in women [27–31].

In a Cochrane meta-analysis, it was concluded that ketamine decreased postoperative nausea and vomiting [3]. At the same time, that study noted that ketamine's adverse effects, when the drug was used as an analgesic agent, were mild or absent; though the study declared that the interpretation of its results should be done with caution, because the studies cited in the meta-analysis had been heterogeneous regarding study design [3, 4]. The results of that meta-analysis are in contradiction with our findings, because we had a lower incidence of postoperative complications in the diclofenac suppository group.

However, postoperative side effects are demonstrated to be more frequent in certain patient groups [10]. So, it seems that the results of our study regarding increased postoperative side effects are justifiable when considering women undergoing general anesthesia in surgeries of less than 1 h, when the patients have received intravenous ketamine during the first minutes after anesthesia induction.

In previous studies [3–8], it has been demonstrated that, during general anesthesia, when intravenous ketamine was used as an adjuvant analgesic, the incidence of hallucinations was not high and the occurrence of hallucinations did not dependent on premedication with benzodiazepine derivatives; however, some of these studies have claimed that there is not a clear role for ketamine as a part of perioperative analgesic regimens [5–7, 10].

In another study performed on patients undergoing cesarean delivery with spinal anesthesia, 10 mg intravenous ketamine was compared with placebo for controlling postoperative pain. The study concluded that low-dose ketamine had no additional acute analgesic effects during the postoperative period [4, 5]. The results of that study support, in part, our findings that diclofenac suppositories were more effective than intravenous ketamine. However, there are other studies reporting positive effects of ketamine in suppressing acute pain [2, 9, 14, 18, 32–35], even in modes other than intravenous and systemic administration; for example, in intravenous regional anesthesia (IVRA) [7]. We also note that there are studies that do support the role of NSAIDs for suppressing postoperative acute pain [18].

There are a number of limitations of our study. First of all, we had 2 groups and the study lacked a 3rd group of control patients to compare the effects of placebo with each of the two groups, or even a 4th group receiving both ketamine and diclofenac. Secondly our patients were all

female, which limits the generalization of our results to other patient groups, such as children and men. However, on the other hand, this could be a positive point because the study focused on women and the importance of postoperative ketamine side effects in women cannot be overemphasized.

Finally, the results of this study demonstrated that the administration of diclofenac as 100-mg suppositories was more effective in suppressing acute postoperative pain than intravenous ketamine in women undergoing elective gynecologic laparoscopy, and there were fewer complications after the administration of diclofenac.

**Conflict of interest** None.

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