Doi: 10.5152/TJAR.2020.787

Original Article

Pain

Turkish Journal of Anaesthesiology & Reanimation

Effects of Low-Dose Ketamine Infusion on Alleviating the Opioid Burden for Patients Undergoing Myomectomy Surgery

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Cite this article as: Wahdan AS, Mohamad M M, Helmy NY, Shehata GH, Salama AK. Effects of Low-Dose Ketamine Infusion on Alleviating the Opioid Burden for Patients Undergoing Myomectomy Surgery. Turk J Anaesthesiol Reanim 2021; 49(1): 52-7.

Abstract

Objective: Recent research has focused on the use of N-methyl-D-aspartate (NMDA) receptor antagonists for pain management. Several drugs are known to have this action, including ketamine, which exerts its main analgesic effect through NMDA receptor antagonism. This study aimed to evaluate the effect of low-dose ketamine infusion on opioid exposure for patients undergoing myomectomy surgery under general anaesthesia.

Methods: A total of 70 women were included in this prospective double-blind trial study. The patients included in this study were American Society of Anaesthesiologists physical status I–II, aged between 18 and 50 years and scheduled for laparotomy myomectomy surgery. Patients were randomised to receive either a bolus of 0.2 mg kg^{-1} of ketamine followed by a continuous infusion of 0.2 mg kg^{-1} hr^{-1} during the operation or a placebo of normal saline. Both groups also received morphine as needed for pain relief. The primary outcome was the total amount of morphine used during the intraoperative and postoperative periods. Intraoperative and postoperative mean blood pressure, heart rate and postoperative visual analogue scale for pain were assessed.

Results: Total mean morphine consumption was significantly lower in the ketamine group than in the control group (26±3.5 mg vs. 34.7±3.3 mg, respectively, $p<0.05$). However, there were no statistical differences between the groups regarding haemodynamics, postoperative pain score and complications.

Conclusion: The use of ketamine in low infusion doses intraoperatively during an elective myomectomy procedure produced an opioid-sparing effect by reducing perioperative morphine consumption without significant side effects.

Keywords: Analgesia, ketamine, morphine, uterine myomectomy

Introduction

Approximately 20%–50% of all women suffer from uterine leiomyoma (fibroids), making it the most frequent gynaecological neoplasm affecting women throughout their lives (1). Both medical and surgical management can be used for this benign tumour. Myomectomy via laparotomy is one of the surgical methods for removing these masses. A multimodal pain management regimen is required, both intraoperatively and postoperatively, for patients undergoing abdominal surgery, as poorly controlled acute pain may cause a variety of unfavourable outcomes, including prolonged hospital stay, distress, delirium or even the development of chronic pain (2). The source of pain in these procedures is primarily somatic, arising from the incision made in the abdominal wall, as well as visceral from visceral trauma (3). Commonly used analgesia regimens could be either systemic drugs, including paracetamol, non-steroidal anti-inflammatory drugs, opioids, ketamine, α-2 adrenergic agonists or regional analgesia via an epidural catheter (4). Morphine has traditionally been considered the primary opioid for postoperative analgesia in these patients; however, it has been associated with several adverse effects. Therefore, finding an alternative approach that would allow a decrease in postoperative opioid use is deemed essential (5). Several studies have found that the perioperative use of a low-dose ketamine infusion can be beneficial, not only as an analgesic but also to decrease

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Received: 31.05.2020 Accepted: 17.07.2020
Available Online Date: 24.12.2020

the opioid dosage required (6). Ketamine is a non-selective N-methyl-D-aspartate (NMDA) receptor antagonist. It abolishes peripheral afferent noxious stimuli. It leads to a decrease in opioid usage by inhibiting central nociceptor sensitisation with excellent analgesia properties even in sub-anaesthetic doses (7, 8). However, the beneficial effects of low-dose ketamine infusion for pain management are still debated, as the optimal duration and dosage have not yet been established. The infusion dose may be limited because of its negative impact on psychotomimetic status (9-11).

This study aimed to evaluate the effect of low-dose ketamine infusion on perioperative opioid burden and its possible replacement of high-dose morphine for patients undergoing myomectomy under general anaesthesia.

Methods

This study was approved by Research and ethics Committee of Cairo University, Cairo, Egypt. Written informed consent was obtained from each patient prior to enrolment. A total of 70 women aged 18 and 50 years, with an American Society of Anaesthesiologists (ASA) physical status of I or II, who were scheduled for an elective myomectomy under general anaesthesia were evaluated. Patients were excluded if any of the following criteria were present: refusal to participate, ASA physical status of III or IV, body mass index (BMI) >45, a history of epilepsy, allergy to any of the study agents or a history of oral or parenteral analgesics within 24 hours prior to the procedure. Patients were randomised to the ketamine or control groups using sealed envelopes containing even or odd numbers from a computer-generated table. Patients with even numbers were allocated to the ketamine group, and patients with odd numbers were allocated to the control group. The randomisation table was designed by a research assistant who was not otherwise involved in the study. Only the clinical pharmacists had access to the randomisation table. They were responsible for preparing 2 syringes, containing either 50 mL of ketamine at a dose of 2 mg mL^{-1} or 50 mL normal saline. The syringes were then coded for intraoperative administration. Investigators, clinicians, patients and research assistants were all blinded to the group assignment. During the preoperative visit, details of the procedure, including the visual analogue scale score (VAS) of pain (ranging from 0, no pain, to 10, worst imaginable pain) and analgesia administration on request, were explained to the patients by both the surgeon and the anaesthetist.

Main Points:

- It is important to find alternatives to opioids for postoperative analgesia.
- Ketamine blocks peripheral afferent noxious stimuli, thus requiring less morphine.
- Constant infusion of low-dose ketamine reduces perioperative opioid consumption.

On arrival in the operating room, a 20-gauge catheter was inserted, and 4 mg of ondansetron and 50 mg of ranitidine were administered intravenously. Standard monitoring of non-invasive blood pressure, electrocardiogram, and Oxygen saturation (SpO_2)were implemented for all patients. All patients were pre-oxygenated using 100% fraction of inspired oxygen (FiO2) for 3 minutes. Anaesthesia was induced using IV propofol (2 mg kg^{-1}) and morphine sulphate (0.1 mg kg^{-1}). After loss of consciousness was confirmed, an intravenous injection of 0.1 mg kg^{-1} of cisatracurium was administered. Upon confirming adequate muscle relaxation, an endotracheal tube was inserted, and the patient was mechanically ventilated. Infusion of the study drug was initiated prior to the surgical incision. In the ketamine group, a bolus dose of 0.2 mg kg^{-1} ketamine hydrochloride (Rotexmedica GmbH Arzneimittelwerk, Germany) was injected slowly over 5 minutes, which was then continued at an infusion rate of 0.2 mg kg^{-1} h^{-1} until the end of surgery. In the control group, normal saline was administered as a loading dose and then infused at the same rate as the control group throughout surgery. Anaesthesia was maintained using isoflurane (MAC 1), 50% FiO_2 and intermittent boluses of cisatracurium (0.03 mg kg^{-1}) every 20 minutes.

During surgery, haemodynamics including heart rate (HR) and mean arterial blood pressure (MAP) were recorded every 30 minutes until the end of the operation. If there were any signs of inadequate analgesia, such as an increase in MAP and HR >20% from pre-induction values, additional intraoperative morphine (0.05 mg kg^{-1}) (Hameln Pharmaceuticals Ltd., United Kingdom) was administered to both groups.

At the end of the procedure, cisatracurium and the inhaled gas were discontinued. The patients' neuromuscular blockade was reversed with 0.05 mg kg^{-1} neostigmine and 0.02 mg kg^{-1} atropine and when extubation criteria were met, the endotracheal tube was removed. The patients were subsequently transferred to the postanaesthesia care unit (PACU) where an assessment of their vital signs (MAP and HR) and the VAS were performed. After discharge from the PACU, the patients' vital signs and pain were assessed every 4 hours for 24 hours. A standard postoperative analgesia regimen of 1 g IV of paracetamol (Perfalgan, USA) every 6 hours was given during the first 24 hours to each patient. Furthermore, boluses of 0.04 mg kg^{-1} morphine IV were given when the VAS was ≥4 or for significant patient complaints of pain between the assessment intervals in both groups. The primary outcome was total morphine requirement, including both intraoperative and postoperative periods. Secondary outcomes included

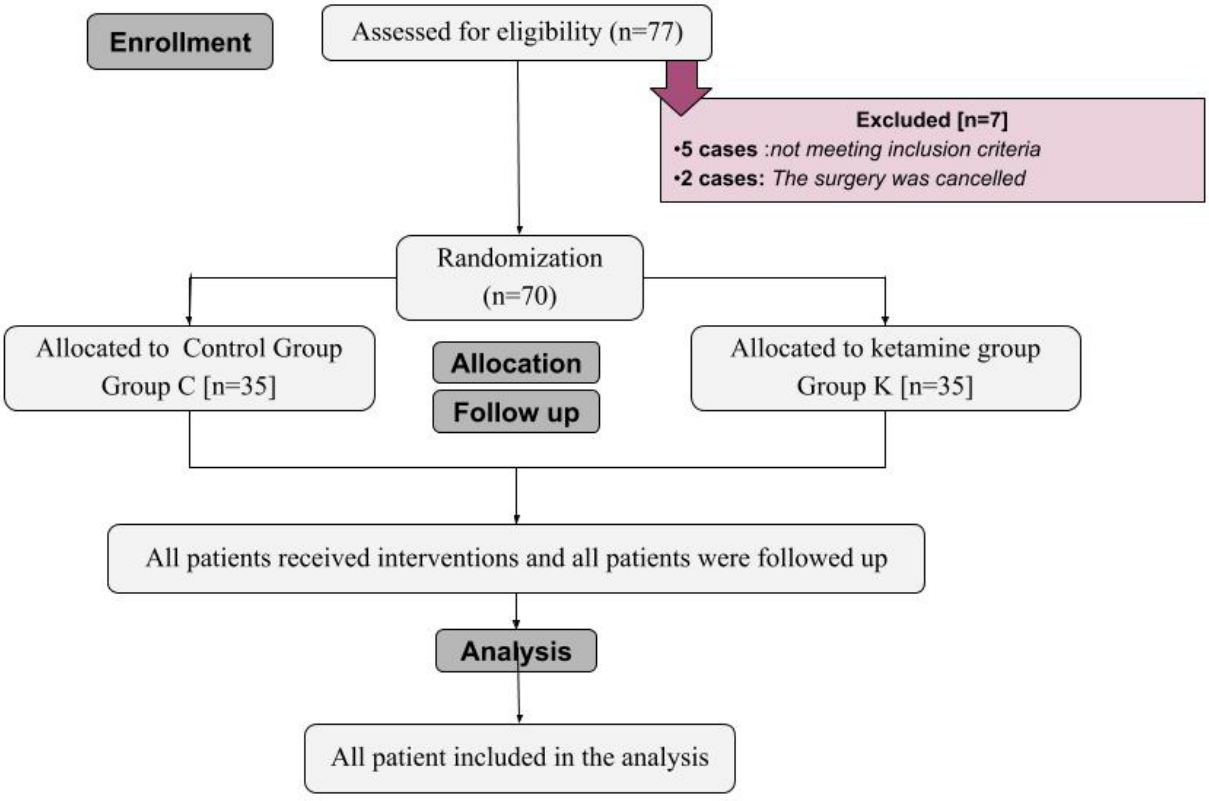

Figure 1. Consort flow diagram

intraoperative and postoperative MAP, HR, SpO_2, duration of surgery and time to extubation. Ambulation, length of hospital stay and VAS were assessed for 24 hours, and postoperative complications such as sedation and the occurrence of hallucinations were evaluated.

Statistical analysis

The unpaired t-test for independent samples, using G-power software version 3.1.9.2 (Universität Kiel, Germany), was performed with total cumulative morphine consumption as the primary outcome variable. A prior study (12) found that the total cumulative morphine consumption was 73.4 mg±34.8 mg in the control group and 47.9 mg±26.2 mg in the ketamine group. Using a power of 0.95 and an alpha error of 0.05, a minimum sample size of 33 patients was required. A total of 35 were recruited for each group to compensate for dropouts.

IBM Statistical Package for the Social Sciences software version 25.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for data management and analysis. Descriptive statistics included mean±SD, median (interquartile range) and number (percent). Comparison of numerical variables between the groups was performed using the student t-test for independent samples. Comparison of arterial blood pressures within the group at different time points was performed using the paired t-test. The chi-square test was used to compare categorical data, and a p value <0.05 was considered statistically significant.

Results

A total of 77 patients were assessed for eligibility, and 7 patients were excluded as they either refused to participate or did not meet the inclusion criteria. A total of 70 patients completed the study and were analysed (Figure 1).

There was no statistically significant difference between the groups regarding demographic data (age, BMI and ASA). The average amount of ketamine used in the K group was 66.21±9.3 mg (Table 1).

There was a significant difference between the groups for both intraoperative and postoperative morphine consumption ($p<0.05$). Intraoperatively, morphine use was 9.7±2.7 µg and 15.6±0.97 mg in the K and C groups, respectively. Postoperative morphine consumption was 16.34±3 mg and 19±3.2 mg between the K and C groups, respectively ($p<0.05$) (Table 2).

There was no statistical difference between the groups regarding operative data (duration of anaesthesia, surgical time and time to extubation). Furthermore, no differences were not-

Table 1. Comparison of demographic data, surgical factors, length of hospital stay and operative data

	Ketamine group (n=35)	Control group (n=35)	P-value
Age (year)	43.17±11.42	40.46±10.43	0.303
BMI (kg m^{-2})	30.03±5.2	28.8±3.3	0.228
ASA	1 (1–2)	1 (1–2)	0.231

Data are presented as mean±SD or median (interquartile range)
BMI: body mass index; ASA: American Society of Anaesthesiologists

Table 2. Comparison of intraoperative and postoperative morphine use

	Ketamine group (n=35)	Control group (n=35)	P-value
Intraoperative morphine consumption (mg)	7.6±2.1*	11.11±2.32	<0.001
Postoperative morphine consumption (mg)	16.34±3*	19±3.2	<0.001
Total morphine consumption (mg)	24±3.3*	30.20±3.9	<0.001

*Statistically significantly lower compared to the control group (p<0.05)
Data are presented as mean±SD

Table 3. Operative data and length of hospital stay

	Ketamine group (n=35)	Control group (n=35)	P-value
Surgical time (minutes)	130.74±31.42	128.69±29.22	0.778
Duration of anaesthesia (minutes)	185.97±34.43	177.5±27.16	0.260
Time to extubation (minutes)	19.34±6.9	17.26±5.46	0.165
Ambulation (postoperative hours)	12.69±3.8	11.6±3.3	0.217
Length of hospital stay (days)	2.6±1.1	2.9±1.2	0.222

Data are presented as mean±SD

Table 4. Postoperative complications

	Ketamine group (n=35)	Control group (n=35)	P-value
Sedation	2 (5.7)	6 (17.14)	0.112
Hallucinations	6 (17.14)	2 (5.7)	
Nausea	3 (8.6)	7 (20)	
Vomiting	1 (2.9)	3 (8.6)	

Data represented as n (%)

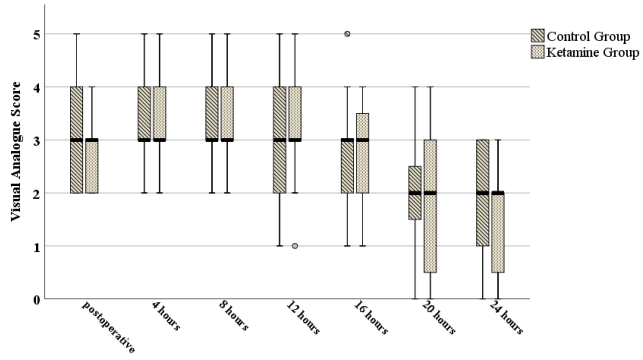

Figure 2. Postoperative visual analogue scale (Data are presented as median, range

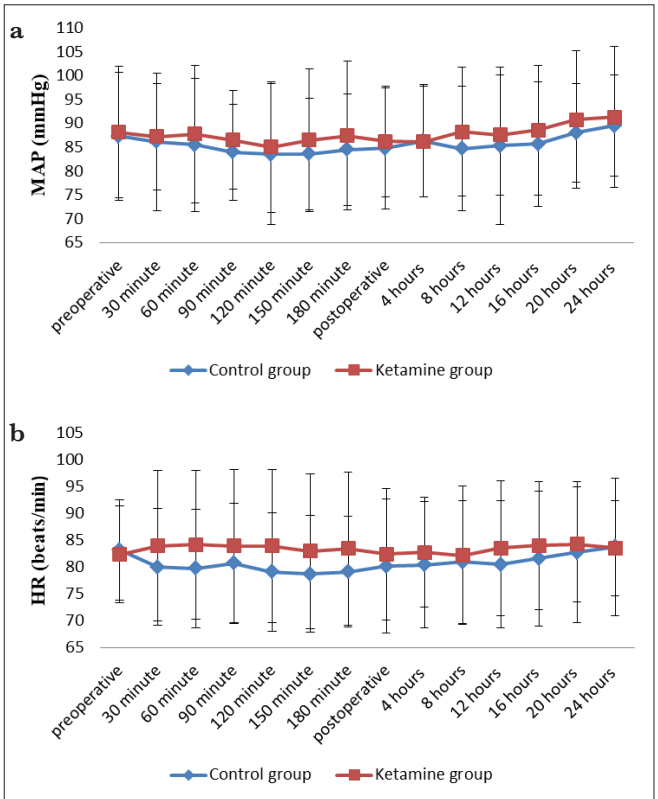

Figure 3. a, b. Mean arterial blood pressure (Data are presented as mean±SD)

ed for the length of postoperative hospital stay between the groups (Table 3).

The postoperative VAS was compared every 4 hours, for 24 hours, with no significant differences between the groups (Figure 2). Vital signs were also compared for changes in HR and MAP intraoperatively every 30 minutes, and postoperatively every 4 hours, for a total of 24 hours, with no significant differences between the groups (Figures 3a and b). There was also no significant difference in the occurrence of complications recorded between the groups (Table 4).

Discussion

This study found that the addition of a low-dose ketamine infusion enabled a decrease in the adjunctive use of morphine during intraoperative and postoperative periods with a reduction of side effects in patients undergoing myomectomy surgery. Traditionally, opioids have been considered effective for postoperative analgesia for multiple procedures. However, it is important to find an equally effective alternative to minimize their adverse effects. The use of an infusion of low-dose ketamine has been found to be effective for both pain management and a reduction in postoperative opioid requirements. However, ketamine's mode of action remains unclear. One theory suggests that ketamine has an NMDA antagonistic effect (13), whereas another theory postulates that ketamine's effect is a result of decreased connectivity in the areas of the brain modulating pain sensation (14). Alternatively, a third theory states that ketamine interacts with the μ- and δ-opioid receptors, resulting in its anti-nociceptive outcome (15). In this study, a low dose of ketamine (0.2 mg kg^{-1}) was used as a loading dose followed by infusion at a rate of 0.2 mg kg^{-1} hr^{-1}, as it was considered the proper dose to provide analgesia without complications.

The results of this study are similar to the findings of Kim et al. (16) who used ketamine for patients undergoing lumbar spinal fusion, at an infusion dose of 2 μg kg^{-1} min^{-1} following a bolus dose of 0.5 mg kg^{-1}. They noted a substantial decrease in postoperative fentanyl requirements, with a favourable response for postoperative analgesic effect as well as duration of effect. Another study by Cengiz et al. (17) used an intraoperative ketamine infusion dose of 6 μg kg^{-1} min^{-1} for patients undergoing total knee replacement surgery. They found a prolonged analgesic effect as well as a reduction in the amount of morphine required. The study of Goswami et al. (18) used a ketamine bolus dose of 0.75 mg kg^{-1} followed by an infusion of 10 mg kg^{-1} min^{-1} and found a reduction in both analgesics required and pain scores postoperatively.

Ilkjaer et al. (19) studied 60 patients undergoing renal surgeries with combined general and epidural anaesthesia. Their patients received either a preoperative bolus dose of 10 mg of ketamine, followed by an infusion of 10 mg hr^{-1} for 48 hours following the operation or a placebo. They were unable to demonstrate an additive analgesic or opioid-sparing effect of ketamine combined with epidural bupivacaine at 0–24 hours or epidural morphine at 24–48 hours following surgery. Their results may be because of using a lower dose and a different mode of anaesthesia. In another study (20), 120 patients were randomised to 1 of 3 groups: 0.15 mg kg^{-1} ketamine intravenously, 0.5 mg kg^{-1} ketamine intravenously or normal saline. This study concluded that a single intravenous dose of ketamine did not reduce postoperative analgesic requirements or postoperative pain at 3 months. However, this study did not include a continuous infusion following a bolus dose and involved different types of surgery, compared with our study (20).

Some of the common adverse effects of ketamine include insobriety, nausea, vomiting, psychotomimetic effects, light headedness, dizziness and headaches, particularly with long-term use. However, the most common concerns involve a decrease in brain function, including cognition, memory and mood (21). In this study, there were no statistically significant differences between the 2 groups. However, some studies have found that the use of sub-anaesthetic ketamine doses may cause a temporary increase in psychiatric symptoms such as the positive and negative symptoms of schizophrenia as well as dissociative and manic symptoms. However, they occurred at the time of injection and resolved within 1 hour (22, 23).

The primary limitation of this study was the fact that no 3rd group was used as a placebo group, to clarify the comparison between the effects of the study drugs to no drugs. Moreover, a relatively small sample size was included. The patients in the study were only followed up for 24 hours after surgery. Therefore, the study cannot address the question of whether perioperative ketamine influences pain and analgesia consumption over a longer period. In addition, the amount of inhalational anaesthetic was not measured, and it might have affected the analgesia experienced by the patients. In future studies, it would be useful to have a 3rd comparison group to be used as a placebo as well as to measure the amount of inhalational anaesthetic provided to each patient. Additional research is also needed to determine an optimal bolus and infusion dose of ketamine.

Conclusion

During an elective myomectomy procedure, the use of ketamine in low infusion doses intraoperatively produced an opioid-sparing effect by reducing perioperative morphine consumption without significant side effects.

Ethics Committee Approval: Ethics committee approval was received for this study from the Research and ethics Committee of Cairo University, Cairo, Egypt.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – N.Y.H.; Design – A.K.S., M.M., A.S.W; Supervision – N.Y.H., G.H.S.;Data Collection and/or Processing – M.M.M; Analysis and/or Interpretation – A.S.W.; Literature Search – M.M.M.; Writing Manuscript – M.M.M, A.S.W.; Critical Review – A.K.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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