Comparison of low-dose ketamine to methadone for postoperative pain in opioid addicts: a randomized clinical trial

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Background: Postoperative pain can lead to several complications. The effectiveness of different opioids in relieving pain after surgery has been widely studied. However, managing pain in patients with opioid addiction is still challenging. This study aimed to examine the impact of ketamine and methadone on postoperative pain in patients with addiction.

Methods: This was a non-inferiority randomized clinical trial. All included patients were monitored for morphine use, pain scores, and vital signs every 3 h. The intervention group received 0.5 mg/kg ketamine administered intravenously every 6 h. The control group received 5 mg of methadone intramuscularly every 8 h. The patient received intravenous morphine if their visual analog scale was above 3. All side effects in each group were recorded.

Results: Two hundred and twenty patients were included in this study. There were 127 men (57.7%) with an average age of 57.1 ± 19.5 and 93 women (42.3%) with an average age of 57.1 ± 21.0. There were no significant differences in demographic characteristics between the groups. There was no significant difference in the dose or frequency of morphine administration between groups. There was no significant difference between the groups in pain scores and vital signs at different time points. Drug side effects, including delirium and gastrointestinal symptoms, did not differ significantly between the methadone and ketamine groups.

Conclusions: Our clinical data support the hypothesis that ketamine is not inferior to methadone in patients with addiction. Future randomized clinical trials are needed to confirm these observations.

Keywords: Addict; Clinical trial; Ketamine; Methadone; Postoperative pain.
lications such as restlessness, sympathetic hyperactivity, and rise in blood pressure and heart rate [2,3].

Some methods and medications are used to alleviate postoperative abdominal pain, such as narcotics, nonsteroidal anti-inflammatory drugs, epidural catheters, and nerve blocks [4].

It has been shown that chronic opium abusers, such as addicted or dependent persons, have lower pain thresholds.

Intraoperative administration of ketamine in addicted patients has been shown to reduce postoperative pain relief use. However, its use is limited by the psychomimetic effects caused by the drug [5,6]. Furthermore, some patients may require methadone administration every 4–8 h to maintain its analgesic effects [7]. Ketamine, an N-methyl-d-aspartate (NMDA) receptor antagonist, has analgesic effects on both acute and chronic pain. Evidence suggests that ketamine can reduce pain by facilitating the inhibition of pain perception through descending pathways, enhancing the analgesic effects of narcotics and preventing the development of resistance to narcotics [8].

In addition to ketamine, analgesics such as methadone are often used due to their ability to reduce and control pain. Methadone is potent as morphine but has a longer duration of action and variable plasma half-life (ranging from 13 to 100 h).

Given the proven pain-relieving properties of ketamine, it may be a suitable alternative to opioids if its effect is comparable to methadone in managing pain. However, no study has compared low-dose ketamine with methadone for controlling postoperative pain in patients with opioid addiction. Therefore, this study aimed to compare the effectiveness of low-dose ketamine with methadone as the main pain control in managing postoperative pain in smoke-opiod-addicted patients who were diagnosed based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.

**MATERIALS AND METHODS**

**Study design and participants**

This was a single-blind, two-arm, randomized clinical trial. It was conducted in the surgical intensive care unit (ICU) of the university’s educational center. The study population included addicted patients who were undergoing abdominal surgery and then admitted to the ICU of Imam Reza and Ghaem Hospitals, Mashhad University of Medical Sciences, Mashhad, Iran, between September 2021 and March 2023. Addicted patients are known consumers of smoke opium for more than 6 months and were chosen based on the DSM-5 diagnostic criteria (with persistent desire or unsuccessful efforts to cut down or control opioid use; spending a great deal of time of activities necessary to obtain opioids, use opioids, and recover from their effects; having cravings or a strong desire or urge to use opioids.)

The inclusion criteria were smoking opium-addicted patients aged between 20 and 65 years who required post-surgery ICU care, an American Society of Anesthesiologists classification score of one or two, and a history of daily drug use in the past six months.

The exclusion criteria were known sensitivity to ketamine or methadone, history of severe systemic disease or psychiatric illness, high blood pressure or pulmonary artery pressure, increased intracranial pressure, history of alcohol or psychoactive substance use, QT interval abnormality, pregnancy, and prohibition of intramuscular injection. A consortium flowchart of this study is shown in Fig. 1.

The primary outcome was the dose and frequency of the used morphine, and the secondary outcome was pain (according to visual analog scale [VAS] score), blood pressure, pulse rate, temperature, and o2 saturation.

Purely and only as a safe treatment regimen and as a trial, in the ketamine group, 0.5 mg/kg of ketamine was administered intravenously in the ICU every six h and in the methadone group, 5 mg of methadone (as a standard treatment) was administered intramuscularly every eight h during 24 h after surgery. Eligible patients were randomly allocated to the methadone or ketamine groups.

After obtaining written informed consent, on the surgical bed in the operating room, after monitoring the patient, all patients underwent standard monitoring of respiratory (respiratory rate), cardiovascular (electrocardiogram and pulse rate), and blood pressure monitoring and appropriate venous access. In both groups, midazolam 0.02 mg/kg and fentanyl 3 μg/kg were prescribed intravenously as premedication. Intravenously induction of anesthesia was achieved with propofol 1.5 mg/kg and atracurium 0.5 mg/kg, and after intubation of the patient, intravenous anesthesia maintenance drugs were administered in the form of propofol 100 μg/kg/min infusion, with fentanyl used as needed at intervals of 30 to 60 min in case of tachycardia, tears, sweating, etc. At the end of the surgery, the tracheal tube was removed with the help of neostigmine 0.5 mg/kg and atropine 0.02 mg/kg for reversing of effect of Non-depolarization Muscu-
lar Blocking agents (NMBAs), and the patient was awakened.

The VAS was used to evaluate pain. On this scale, zero represents the lowest pain level, and 10 represents the highest pain level.

All patients were administered 1 g of Paracetamol (with commercial name of Apotel) intravenously every 8 h in the ICU, and if the pain control was inadequate (VAS > 3), 0.05 mg/kg of morphine was prescribed every 3 h.

The total dose of morphine consumed within 24 h was recorded. An anesthesiologist or trained nurse was present with the patient throughout the procedure and during discharge. Patients were assessed for recovery every 3 h to record the pain score and at the end of 24 h for the total amount of morphine prescribed and the highest postoperative pain score in the ICU. In addition, personnel records the data on a data collection sheet. Data included pain scores, any complications caused by narcotics (nausea, itching), or any hallucinations (hearing or visual) caused by ketamine.

Block randomization was performed in this study. We randomly used block sizes of 6, 8, and 10 randomly. In each block, there was an equal number of control and intervention groups. After generating a random sequence, it was concealed. Each sequence was inserted into sealed envelopes so that the content of the envelope was not visible from the outside. Due to the difference in the mode of medication administration between the groups, blinding of the patients was not possible. The person who prescribed the medication to the patients differed from those who evaluated the patient outcomes. The person who evaluated the patient outcomes was unaware of the patient allocation.

The outcome assessors were blinded in the present study.

This study was approved by the local ethics committee (No. IR.MUMS.MEDICAL.REC.1400.150) and was registered in the Iranian Registry of Clinical Trials (code: IRCT20111212008384N8 on 24/2/2022).

**Statistical analysis**

Data were analyzed using the SPSS software, version 22.0 (IBM Co.). The association between qualitative variables was tested using Fisher’s exact test or the chi-square test. Quantitative variables were compared using independent sample t-tests. Repeated-measures ANOVA was used to determine changes in quantitative variables over time. The P < 0.025 was considered statistically significant.
Sample size

No eligible published articles evaluated the effect size. According to expert opinions, the use of methadone during surgery in addicted patients leads to less opioid consumption in almost 82% of patients. A 15% lower response (fewer requests for morphine) to a low dose of ketamine compared to methadone was considered non-inferior as the margin was considered 15%. Considering a significance level of 0.025, a power of 0.8, and dropout, and using the formula for two independent proportions, a sample size of 111 patients per group was considered appropriate.

RESULTS

This study included 220 patients (127 men [57.7%] and 93 women [42.3%]). The average age of patients in the ketamine and methadone groups was 57.2 ± 16.0 and 57.5 ± 16.1 years, respectively. The mean body mass index of the patients was 24.2 ± 2.9 kg/m². Most patients (93.1%) had no underlying disease. The demographic and baseline characteristics are presented in Table 1. The mean dose of administered morphine in the time of recovery, 3, 6, 9, 12, 15, 18, 21, and 24 h after surgery was 3.1 ± 0.9, 2.9 ± 0.6, 2.9 ± 0.8, 2.9 ± 0.7, 3.1 ± 1.0, 3.4 ± 1.0, 3.4 ± 1.0, 3.4 ± 1.1, 2.6 ± 0.2 and 0, respectively. The frequencies of morphine use in the study population were as follows: once (23 patients, 10.5%), twice (37 patients, 16.8%), three times (50 patients, 22.7%), four times (31 patients, 14.1%), five times (26 patients, 11.8%), six times (6 patients, 2.7%), and seven times (7 patients, 3.2%). A total of 40 (18.2%) patients did not receive morphine. There was no significant difference in the frequency of morphine use between groups. The data for the groups at different time points are presented in Table 2.

There were no significant differences in pain scores over time (P = 0.2) or at different time points between the methadone and ketamine groups. The data are presented in Table 3.

There was no significant difference between ketamine and methadone groups in systolic and diastolic blood pressure (P = 0.5 and P = 0.7 respectively), pulse rate (P = 0.8), respiratory rate (P=0.5), body temperature (P = 0.9), and blood

Table 1. Demographic and Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>ketamine group</th>
<th>methadone group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>62 (56.9)</td>
<td>65 (58.6)</td>
</tr>
<tr>
<td>Men</td>
<td>47 (43.1)</td>
<td>46 (41.4)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57.2 ± 16.0</td>
<td>57.5 ± 16.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 ± 2.9</td>
<td>24.4 ± 2.9</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>5 (4.5)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>DM</td>
<td>2 (1.8)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>CHF</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>COPD</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>No disease</td>
<td>102 (93.5)</td>
<td>103 (92.8)</td>
</tr>
</tbody>
</table>

Values are presented as number (%), mean ± SD, or number only. BMI: body mass index; HTN: hypertension; DM: diabetes mellitus; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease.

Table 2. Comparison of Dose and Frequency of Administered Morphine in the Ketamine and Methadone Groups at Different Times

<table>
<thead>
<tr>
<th>Variable</th>
<th>At the time of recovery</th>
<th>3 h</th>
<th>6 h</th>
<th>9 h</th>
<th>12 h</th>
<th>15 h</th>
<th>18 h</th>
<th>21 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>3.1 ± 0.9</td>
<td>3.0 ± 0.7</td>
<td>2.9 ± 0.8</td>
<td>2.9 ± 0.7</td>
<td>3.1 ± 1.0</td>
<td>3.3 ± 1.0</td>
<td>3.3 ± 1.1</td>
<td>2.6 ± 0.2</td>
<td>0</td>
</tr>
<tr>
<td>Methadone</td>
<td>3.0 ± 0.9</td>
<td>2.8 ± 0.5</td>
<td>2.9 ± 0.8</td>
<td>3.0 ± 0.8</td>
<td>3.1 ± 1.0</td>
<td>3.6 ± 1.0</td>
<td>3.6 ± 1.2</td>
<td>2.6 ± 0.2</td>
<td>0</td>
</tr>
<tr>
<td>P value</td>
<td>0.8</td>
<td>0.3</td>
<td>0.9</td>
<td>0.5</td>
<td>0.8</td>
<td>0.2</td>
<td>0.4</td>
<td>0.9</td>
<td>-</td>
</tr>
<tr>
<td>Frequency of patients with morphine use (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>67 (61.4)</td>
<td>30 (27.5)</td>
<td>52 (47.7)</td>
<td>43 (39.4)</td>
<td>38 (34.8)</td>
<td>25 (22.9)</td>
<td>17 (15.5)</td>
<td>8 (7.3)</td>
<td>0</td>
</tr>
<tr>
<td>Methadone</td>
<td>74 (66.6)</td>
<td>27 (24.3)</td>
<td>63 (56.7)</td>
<td>41 (36.9)</td>
<td>45 (40.5)</td>
<td>28 (25.2)</td>
<td>19 (17.1)</td>
<td>12 (10.8)</td>
<td>0</td>
</tr>
<tr>
<td>P value</td>
<td>0.9</td>
<td>0.8</td>
<td>0.9</td>
<td>0.6</td>
<td>0.8</td>
<td>0.6</td>
<td>0.7</td>
<td>0.9</td>
<td>-</td>
</tr>
<tr>
<td>Number of morphine use</td>
<td>No use</td>
<td>1 time</td>
<td>2 time</td>
<td>3 times</td>
<td>4 times</td>
<td>5 times</td>
<td>6 times</td>
<td>7 times</td>
<td>-</td>
</tr>
<tr>
<td>Ketamine</td>
<td>23 (21.1)</td>
<td>11 (10.1)</td>
<td>19 (17.4)</td>
<td>22 (20.2)</td>
<td>17 (15.6)</td>
<td>11 (10.1)</td>
<td>2 (1.8)</td>
<td>4 (3.7)</td>
<td>-</td>
</tr>
<tr>
<td>Methadone</td>
<td>17 (15.3)</td>
<td>12 (10.8)</td>
<td>18 (16.2)</td>
<td>28 (25.2)</td>
<td>14 (12.6)</td>
<td>15 (13.5)</td>
<td>4 (3.6)</td>
<td>3 (2.7)</td>
<td>-</td>
</tr>
<tr>
<td>P value</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD.
Comparison of ketamine to methadone for postoperative pain

Table 3. Comparison of Pain Score in the Ketamine and Methadone Groups at Different Times

<table>
<thead>
<tr>
<th>Variable</th>
<th>At the time of recovery</th>
<th>3 h</th>
<th>6 h</th>
<th>9 h</th>
<th>12 h</th>
<th>15 h</th>
<th>18 h</th>
<th>21 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Ketamine</td>
<td>4.1 ± 2.1</td>
<td>3.3 ± 1.9</td>
<td>3.7 ± 1.8</td>
<td>3.7 ± 1.8</td>
<td>2.9 ± 1.4</td>
<td>3.0 ± 1.5</td>
<td>2.3 ± 0.9</td>
<td>2.1 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>4.5 ± 1.8</td>
<td>3.2 ± 1.5</td>
<td>3.9 ± 1.7</td>
<td>3.6 ± 1.8</td>
<td>3.9 ± 1.6</td>
<td>3.2 ± 1.6</td>
<td>3.3 ± 1.7</td>
<td>2.5 ± 1.0</td>
<td>2.2 ± 0.8</td>
</tr>
<tr>
<td>P value</td>
<td>0.2</td>
<td>0.5</td>
<td>0.3</td>
<td>0.6</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD.

oxygen saturation (P = 0.4) over time and in different time points (data not shown). There was a significant difference in the measured QTc levels over time between the groups (P = 0.006). There was a significant difference between ketamine and methadone groups 3 h (416.7 ± 33.4 and 427.5 ± 40.1, respectively; P = 0.03), 6 h (411.2 ± 36.3 and 425.0 ± 41.1, respectively; P = 0.009), 15 h (412.2 ± 36.2 and 423.0 ± 43.6, respectively; P = 0.04), 18 h (412.2 ± 35.3 and 423.5 ± 43.8, respectively; P = 0.03), and 21 h (411.7 ± 35.1 and 424.6 ± 44.2, respectively; P = 0.01) after surgery.

**DISCUSSION**

This study was conducted to compare the effects of low-dose ketamine with those of methadone in controlling postoperative pain in patients with smoke-opioid addiction. Based on our results, as the main treatment of addicted patients for postoperative pain, the effect of ketamine on pain was similar to the effect of methadone, and there was no difference in terms of the effect on the amount of post-operative pain between ketamine and methadone. The QTc levels at 0, 3, 6, 15, 18, and 21 h differed significantly between the methadone and ketamine groups, and the ketamine group generally had a shorter mean QTc than the methadone group.

In addicted patients, owing to problems with drug use, the responses to painkillers are not appropriate, and they sometimes require very high doses of narcotics. It is well known that pain management during and after surgery in addicted patients requires very precise prescription of narcotics for analgesia [5,9]. These patients usually have chronic pain and psychiatric problems such as anxiety and depression, and suffer from drug resistance or drug-induced hyperalgesia, which makes the treatment of acute and chronic postoperative pain difficult [10].

Ketamine and methadone are drugs that are used to reduce pain. Ketamine is used as an anesthetic and analgesic drug [11]. Ketamine leads to central nervous system depression and produces a dissociative anesthetic state in a dose-dependent manner. Available evidence shows that ketamine can reduce pain by facilitating the inhibitory control of pain perception through the descending pathways, increasing the analgesic effect of narcotics, and preventing the development of narcotic resistance. Intraoperative administration of ketamine in addicted patients has a proven role in reducing drug use [10,11].

Methadone is a unique long-acting μ-opioid receptor agonist that produces long-lasting analgesia at higher doses (24–36 h at doses greater than or equal to 20 mg) [12]. Two studies have investigated the analgesic effects of a single intraoperative dose of methadone in adult patients undergoing spinal surgery. Gottschalk et al. [13] reported that subjects receiving 0.2 mg/kg methadone had a 50% lower need for opioids at 48 h compared to those receiving continuous infusions of sufentanyl. A randomized trial with 120 patients receiving either 0.2 mg/kg methadone or 2 mg hydromorphone at the end of spine surgery showed similar results [14]. Although both studies reported lower pain scores in patients receiving methadone, pain intensity was still described as moderate during the first 2 postoperative days [11].

Similar to our study, the effects of methadone on postoperative pain reduction have been investigated. Our study also investigated the effects of ketamine compared with methadone and found no significant difference in their effectiveness in reducing postoperative pain.

Both methadone and ketamine inhibit NMDA receptors [15], bind to the μ-opioid receptors [16], and increase serotonin and norepinephrine concentrations in the brain [17]. A randomized clinical trial including 150 opioid-dependent patients found that those who received S-ketamine infusions required 35% less morphine in 24 h than the placebo group [18]. A similar trial reported that patients who received ketamine infusions required 30–37% less morphine 24–48 h after surgery than those who received saline [9]. However, pain scores were between 4–6 (on a scale of 0–10) in the ketamine groups in both studies and did not differ significantly from the placebo groups in terms of pain intensity [10,18]. In
contrast, our study did not find a significant effect of ketamine on postoperative pain, and there was no difference in its effectiveness compared to that of methadone. A meta-analysis of 14 randomized trials reported that patients who received adjunctive ketamine for spine surgery needed fewer narcotics in the first 24 h but had slightly lower pain scores than controls [19]. This research suggests that the use of adjunctive ketamine in spine surgery patients reduces opioid use in the first 24 h, but may have only a small effect on postoperative pain scores, which is consistent with the results of our study.

Postoperative side effects may occur with methadone or ketamine, including nausea/vomiting, respiratory depression, pruritus, tachycardia/hypertension, and hallucinations/lucid dreams [20,21]. Previous reviews and meta-analyses have suggested that the incidence of adverse outcomes is not higher in patients receiving methadone [14] or ketamine [21] compared to the control group. In our trial, the rates of complications related to the respiratory system (hypoxemia and hypoventilation), central nervous system (sedation, hallucinations, and dizziness), and digestive system (nausea and vomiting) were low, and no significant differences were observed between the groups. Moreover, the overall incidences of cardiac, respiratory, gastrointestinal, neurological, infectious, and renal complications during hospitalization did not differ between the ketamine and methadone groups. Consistent with our findings, previous studies have also shown no significant differences in side effects between the ketamine and methadone groups. However, in our study, in addition to common complications, QTc interval prolongation, a risk factor for malignant ventricular arrhythmia due to methadone administration, was also investigated and was found to be significantly lower in the ketamine group than in the methadone group.

The optimal dosing regimen for methadone and ketamine, whether used alone or in combination, remains unclear and requires further investigation. Therefore, additional studies are needed to determine the most effective doses of these medications. Finally, future studies should incorporate specific pain control protocols to enhance the accuracy and consistency of pain level measurements.

In conclusion, our findings suggest that there is no significant difference in the efficacy of ketamine and methadone in morphine use as a postoperative rescue analgesia in opioid-addicted patients undergoing abdominal surgeries. Both drugs demonstrated similar effects in reducing pain and postoperative complications. Additionally, digestive symptoms, such as vomiting and constipation, and neurological symptoms, such as delirium, were comparable between the two drugs. Therefore, clinicians may choose to use either methadone or ketamine, based on individual patient factors and clinical judgment.

FUNDING

None.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Comparison of ketamine to methadone for postoperative pain


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