Evaluating the analgesic and sedative effects of intravenous ketamine versus morphine administration on relieving long/short bone-fracture pain in the upper/lower limbs; a phase II clinical trial

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Introduction
The importance of pain control in patients with limb trauma admitted to emergency departments as well as its complications is among the main concerns in post-emergency care, which also contributes to the accelerated improvement of patients’ conditions in a significant manner. In addition to inducing physical discomfort in patients, pain can lead to complications, such as hypertension, cardiac arrhythmias, heart attacks, urinary retention, increased length of stay in hospital, and treatment costs. In this sense, fractures are the common causes of severe pain, and pain relief is assumed as the primary concern among patients with emergency conditions. In this regard, physicians need to find drugs having fewer side effects and no risks, such as morphine sulfate, and even provide more rapid-onset pain relief. Selecting and prescribing appropriate and effective analgesics can thus boost the cooperation between patients and physicians, enhance outcome achievement, and bring about higher levels of satisfaction with the quality of services delivered in emergency departments.

Objective: The present study was to evaluate the analgesic and sedative effects of intravenous (IV) ketamine versus morphine administration on relieving long/short bone-fracture pain in the upper/lower limbs.

Methods: The present study was conducted as a double-blind randomized clinical trial. For this purpose, the effect of ketamine and morphine were initially examined using IV ketamine and morphine administration, respectively. The duration of the analgesic effect, the amount of pain relief, and the complications for each drug, including apnea, bradycardia, tachycardia, altered level of consciousness, nausea, vomiting, hypertension/hypotension, seizures and disturbed sleep were compared, and then the preferred method was introduced. The study results indicated that the potency of the low-dose ketamine infusion in relieving pain in patients was comparable to that of morphine.

Results: In this study, 120 patients in total, including 60 cases receiving ketamine and 60 individuals receiving morphine, were recruited. The participants’ age range was between 19-70 years. Among patients, aged 18-65 years with limb trauma, and admitted to hospital emergency departments. Afterward, the duration of the analgesic effect, the amount of pain relief, according to the visual analog scale (VAS) outcomes, and the complications for each drug, including apnea, bradycardia, tachycardia, altered level of consciousness, nausea, vomiting, hypertension/hypotension, seizures and disturbed sleep were compared, and then the preferred method was introduced. The study results indicated that the potency of the low-dose ketamine infusion in relieving pain in patients was comparable to that of morphine.

Conclusion: It was concluded that ketamine could be administered as an alternative to IV morphine to reduce long/short bone-fracture pain in the upper/lower limbs.
inflammatory cytokines are further found in central sensitization following nerve injury and inflammation, which is associated with the development of contralateral hyperalgesia and allodynia (7). Ketamine is also known as a drug promoting inflammatory homeostasis. Locally, ketamine may interfere with the earlier mediators of primary immunity. It further prevents the exacerbation and extension of local inflammation without blunting the local process and delaying the inflammatory resolution. As well, ketamine prevents the general anti-pro-inflammatory mechanisms to overcome the pro-inflammatory effects. In other words, it is immunomodulatory rather than immunosuppressive (8). Previous studies have thus far revealed that ketamine causes some side effects, such as restlessness, transient apnea (0.8%), nausea and vomiting (8.4%), nightmares (2%), elevated intraocular pressure, and increased intracranial pressure (9, 10). It also increases blood pressure, heart rates, cardiac outputs, skeletal muscle tones, and salivary secretion (11). A previous study reflected on antinociception of metoclopramide, ketamine, or their combinations in mice. This study reported that the combination of ketamine-metoclopramide had a greater effect on relieving pain than ketamine alone (12).

Objectives
Given that ketamine is the main drug, widely administered in sedation in emergency departments, there is a need for further studies on its effectiveness and creation time. Therefore, the present study aimed to evaluate the analgesic and sedative effects of IV ketamine versus morphine administration on relieving fracture pain. The results indicated that the potency of the low-dose ketamine infusion in reducing pain was comparable to that of morphine.

Patients and Methods
Study design
The present study, as a double-blind randomized clinical trial, was conducted on a statistical population consisting of all patients with limb trauma, aged 18-65 years, and directly admitted to emergency departments. The individuals with a history of allergies to ketamine and morphine, showing the evidence of brain abnormalities, such as hydrocephalus, microcephaly, tumors, increased intracranial pressure, seizures, as well as a history of apnea, respiratory and airway problems, cardiovascular diseases, severe brain trauma, no sedation with a predetermined dose, need for a higher dose, and low levels of satisfaction were excluded.

Accordingly, normal saline serum, serum set, micro-set, a 5 cc syringe (containing ketamine diluted with a vial of distilled water, each cc with 10 mg of ketamine), and a 10 cc syringe (with two vials of distilled water) were provided in the first box, and normal saline, serum set, micro-set, a 5 cc syringe (containing distilled water), and a 10 cc syringe (including diluted morphine with two vials of distilled water, each cc with 1 mg of morphine) were put in the second box, along with the drug injection instructions. The recommended or prescribed daily dose plus the method of dealing with possible side effects were also placed secretly in one part of the box, therefore the sample would be taken out of the research project and referred to the supervising physician to treat the complications immediately. The clinical research physician also examined the patients, and their clinical history was obtained.

As well, a nurse randomly selected a box, and the medication was prescribed according to the protocol recorded there, based on the supervision of the emergency physician at a predetermined dose for sedation and relief. Upon prescribing the drug, the clinical research physician began to measure blood pressure and record sedation and relief using the visual analog scale (VAS) at minutes 0, 5, 15, 30, and 60 without knowing how to prescribe the drug and the prescribed dose, according to the examination form, and then recorded them respectively as quantitative and qualitative variables in the relevant tables. Afterward, the physician recorded the onset of sedation and relief by asking the patients, using the same form, about pain relief at certain intervals.

During sedation and relief, the attending physician also examined and recorded the side effects, including nausea, visual disturbance, vomiting, apnea-based pulse rate, breathing, and seizures.

In case of any complications, the patients were excluded from the research and treated properly.

At the end of the procedure, the executing physician was informed about the way of prescribing the drug. The prescribed dose by the physician or the emergency nurse, as well as the patients’ case documentation for recording them in the examination form.

The patients’ pain severity and recovery status were further determined, according to the VAS outcomes. Pain severity was evaluated from zero to 10, in which zero was defined as analgesia, 1-3 showed mild pain, 4-6 represented moderate pain, and 7-10 was in severe pain (13).

Statistical analysis
The chi-square test and t-test were employed to compare qualitative and quantitative variables in both routes, respectively. The analysis of variance (ANOVA) was also utilized to compare each group in terms of the quantitative data by modifying the confounding variables. The P value less than 0.05 was further considered significant. All the data were analyzed using the SPSS statistics software.
Results
In total, 120 patients – 60 cases receiving ketamine and 60 individuals receiving morphine – with the mean age of 47.04 ± 12.57 years (19-70 years old) including 89 men (74.2%) and 31 women (25.8%) were selected (Figure 1). The individuals' mean weight was also 65.68±11.92 (40-90 kg) and the highest frequency of fractures was related to the forearm bone (31.7%) and then leg (22.5%). The study results also indicated that 60% of the cases in the group receiving ketamine had shown some complications, since only 10% of those in the group taking morphine had demonstrated the aforementioned side effects. Besides, no significant relationship was observed between the VAS values, systolic and diastolic blood pressure values, pulse rate, respiratory rate, and oxygen saturation in both groups receiving IV ketamine versus morphine at different times (Tables 1-7).

Discussion
In managing trauma patients, the priority often goes into evaluating the mechanism of injury, hemodynamic parameters, and mental status, while narcotics are typically involved in assessing their levels of consciousness under these conditions, however some patients require constant monitoring (14). These drugs may also have interaction with other drugs; thus, they should be administered with caution (3). In this regard, a large and growing body of literature has thus far shed light on alternative treatments. Analgesics, such as IV, oral, or rectal ketamine, have been accordingly investigated (15).

The present study aimed to evaluate the efficacy and side effects of IV ketamine and morphine administration on relieving and sedating patients suffering from the upper/lower limb fracture pain.

In this line, Ding et al compared the potency of a combination of morphine and ketamine versus high-dose morphine alone in relieving pain in patients with acute pain. They found that using the combined ketamine-morphine was much better in relieving pain, and had even caused analgesia in patients compared with high-dose morphine administration alone (16). In a similar study by Johansson et al, the effect of a combination of low-dose morphine and ketamine had been also compared with morphine alone in terms of relieving patients’ pain, however no significant difference had been observed (17). These studies had used a combination of morphine and ketamine and morphine alone.

Their results were consistent with our findings, in which the ketamine alone was more effective than morphine in relieving fracture pain, although some researchers had examined the potency of ketamine and morphine separately.

Similarly, Barkan et al compared the effects of midazolam placebo and midazolam and oral ketamine, for the sedation of 60 children, aged 1-7 years old, during wound healing. They showed that the combination of midazolam...
and ketamine had caused profound sedative effects (18). The results of a randomized controlled trial had further shown that low-dose ketamine had not produced a greater reduction in numeric rating scale pain scores compared with morphine, for acute pain in emergency departments. However, low-dose ketamine had induced a significant analgesic effect, within five minutes, and had provided a moderate reduction in pain for two hours (19). The results of another randomized controlled trial had also demonstrated that IV low-dose ketamine at 1 mg/kg had provided comparable analgesic effectiveness of IV morphine in the acute treatment of severe painful sickle cell crisis among children in a day care center. However, it was associated with the high incidence of several transient, non-life-threatening, and mild side effects. IV ketamine at 1 mg/kg could be thus a reliable alternative to morphine in the management of severe painful sickle cell crisis, especially in a resource-limited area, where morphine was not readily available (20). These results were in line with the findings of the present study, which had confirmed the improving effects of ketamine at various times. In another investigation, sub-dissociative IV ketamine administered at 0.3 mg/kg had further provided analgesic effectiveness and apparent safety, compared to that of IV morphine for short-term treatment of acute pain in emergency departments (21).

**Conclusion**

The study results demonstrated that ketamine could be administered as an alternative to morphine administration to reduce the long/short bone-fracture pain in the upper/lower limbs without significant adverse effects.

**Limitations of the study**

| Time                        | Group     | Number | Mean     | Standard deviation | Statistics | P value |
|-----------------------------|-----------|--------|----------|--------------------|------------|---------|
| Before taking the drug      | Ketamine  | 60     | 8.4833   | 1.53481            | 1523.5     | 0.132   |
|                             | Morphine  | 60     | 7.9333   | 1.89439            |            |         |
| 5 minutes after taking the drug | Ketamine  | 60     | 4.6167   | 2.00078            | 1562.5     | 0.207   |
|                             | Morphine  | 60     | 4.2167   | 2.45703            |            |         |
| 15 minutes after taking the drug | Ketamine  | 60     | 3.6000   | 1.79642            | 1509.5     | 0.123   |
|                             | Morphine  | 60     | 3.2167   | 2.53178            |            |         |
| 30 minutes after taking the drug | Ketamine  | 60     | 2.9833   | 1.48999            | 1485.5     | 0.091   |
|                             | Morphine  | 60     | 2.8500   | 2.29092            |            |         |
| 60 minutes after taking the drug | Ketamine  | 60     | 2.8000   | 1.52716            | 1520.5     | 0.130   |
|                             | Morphine  | 60     | 2.7500   | 2.27458            |            |         |
Table 4. Comparison of PR between ketamine and morphine groups at different times

| Time                        | Group     | Number | Mean     | Standard deviation | Statistics | P value |
|-----------------------------|-----------|--------|----------|--------------------|------------|---------|
| Before taking the drug      | Ketamine  | 60     | 82.3833  | 11.33480           | 1470.0     | 0.081   |
|                             | Morphine  | 60     | 79.1167  | 11.7930            |            |         |
| 5 minutes after taking the drug | Ketamine  | 60     | 77.9333  | 8.62764            | 1504.5     | 0.118   |
|                             | Morphine  | 60     | 75.5167  | 13.50768           |            |         |
| 15 minutes after taking the drug | Ketamine  | 60     | 76.9333  | 7.79149            | 1531.5     | 0.156   |
|                             | Morphine  | 60     | 74.4833  | 11.42921           |            |         |
| 30 minutes after taking the drug | Ketamine  | 60     | 76.6000  | 7.13159            | 1556.0     | 0.197   |
|                             | Morphine  | 60     | 74.2167  | 10.83793           |            |         |
| 60 minutes after taking the drug | Ketamine  | 60     | 76.6167  | 7.11430            | 1553.0     | 0.192   |
|                             | Morphine  | 60     | 74.1833  | 10.79154           |            |         |

Table 5. Comparison of RR between ketamine and morphine groups at different times

| Time                        | Group     | Number | Mean     | Standard deviation | Statistics | P value |
|-----------------------------|-----------|--------|----------|--------------------|------------|---------|
| Before taking the drug      | Ketamine  | 60     | 19.0000  | 3.96168            | 1556.5     | 0.195   |
|                             | Morphine  | 60     | 17.8833  | 3.36528            |            |         |
| 5 minutes after taking the drug | Ketamine  | 60     | 16.8667  | 2.65632            | 1795.0     | 0.979   |
|                             | Morphine  | 60     | 16.8167  | 2.50576            |            |         |
| 15 minutes after taking the drug | Ketamine  | 60     | 16.3667  | 2.09087            | 1722.5     | 0.677   |
|                             | Morphine  | 60     | 16.4333  | 2.06148            |            |         |
| 30 minutes after taking the drug | Ketamine  | 60     | 16.4333  | 2.06969            | 1773.5     | 0.887   |
|                             | Morphine  | 60     | 16.3667  | 1.93072            |            |         |
| 60 minutes after taking the drug | Ketamine  | 60     | 16.4833  | 2.06251            | 1785.5     | 0.938   |
|                             | Morphine  | 60     | 16.3833  | 1.92302            |            |         |

Table 6. Comparison of O₂ saturation between ketamine and morphine groups at different times

| Time                        | Group     | Number | Mean     | Standard deviation | Statistics | P value |
|-----------------------------|-----------|--------|----------|--------------------|------------|---------|
| Before taking the drug      | Ketamine  | 60     | 98.4667  | 1.78949            | 1707.5     | 0.610   |
|                             | Morphine  | 60     | 98.6333  | 1.82233            |            |         |
| 5 minutes after taking the drug | Ketamine  | 60     | 98.6833  | 1.61026            | 1736.5     | 0.725   |
|                             | Morphine  | 60     | 98.6500  | 1.83030            |            |         |
| 15 minutes after taking the drug | Ketamine  | 60     | 98.7167  | 1.61656            | 1747.5     | 0.771   |
|                             | Morphine  | 60     | 98.7167  | 1.68836            |            |         |
| 30 minutes after taking the drug | Ketamine  | 60     | 98.6833  | 1.61026            | 1702.0     | 0.587   |
|                             | Morphine  | 60     | 98.6833  | 1.76108            |            |         |
| 60 minutes after taking the drug | Ketamine  | 60     | 98.6833  | 1.61026            | 1708.0     | 0.611   |
|                             | Morphine  | 60     | 98.6833  | 1.92302            |            |         |

Table 7. Comparison of both groups for adverse events

| Adverse events | Group     | Patients | Number | Ratio | P value |
|----------------|-----------|----------|--------|-------|---------|
| Drowsiness     | Ketamine  | Reported | 34     | 0.566 | <0.001  |
|                |           | Not reported | 26   |     |         |
|                | Morphine  | Reported | 1     | 0.016 |         |
|                |           | Not reported | 59   |     |         |
| Vomiting       | Ketamine  | Reported | 2     | 0.033 | 0.156   |
|                |           | Not reported | 58   |     |         |
|                | Morphine  | Reported | 0     | 0.000 |         |
|                |           | Not reported | 60   |     |         |
| Nausea         | Ketamine  | Reported | 0     | 0.000 | 0.156   |
|                |           | Not reported | 60   |     |         |
|                | Morphine  | Reported | 5     | 0.083 |         |
|                |           | Not reported | 55   |     |         |
The present study had some limitations; for instance, the patients were not followed up for a long time to determine the adverse effects. The research design also did not allow for repeating the drug administration. Therefore, the effects of repeated drug administration on pain relief were simply examined.

Authors' contribution
MM conceived the manuscript and revised it. HM, MAF, and AKh did the statistical analysis, wrote the manuscript, and prepared the tables and figures. All authors read and approved the manuscript.

Conflicts of interest
The authors declare no competing interests.

Ethical issues
This study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, also approved this study. As well, the Institutional Ethical Committee at Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, endorsed all the study protocols (IR.AJUMS.REC.1396.248). Accordingly, written informed consent was taken from all participants before any interventions. This study was one part of the thesis for emergency medicine residency fulfilled by Azam Khilghi at this university. The trial protocol was further authorized in the Iranian Registry of Clinical Trials (identifier: IRCT20170716035105SN3; https://en.irct.ir/trial/26628). Besides, the ethical issues, including plagiarism, data fabrication, and double publication were completely observed by the authors.

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