

## ORIGINAL RESEARCH

## Comparison of Intravenous Ketamine with Morphine in Pain Relief of Long Bones Fractures: a Double Blind Randomized Clinical Trial

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### Abstract

**Introduction:** The selective medication for pain control in many clinical situations is morphine but its complications prevent its widespread use. Ketamine has been introduced as an alternative for morphine in some studies. However, the efficacy of its solitary use has not yet been evaluated. Therefore, the present study was undertaken to evaluate the effect of ketamine alone in relieving pain in trauma patients referring to an emergency unit. **Methods:** In this double-blind clinical trial, patients with long bone fractures were randomly divided into two groups of treatment with intravenous (IV) morphine at a dose of 0.1 mg/kg and treatment with IV ketamine at a dose of 0.5 mg/kg. Pain severity of the patients was recorded before and 10 minutes after injection based on numeric rating scale. The means in the two groups were compared using independent t-test. Then the Kaplan-Meier curve and log rank analysis were used to evaluate the success of treatment. **Results:** 126 patients were included in this study. The mean ages of the patients in the morphine and ketamine groups were 33.6±14.3 and 35.1±13.5 years, respectively (P=0.54). After therapeutic intervention, the pain severity significantly decreased in ketamine (2.7±1.8; P<0.0001) and morphine (2.4±1.5; P<0.0001) groups, with a similar effect of both medications on alleviating pain (P=0.28). The success rate of the treatment at 10-minute interval in groups receiving ketamine and morphine were 59 (93.65%) and 61 (96.8%) patients, respectively (P=0.62). **Conclusion:** The results of the present study showed that administration of ketamine at a low dose (0.5 mg/kg) results in a significant decrease in the severity of acute pain in patients with fractures of long bones. This palliative effect is very similar to that of morphine.

**Key words:** Bone fracture; pain management; analgesia; ketamine; morphine

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### Introduction:

Fractures have a high incidence rate in traffic accidents and are one of the three most important complications during accidents (1). Each year millions of people all over the world suffer from bone fractures, the complications of which threaten the patients' health for several years (2, 3). One of the most important measures in the management of such patients in the emergency unit is fixation and pain control. Opioids are one of the main and most effective medications to relieve pain (4, 5) by suppression of pain center in the CNS through stimulation of  $\mu$  and  $\delta$  receptors. However, complications such as dependence, tolerance, suppression of respiratory center and activation of vomiting center are some of their problems (6). Other medications are NSAIDs, which prevent synthesis of

prostaglandin E2 by inhibiting cyclooxygenase. Nonetheless, this group of medications has gastrointestinal complications and even some of them exhibit renal and hepatic toxicity (7). Paracetamol, Aminophylline, Tramadol, Nefopam etc are some other drugs that have been evaluated in different studies for pain relief. Apart from these medications, ketamine is another medication, which has been introduced. It is one of the medications, which is used for general anesthesia and sedation. Ketamine is an antagonist of N-methyl-D-aspartate (NMDA) (8, 9) and is used in IV, intramuscular, enteric, subcutaneous, intra-nasal, rectal and epidural forms. However, at higher doses it can have complications such as hallucination, dysphoria, nightmares, an increase in intracranial pressure, hypertension, tachycardia, tremors and clonic-tonic seizures (10, 11). Several studies have shown that ketamine is effective in pain relief; however, in the majority of studies available, ketamine has been used in conjunction with other analgesics and no study is available in which use of this medication alone has been comprehensively evaluated for

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pain relief. On the other hand, studies available have not evaluated the use of this medication in trauma patients in emergency units. Therefore, the present study was designed to evaluate the effect of ketamine alone on pain relief in trauma patients referring to an emergency unit of a third-level hospital.

#### Methods:

##### Study design and setting

The present double-blind clinical trial was carried out in 2012-2013 in Al-Zahra and Ayatollah Kashani Educational Centers in Isfahan, Iran. The subjects consisted of patients with fractures of long bones, referring to the emergency unit. The patients were included in the study consecutively. The protocol of the study was approved by the Ethics Committee of Isfahan University of Medical Sciences. The Helsinki Research Protocol was observed during the whole study period. The study was registered in Iranian registry of clinical trial (IRCT number: IRCT2015042812072N3).

##### Subject

The inclusion criteria consisted of an age range of 18-55 years, fractures of long bones and consent to participate in the study. Exclusion criteria consisted of drug abuse, trauma to the head, symptoms and signs of increased intracranial pressure, a decrease in consciousness level, respiratory problems, a history of asthma, contraindications for ketamine (i.e. a history of cardiac problems, especially congestive heart failure, ischemic cardiac conditions, hypertension and patients with cerebrovascular attack) and morphine (i.e. asthma, respiratory problems, hemodynamic instability). In addition, in case of any allergic reaction to any of the medications used, the patient was excluded from the study. The sample size was estimated at 63 subjects in each group based on numeric rating scale (NRS) at 95% confidence interval, a study power of 80%, a standard deviation of 1.6 for pain severity and a minimum difference significance of 2 between the two groups (12).

##### Intervention

First the patients' demographic and clinical data were recorded, which consisted of background diseases, drugs taken, drug abuse, drug allergies, the last meal eaten, location of fracture and severity of pain. Then the eligible patients were randomly divided into two groups: the group receiving IV morphine at a dose of 0.1 mg/kg and the group receiving IV ketamine at a dose of 0.5 mg/kg. To make sure of the double-blind protocol of the study, preparation of the solutions, injections and registration of the results were carried out by three different physicians who had no contact or relationship with each other. The data on the injection of medications were available only to the chief researcher and the medical care personnel were granted access to such data only when drug complications arose. In such a case, the patient in question was excluded from the

study. The severity of pain was registered before injection and 10 minutes after injection based on NRS (13). In cases in which pain did not subside after 10 minutes (a decrease in pain severity equal to or less than 3), the patient received half the initial dose again. Finally, drug side effects in patients were evaluated and recorded.

##### Statistical analysis

Data were entered into SPSS 11.5 and were analyzed after being transferred to STATA 11.0 software. The severity of pain before administration of medications and 10 minutes after initiation of treatment, was reported as means  $\pm$  standard deviations and analyzed using independent t-test. Then Kaplan-Meier curves and log rank analysis were used to evaluate the success of treatment, which was defined as a decrease of 3 scores in pain severity. Statistical significance was set at  $P < 0.05$  in all the analyses.

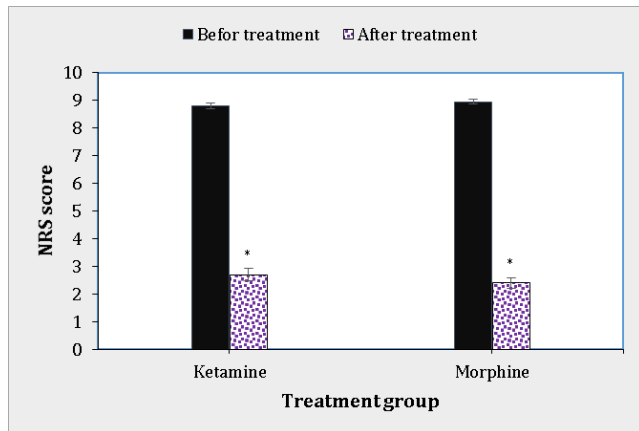
##### Results:

126 patients were included in the study and randomly divided into two equal groups of morphine and ketamine. The mean ages of the patients in the morphine and ketamine groups were  $53.6 \pm 14.3$  and  $35.1 \pm 13.5$  years, respectively ( $P = 0.54$ ). Forty-five (71.4%) and 51 (80.95%) patients were male in the ketamine and morphine groups, respectively ( $P = 0.21$ ). Table 1 shows the site of fractures. The mean pain severity scores at admission in the ketamine and morphine groups were  $8.8 \pm 0.8$  and  $8.95 \pm 0.8$ , respectively ( $P = 0.32$ ). After therapeutic intervention, the severity of pain decreased significantly in the ketamine ( $2.7 \pm 1.8$ ;  $P < 0.001$ ) and morphine groups ( $2.4 \pm 1.5$ ;  $P < 0.001$ ), with no significant differences between the two groups ( $P = 0.28$ ), indicating that both medications are equally effective in alleviating pain (Figure 1). Kaplan-Meier curve showed that five minutes after initiation of injection, ketamine and morphine resulted in a successful decrease in pain severity in 33 (52.4%) and 38 (60.3%) patients, respectively. This rate increased to 59 (93.65%) and 61 (96.8%) patients, respectively, after 10 minutes. Log rank test did not show any significant difference in success rates between the two groups ( $P = 0.62$ ) (Figure 2). None of the patients receiving morphine exhibited any complications; however, during the intervention, six patients (9.5%) receiving ketamine developed emer-

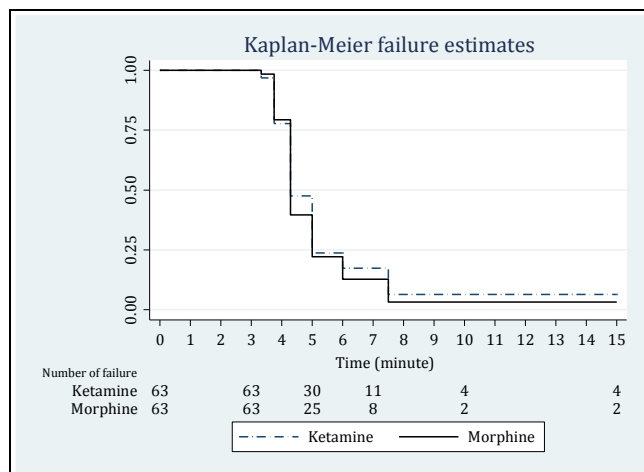
**Table 1:** Demographic variables (%) of patients [↑](#)

Variable	Ketamine	Morphine	p
<b>Gender</b>			
Male	45 (71.4)	51 (81.0)	0.2
Female	18 (28.6)	12 (19.0)	
<b>Site of fracture</b>			
Upper extremities	23 (37.1)	30 (48.4)	0.2
Lower extremities	39 (62.9)	32 (51.6)	
<b>Baseline pain score</b>	$8.8 \pm 0.8$	$8.95 \pm 0.8$	0.32





**Figure 1:** Means (SD) of pain severity in patients receiving ketamine and morphine before and after intervention. \* indicates significant difference from the period before intervention at  $P<0.001$ . NRS: numeric rating scale. [↑](#)



**Figure 2:** The treatment success rate in the morphine and ketamine groups at different time intervals. [↑](#)

gence phenomenon ( $P=0.28$ ). and four patients (6.3%) in this group required a rescue dose due to the short period of the drug effect ( $P=0.12$ ).

#### Discussion:

The results of the present study showed that administration of a low dose of ketamine (0.5 mg/kg) results in a significant decrease in pain severity of long bone fractures. This analgesic effect is very similar to that of morphine. The incidence of drug complications was higher in the ketamine group compared to the morphine group ( $P=0.028$ ), with emergence phenomenon in four subjects. Although the incidence of this complication was higher in the ketamine group, other studies have emphasized that since ketamine is one of the safest and most appropriate medications for sedation in emergency wards, such a complication should not preclude its use because this complication is resolved

spontaneously without any therapeutic intervention (14).

The majority of studies available have evaluated the efficacy of combination treatment with morphine/ ketamine in decreasing pain due to fractures. Galinski et al showed that use of low doses of ketamine decreases the need for morphine up to 26% and its efficacy when administered alone is similar to that of morphine in alleviating pain (5). Weinbroum et al evaluated the simultaneous administration of morphine/ketamine compared with morphine alone in decreasing pain severity after surgery and showed that simultaneous administration of morphine and ketamine results in a significant decrease in pain severity perception by patients (15). A systematic review, too, showed that use of ketamine as a supplementary medication results in a decrease in the need for morphine, preventing unfavorable complications (16).

McCarty et al, too, reported that ketamine is an appropriate, rapid and safe sedative agent, which facilitates reduction of fractures in children in the emergency unit. However, they claim that ketamine should only be administered in locations, such as emergency units, where precise monitoring of patients is possible and an experienced physician is available in the center for the management of airways (17). Snijdelaar et al reported that the combination of ketamine/morphine significantly decreases the need for morphine and has better analgesic effects (18). Jennings et al reported similar findings but emphasized that more minor complications are seen with a combination of morphine/ketamine (12).

One of the most important limitations of the present study was a short follow-up period of patients. In the present study, all the patients were evaluated for only 10 minutes, which precluded evaluation of the effect of ketamine at longer periods. Therefore, it is suggested that in future studies the efficacy of the medication be evaluated at longer follow-up periods. Another shortcoming of the present study was the absence of a placebo group. Due to ethical considerations, it was not possible to follow the patients without any medicinal intervention and use only placebo. It was shown in the present study that IV administration of ketamine results in pain relief in bone fracture patients. However, the effect of this medication on the recurrence of pain is still unknown. Therefore, it is possible that further administration of the medication will prevent recurrence of pain. In addition, the efficacy of other routes for administration of the medication, such as intramuscular, intranasal and local use, should be evaluated in future studies. In addition, use of different administration regimens, such the continuous use or infusion, should be evaluated in future studies.

#### Conclusion:

The results of the present study showed that admin-



istration of a low dose of ketamine (0.5 mg/kg) results in a significant decrease in the severity of acute pain in patients with fractures of long bones. This analgesic effect is very similar to that of morphine.

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#### **Conflict of interest:**

None

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#### **Authors' contributions:**

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

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