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Research Article

Comparison of intranasal ketamine versus intravenous morphine in pain relief of patient with bone fracture

Short title: Intranasal ketamine for pain relief

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ABSTRACT

Background& Aims: Bone fractures are one of the three most important complications during accidents that fixation and pain control are the most important management for these complications. The aim of this study was to compare the effect of intranasal ketamine versus intravenous morphine in treatment of pain in patients with bone fractures.

Methods: In this double-blind clinical trial, 104 patients with bone fractures recruited from the Emergency Department (ED) from 2015 to 2016and they were randomly divided into two groups. Patients in the ketamine group received 1mg/kg intranasal ketamine and patients in the morphine group received 0.1mg/kg intravenous morphine. Then the severity of pain, hemodynamic parameters and side effects in both groups were measured ateach 5 minutes.

Results: Results showed that the mean of pain score at different time intervals (from the first 5until 20minutes) in the morphine group were lower than the ketamine group, that in minute of 5, in ketamine group was 5.19 and in morphine group was 3.51 (P<0.001).Moreover, the analgesic effects of morphine was started faster, which was 2.36 min and in ketaminegroup was 5.09 min (P=0.0034). Finally, we found that the complications such as nausea and vomiting were significantly lower in patients receiving intranasal ketamine (9.6% vs 44.2%, P<0.001 and 3.8 % vs 32.7 %, P<0.001).

Conclusions: Giving the shade on light of our study with intranasal ketamine, and its benefits, including needle-free drug delivery, ease of use, non-opioid nature and ready access properties, this novel drug delivery method merits further research in patients with acute pain due to limb fracture. Early application of low doses of ketamine following trauma-induced pain such as limb fracture may provide acute pain relief and reduce the probability of chronic pain and merits further study.

Keywords: Bone fractures, intranasal ketamine, Intravenous morphine, Pain
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INTRODUCTION

Fracture, a disruption of the bony structure of the body, is one of the three most important complications during accidents.Fixation and pain control are the most important management

procedures for bone fractures. On the other word, pain control may decrease the serious complications and hospitalization;therefore, opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are the main and the most powerful pain relievers [2, 3]. However, complications such as dependence, tolerance, suppression of respiratory center and activation of vomiting center are some of opioid's problems [4] and gastrointestinal complications, renal and hepatic toxicity are some of NSAID's problems [5].

Ketamine has been recently introduced as a pain relief agent and antagonist of N-methyl-D-aspartate (NMDA). The liver microsomal enzyme systemmetabolizesketamine by hydroxylation and demethylation ; then, its principal metabolite callednorketamine is produced,of which plasma levels of this metabolite is three times higher than ketamine following oral administration. Bioavailability of ketamine through intravenousadministration is 93%, while in intranasal route, is 30%. Its plasma concentrations reach to peak level within one minute following intravenous administration. The duration of action in a clinical setting is 30 minutes to 2 hours intramuscularly and 4–6 hours orally [6, 7], hence the duration of sedation of intranasal ketamine has been reported to be 69 minutes approximately [8]. It is used in different ways including intravenous, intramuscular, enteric, subcutaneous, intranasal spray, rectal and epidural forms. Ketamine has different complications such as hallucination, an increase in intracranial pressure, hypertension, tachycardia, tremors and tonic-clonic seizures, but all of these accrued at higher doses of ketamine in blood, which is happened in intravenous administration [9], while intranasal administration of ketamine provides safe and timely relief of pain without the time delay or discomfort associated with intravenous placement [10, 11]. To the best of our knowledge, there isn't enough prospective study about the effects of intranasal administration of ketamine in pain relief, therefore, this study was designed to evaluate and compare clinical efficacy of intranasal ketamine in contrast with intravenous morphine in patients with bone fractures.

Methods and Materials

Study design and population: This double-blind, randomized clinical trial was conducted in Emergency Department (ED) of Golestan General Hospital, in Ahvaz in south-west of Iran from November 2015 to May 2016. The clinical and paraclinical findings of patients receiving intranasal ketamine (ketamine group) were compared to patients receiving intravenous morphine (morphine group). The study was approved by Ahvaz Jundishapur Ethical Committee and all participants signed the informed consent prior to enrolment.

Inclusion criteria: Patient aged from 15-65 years who referred to ED with a diagnosis of fracture in long or short bones in the upper or lower limbs based on clinical and paraclinical findings.

Exclusion criteria: Patients with loss of consciousness, hemodynamic,mental retardation, pregnancy and lactation, psychosis, chronic vascular disease, addiction, and dissatisfaction were excluded.

Participants: The study flowchart is shown in figure 1. One hundred six patients with a diagnosis of bone fracture, who had been diagnosed by emergency medicine specialist and based on clinical and paraclinical findings and inclusion and exclusion criteria were included. The participants were randomly allocated into two groups using a block randomization with matched subjects on sex and age. One hundred four patients completed the study; 52 patients in ketamine group and 52 patients in morphine group.

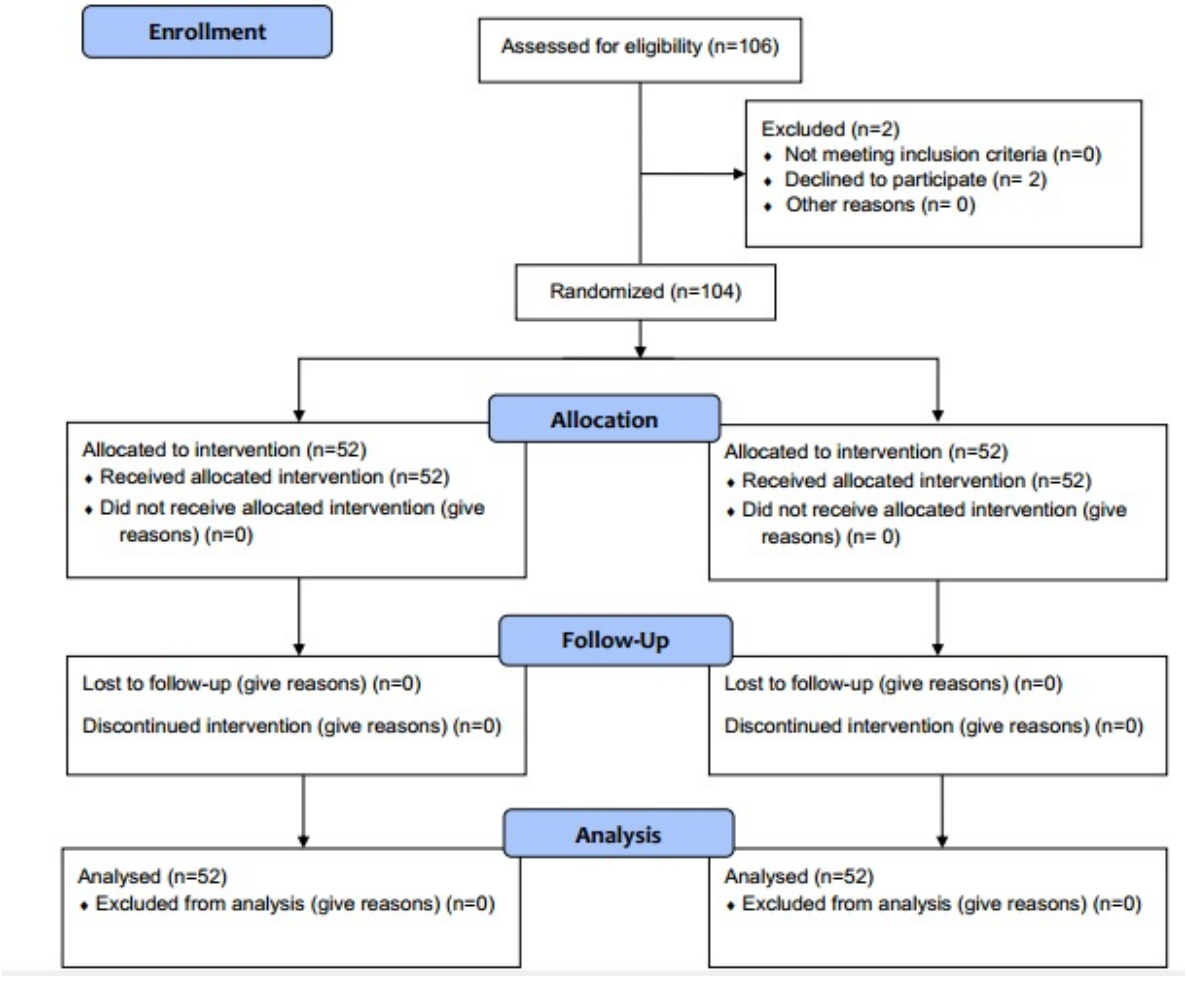
Intervention: After obtaining informed consent, eligible patients were enrolled. The method of intervention and matching the study groups was done according to the Majidinejad et al.'s study [12]. The matching was performed according to age, sex, and location of the fractures. The para clinical findings including blood pressure, respiratory and heart rateswere recorded and estimation of pain severity were measured in both

ketamine and morphine groups before intervention by a 10 centimeter visual analogues scale (VAS). Patients in the ketamine group received 1mg/kg intranasal ketamine (50mg/ml Rotoxmedica, GmbH Arzneimittelwerk,Germany) and patients in the morphine group received 0.1mg/kg intravenous morphine(10mg/ml,DarouPakhsh co., Tehran, Iran). Then if the pain did not decreased, same intervention in both group comps same dosage was repeatedone more time. If the pain did not increase, the patient drops out. Then hemodynamic parameters and estimation of the pain severity in both groups were measured for each five minutes as time intervals up 30 minutes.

Statistical analysis: Data were analyzed and reported only for patients who completed the trial. Statistical analysis was performed using SPSS software version 22. To compare qualitative variables between groups Chi-square test was performed. The severity of pain before and 5 minutes after medications was expressed as means ± standard deviations and assessed using independent t-test. The normal distribution of all studied parameters was checked with Kolmogorov-Smirnov test. Student t-test and paired t-test were used for variables which were distributed in a normal way. The two tailed p-value < 0.05 were considered as significant difference.

RESULTS

Two patients were excludeddue to decline to participate and finally, 104 patients completed the study (Figure 1). **Figure 1.** Flow diagram of the study.



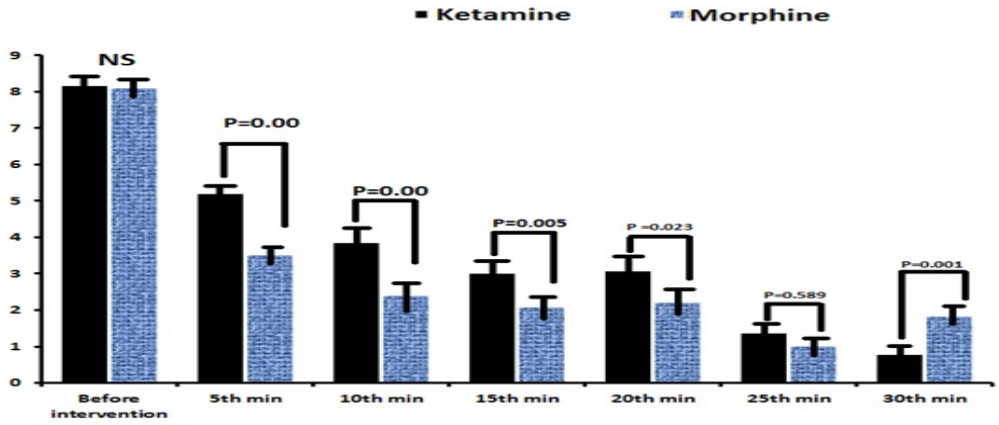
Two groups were matched according to sex and age criteria and fracture site (Table 1).

Table 1. Demographic variables of both intervention groups

Group Variables		Ketamine group (n = 52)	Morphine group (n = 52)	P-value
Age (year)		29.4 ± 11.83	31.42 ± 11.22	0.374
Sex (male)		37 (71.2 %)	43 (82.7 %)	0.163
Fracture	Upper limb	28 (53.8 %)	30 (57.7 %)	0.693
	Lower limb	24 (46.2 %)	22 (42.3 %)	
Nausea		5 (9.6 %)	23 (44.2 %)	<0.001
Vomiting		2 (3.8 %)	17 (32.7 %)	<0.001
Dizziness		4 (7.7 %)	1 (1.9 %)	0.169

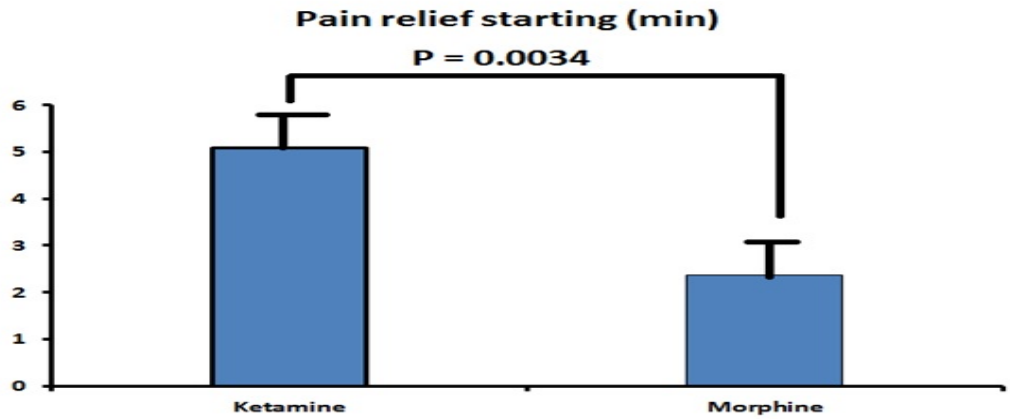
Results showed that the mean of pain score at different time intervals (from the first 5minutes to20 minutes) in the morphine group were lower than the ketamine group. The pain score at 5 minutes in ketamine group was 5.19 and in morphine group was 3.51 (Figure 2, P<0.001). While from 25 to 30 minutes, the analgesic effect of morphine was higher than intranasal ketamine, but only at 30 minutes the difference was statistically significant (Figure 2, P=0.001).

Figure 2. Comparing the pain score changes between two interventional groups.



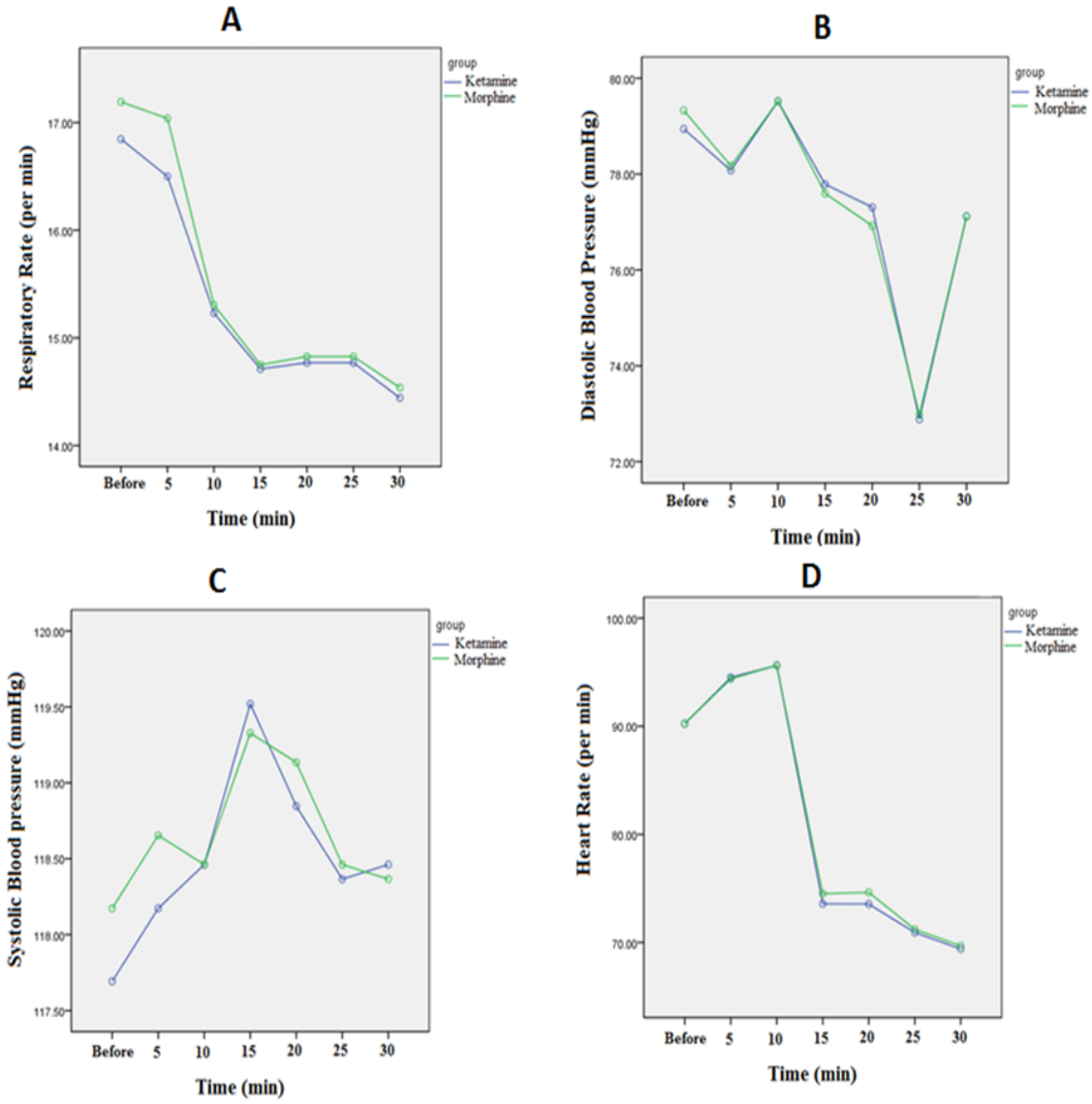
Moreover, the analgesic effects (decrease score) of morphine was started faster, which was 2.36 minutes and in ketamine group was 5.09 min (Figure 3, P=0.0034).

Figure 3. Comparing the pain relief starting (min) between two intervention groups.



There was no significant hemodynamic parameter change between two intervention groups during various time intervals (Figure 4, P>0.05).

Figure 4. Hemodynamic parameters in both ketamine and morphine groups.



Finally, we found that the complications such as nausea and vomiting were significantly lower in patients receiving intranasal ketamine in compare to morphine group (9.6% vs. 44.2%, P<0.001 and 3.8 % vs. 32.7 %, P<0.001, respectively) (Table 2).

Table 2. Comparing the side-effects of both intervention groups

Group Variables	Ketamine group (n = 52)	Morphine group (n = 52)	P-value
Nausea	5 (9.6 %)	23 (44.2 %)	<0.001
Vomiting	2 (3.8 %)	17 (32.7 %)	<0.001
Dizziness	4 (7.7 %)	1 (1.9 %)	0.169

DISCUSSION

This study was aimed to compare the effect of intranasal ketamine versus intravenous morphine in treatment of pain in patients with bone fractures, and showed that prescribing intranasal ketamine the pain score reduced without having serious side effects.

In the study performed by Majidinejad et al.,have been shownthat intravenous ketamine at a low dose (0.5 mg/kg) resulted in a significant decrease in the severity of acute pain in patients with long bones fractures [12].In another study byWeinbroumhas been reportedthat small-dose nasal ketamine and morphine regimen decreasesevere postoperative pain aswell as ketamine reduced morphine consumption, provided rapid and sustained improvement in morphine analgesia, and in subjective feelings of well-being, without unacceptable side effects [13]. Our findings was inline of these researches and showed that pain score reduction and the starting the analgesic effect of ketamine was significantly lower compared to morphine.

In the Majidinejad et al.'s study, intravenous ketamine resultedin a significant decrease in the severity of acute pain in patients with long bones fractures up to 8 minutes; hence from 8 to 20 minutes the analgesic effect was the same [12]. In our study, we showed that intranasal ketamine long-lost up to 20 minutes and its analgesic effect was significantly higher than morphine; while, from 25 to 30 minutes the analgesic effect of morphine was higher. The difference between results of our study and Majidinejad et al., may be due to differencein the route of administration that could lead to longer time to entering the circulation, as well as longer metabolize time [14]. Furthermore, McCarty et al., in their studyshowed that ketamine reliably, safely, and quickly provided adequate sedation to effectively facilitate the reduction of children's fractures in the emergency department [15]. Our results was in agreement with this study that intranasal ketamine showed faster pain relief in compareto intravenous morphine, as well as safer with lower side-effects.

Graudins et al., in their study,observedthat intranasal ketamine at sub-dissociative doses (1mg/kg) is equivalent to intranasal fentanyl (1.5 mcg/kg) for controlling acute moderate to severe pain in children with limb injuries [16].Reid et al., in their study, report that low dose intranasal ketamine (between 0.25 and 0.5 mg/kg) in a prehospital setting had significant effect in treating severe pain in a child with a 3% scald burn noted onset within 3 minutes [17]. Christensen et al. showed that intranasal ketamine with doses of 50 mg had significant effect for treating post-operative pain following wisdom tooth removal (meaningful pain relief was achieved by 14 minutes in 70% of patients) [18]. The intranasal administration is frequently used for opioid delivery in adults and children emergency patients through department and pre-hospital settings [19, 20]. Intranasal ketamine at a dose of 6 mg/kg has been reportedas an effective sedative in pediatric patients during premedication [21].Besides, intranasal ketamine at doses of 10–50 mg was reported to be superior to placebo in controlling chronic pain in adult patients, with no serious side-effects [22].

CONCLUSIONS

Giving the shade on light of our study with intranasal ketamine, and its benefits,includingneedle-free drug delivery, ease of use, non-opioid nature and ready access properties, this novel drug delivery method merits further research in patients with acute pain due to limb fracture. Early application of low doses of ketamine following trauma-induced pain such as limb fracture may provide acute pain relief and reduce the probability of chronic pain and merits further study.

Conflicts of interest: none.

Acknowledgments

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participated in this study, and the Clinical Research Development Units (CRDU) of Ahvaz Golestan hospital.

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