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Efficacy of intranasal ketamine in controlling pain caused by bone fractures: A single-center double blind randomized controlled trial

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ABSTRACT

Introduction: Bone fractures are recognized as the second most prevalent cause of pain for patients seeking treatment in medical facilities. This study aims to evaluate the efficacy of intranasal and intravenous ketamine in comparison to intravenous morphine in alleviating severe pain in patients presenting to emergency departments with various bone fractures.

Method & material: The clinical trial was conducted on patients over the age of 18 who presented at the emergency department of Imam Reza Educational and Medical Center with bone fractures. These patients were divided into three groups for treatment: intranasal ketamine at a dose of 1 mg/kg body weight, intravenous ketamine at a dose of 0.5 mg/kg body weight, and intravenous morphine at a dose of 0.1 mg/kg body weight. The severity of pain experienced by patients was documented using the numerical pain rating scale at the time of admission, and then at 15 min, 30 min, and 60 min after drug administration.

Results: The results of the study revealed that there was no statistically significant difference in the efficacy of pain relief among the three study groups (p=0.77). The interaction of (time*type of drug) had no significant effect on pain intensity (p=0.58). There was no statistically significant difference in side effects reported by patients between the three study groups, with the intranasal ketamine group reporting only minor side effects.

Conclusion: The results of this study showed significant effects of intranasal ketamine and intravenous ketamine in reducing pain in patients with bone fractures. The findings further suggest that the analgesic effect of intranasal ketamine is comparable to that of intravenous ketamine and morphine, with no significant adverse effects observed.

Introduction

Fractures represent the second most prevalent cause of pain for patients seeking treatment in medical facilities [1,2]. The significance of pain management in such cases extends beyond immediate analgesia, encompassing its impact on various short-term and long-term outcomes [1,2]. Pain can increase the susceptibility to disease and impair the immune system. Also pain has psychological effects. Inadequate treatment of pain can cause catecholamine release and increase the risk of acute coronary syndrome, stroke [3]. Various medications are employed in emergency departments to alleviate patients' discomfort [2]. These medications include opioids, non-steroidal anti-inflammatory drugs, Acetaminophen, duloxetine and ketamine [2,4]. The judicious selection of medication for pain control has been demonstrated to play a vital role in the enhancement of patient outcomes during and after hospitalization, the reduction of treatment costs, and the minimization of the risk of chronic pain [5–8]. Several studies have been conducted on the effects of morphine and intravenous ketamine on pain control and have shown their effect on effective pain reduction. Studies have also shown that intravenous ketamine is as effective as intravenous morphine in managing pain in these patients. Ketamine is considered to be less risky for patients in terms of maintaining homeostasis and is preferable to morphine [2,4,9–11]. However, there is currently no compelling evidence to support the hypothesis that intranasal ketamine is as effective as intravenous ketamine or morphine. Further research is required to establish its efficacy and safety [12–14]. This concern becomes particularly significant in situations where venous access is not available [15]. It is essential to investigate the effect of intranasal ketamine and

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compare it with effective and potent analgesics such as intravenous morphine or intravenous ketamine. It is also necessary to investigate the possible side effects of intranasal ketamine and compare it with intravenous morphine or intravenous ketamine. New studies in this area could facilitate the refinement of treatment protocols and the reduction of treatment time. The present study, therefore, sought to compare the efficacy of intravenous and intranasal ketamine with intravenous morphine in the management of severe pain in patients presenting to the emergency department with various bone fractures.

Method & material

Study design and setting

This study was designed as a double-blind, randomized clinical trial. It was conducted using a double-blind methodology, ensuring that neither the participants nor the primary investigators were aware of the treatment assignments. The medication was prescribed by the physician and administered by a nurse, after which a secondary nurse or physician completed the checklist to maintain blinding and accuracy. The trial took place at the Imam Reza (AS) Tabriz Research and Education Center, affiliated with Tabriz University of Medical Sciences, Iran, during the 2023–2024 period. Ethical approval was granted by the Institutional Review Board (IRB) of Tabriz University of Medical Sciences under the ethics code "IR.TBZMED.REC.1401.953." Additionally, the study protocol was officially registered in the Iranian Registry of Clinical Trials under the ID: IRCT20140524017812N4N1.

Participants and sample size

In this study, 156 patients over 18 years of age presenting to the emergency department with bone fractures were randomly assigned to three treatment groups. The inclusion criteria included willingness to participate in the study and completion of a written informed consent form. under 18 years of age, having previous systemic diseases that would contraindicate the use of ketamine or morphine (such as allergy to eggs etc.), having a history of any previous bone surgery and history of long opioid use were exclusion criteria.

The total sample size was determined by employing the F-test method, yielding a calculated total of 138 patients. This number was subsequently estimated to be 156 individuals, considering a potential 10% dropout rate. The sample size for each drug group was estimated to be 52 individuals. GraphPad random assignment software was used to generate the random sequence. Thus, before using the software and creating the sequence, it was decided to name the letter (N) for intranasal ketamine, the letter (K) for intravenous ketamine, and the letter (M) for morphine.

Intervention and definitions

The study employed a 5-fold permuted block randomization method. A double-blind design was implemented, ensuring that both participants and researchers remained unaware of group assignments. Medication administration followed a structured process: a nurse dispensed the prescribed drug as directed by a physician, while a second nurse or physician collected participants' responses via a questionnaire.

Participants were divided into three groups. The first group received an intravenous dose of ketamine at 0.5 mg/kg of body weight, along with four puffs of intranasal normal saline as a placebo. The second group was administered ketamine intranasally at a dose of 1 mg/kg of body weight, accompanied by 1 mL of intravenous normal saline as a placebo. The third group received an intravenous dose of morphine at 0.1 mg/kg of body weight, along with four puffs of intranasal normal saline as a placebo.

The randomization sequence was generated using specialized software, with each assignment enclosed in a sealed envelope. To preserve the integrity of the sequence, a corresponding number was recorded on the envelope's exterior. At the study's outset, demographic data—including age, gender, and medical history—were documented. The location of the fracture and pain severity were assessed using a 0 to 10 Numeric Rating Scale. Pain intensity was recorded before treatment and at 15, 30, and 60 min post-administration, serving as the primary outcome measure. Any potential side effects were also carefully monitored and documented.

To uphold the double-blind nature of the study, three separate individuals were responsible for drug preparation, administration, and data collection. Both patients and assessors remained unaware of the specific treatment received. Pain severity was systematically recorded and analyzed using the numeric rating scale.

Statistical analysis

The data obtained were entered into IBM SPSS Statistics software, version 26. The significance level for this study was set at 0.05. The chi-square test was utilized for the analysis of qualitative variables. In addition, the assumption of a normal distribution of the quantitative variables was initially assessed using the Kolmogorov-Smirnov test. In instances where the data distribution was found to be normal, the one-way analysis of variance test was employed. The Mixed ANOVA model was employed to compare the effect of the drug between groups and to examine the effect of time on pain reduction within groups. This model is capable of analyzing the mean differences between groups (fixed effect of drug) and changes over time (fixed effect of time) and also considers individual changes between participants (random effect of patients). The Mixed ANOVA model is well-suited to data that undergoes repeated measures, facilitating the assessment of the interaction between time and drug groups. Furthermore, the intention-to-treat analysis was conducted to ensure the robustness of the findings.

Results

A total of 156 patients were enrolled in the study. Following the exclusion of 16 participants who did not complete the treatment course, the final analysis comprised data from 46 patients in the intravenous ketamine group, 47 patients in the intranasal ketamine group, and 47 patients in the intravenous morphine group. The CONSORT Diagram showing the flow of participants through each stage of a randomized trial are shown in Fig. 1.

A comparison of the analgesic effect of the drugs used between the three groups revealed no significant difference (p=0.77). Furthermore, the interaction effect of time and type of drug on pain intensity did not have a significant effect (p=0.58). The Demographic and clinical data of the patients studied in the three groups is shown in Table 1. The results of this table indicate that the effect of time on pain intensity is significant, with a substantial decrease in pain intensity observed in all three analgesic drugs over time (p<0.001). However, the results also demonstrate an absence of a significant interaction effect between time and type of drug on pain intensity (p=0.58), indicating that there was no significant difference in changes in pain intensity over time among the different groups.

Despite the statistically significant reduction in pain score observed at all times and for all three drugs, the table indicates that there was no significant difference between intravenous and intranasal ketamine at time points 3 and 4. This finding suggests that the temporal effects of the drugs are sufficiently similar that no substantial difference is observed between subsequent times [3,4]. Furthermore, the significant fluctuations in pain score observed at times 3 and 4 in the intravenous morphine group imply that the effectiveness of morphine increased gradually over the treatment period, while the effect of ketamine remained consistent. A further examination of the changes in pain score over time and the interaction with other variables revealed that the location of the fracture significantly affected the pain score (p=0.03).

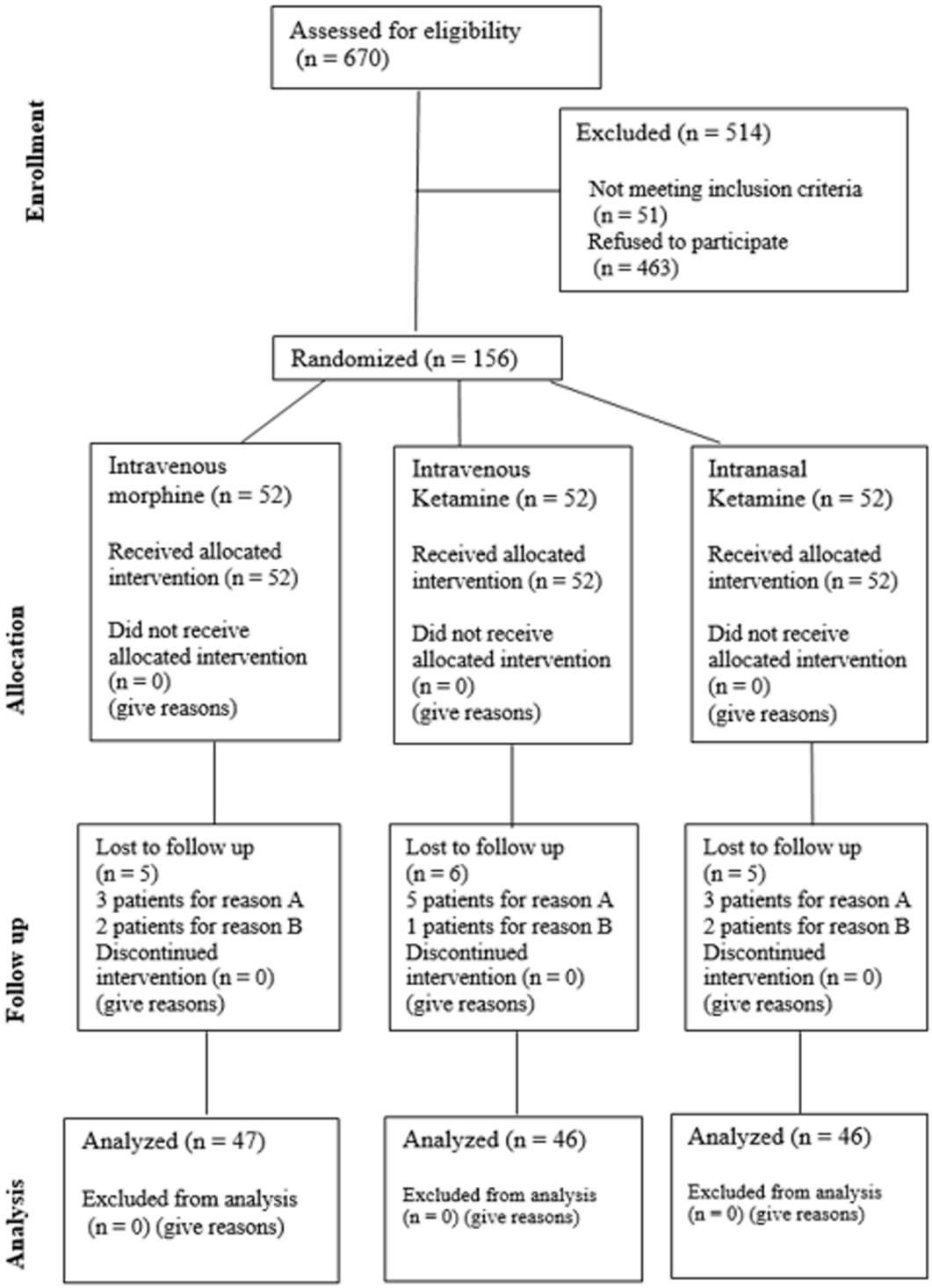

Fig. 1. CONSORT diagram showing the flow of participants through each stage of a randomized trial.
A: Lost to follow up because of leave emergency department with DISCHARGES AGAINST MEDICAL ADVICE
B: Lost to follow up because of refer to another hospital.

Figs. 2 and 3 show relation between fracture location and patients pain and association between the number of fractures and the pain score during the follow up. The pattern of pain change over time varies according to the location of the fracture (upper or lower limb). Patients with lower extremity fractures have reported greater levels of pain. In contrast, the interaction effect of fracture site with drug on the patient's pain level over time demonstrated that there was no significant difference between the three groups, suggesting that fracture site did not affect the effectiveness of the aforementioned drugs in reducing pain over time (p=0.96). However, the number of fractures over time had a significant effect on the pain score and the way pain changed over time (p=0.03).

A further analysis was conducted to compare the interaction effect of fracture number with drug on the patient's pain level over time. This analysis revealed no significant difference between the three groups (p=0.35), suggesting that fracture site did not affect the effectiveness of

Table 1
Some Demographic and clinical data of the patients studied in the three study groups.

Variable	Level of Variable	Intranasal ketamine (N)	Intravenous ketamine(K)	Intravenous morphine (M)
Sex	Male	30(63.8)	31(67.4)	32(68.1)
	Female	17(36.2)	15(32.6)	15(31.9)
Background disease	None	34(72.3)	32(69.6)	29(61.7)
	Chronic renal failure	0(0)	0(0)	1(2.1)
	Chronic obstructive pulmonary disease	3(6.4)	1(2.2)	3(6.4)
	Cerebrovascular accidents	1(2.1)	1(2.2)	1(2.1)
	Depression	0(0)	1(2.2)	1(2.1)
	Diabetes	3(6.4)	4(8.7)	3(6.4)
	High blood pressure	3(6.4)	4(8.7)	6(12.8)
	Hypothyroidism	1(2.1)	1(2.2)	0(0)
	Ischemic heart disease	1(2.1)	2(4.3)	2(4.3)
	Migraine	0(0)	0(0)	1(2.1)
	Pulmonary thromboembolism	1(2.1)	0(0)	0(0)
Mechanism of trauma	Car accident	25(53.2)	26(56.5)	28(59.6)
	Direct trauma	3(6.4)	4(8.7)	4(8.5)
	Fall from a height	19(4.4)	16(34.8)	15(31.9)
Fracture site	Lower	24(51.1)	26(56.5)	27(57.4)
	Upper	17(36.2)	16(34.8)	15(31.9)
	Lower & Upper	6(12.8)	4(8.7)	5(10.6)
Number of fractures	1	29(61.7)	29(63)	30(63.8)
	2	13(27.7)	12(25.5)	12(25.5)
	3	3(6.4)	4(8.7)	2(4.3)
	4	1(2.1)	1(2.1)	3(6.4)
	5	1(2.1)	0(0)	0(0)

the drugs in reducing pain over time. In summary, all three analgesic drugs were found to be effective in reducing pain scores, although the intensity and duration of pain reduction may vary between drugs. Furthermore, no substantial disparities in reported adverse effects were observed among the three groups. The side effects reported in the intranasal ketamine group were not significant.

Adverse events reported in the entire study group after treatment included 94 cases (67.1%) of no complications, 3 cases (2.1%) of agitation or restlessness, 19 cases (13.6%) of dizziness, 8 cases (5.7%) of drowsiness, and 16 cases (11.4%) of nausea, respectively. When comparing the analgesic effect of the drugs used between the three study groups, no significant difference was observed (p=0.77). This finding suggests that the drugs in question did not demonstrate a clear distinction in their analgesic efficacy compared to the other drugs.

Discussion

The findings of this study demonstrated a substantial impact of intranasal ketamine and intravenous ketamine in mitigating pain in patients with bone fractures. Additionally, the analgesic effect of intranasal ketamine was comparable to that of intravenous ketamine and morphine, with no significant adverse effects observed. The results of our study are similar to previous studies [12,16–19]. Given the ineffectiveness of opioids such as morphine in certain patients, including opioid-resistant individuals, and the occurrence of adverse effects such as long-term dependence, depression, respiratory arrest and excessive decrease in blood pressure, ketamine can be considered a suitable alternative [20,21]. Preliminary studies have indicated that ketamine exerts a more pronounced analgesic effect during the early phases of treatment, although the duration of action of morphine has been found to be more protracted [13,22]. The findings of this study demonstrate that the duration of the analgesic effect of morphine exceeds that of ketamine, and that, over time, there is a significant decrease in pain levels among patients. However, previous studies have indicated that the adverse effects reported in the ketamine group were less prevalent than those observed in the morphine group [6,22].

The findings of this study suggest that ketamine may be considered as a treatment option in the management of pain in patients with bone fractures [16,23]. In addition to mitigating acute opioid side effects like respiratory depression, it may also help minimize the long-term consequences of opioid use, such as addiction. This is particularly important in hospital settings, where patients are often prescribed narcotics during their stay and continue receiving them upon discharge for home use. The findings of this study indicate that both intranasal and intravenous ketamine methods are effective in pain management; however, the selection of the most appropriate method should be made depending on the clinical situation and the needs of the physician and patient [24,25]. It is noteworthy that both treatment methods have the potential to be

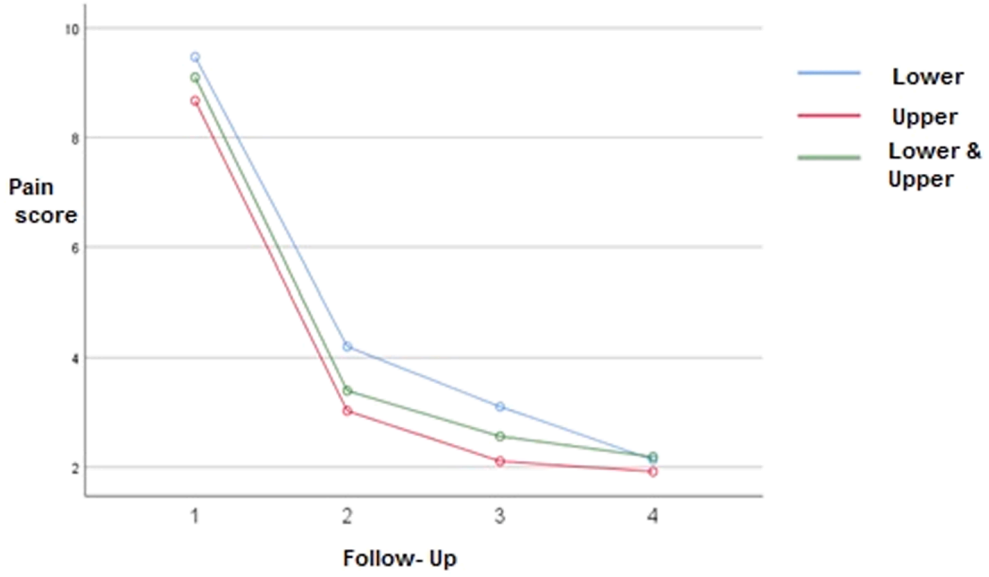

Fig. 2. Relationship between fracture location and patient pain during the follow up.

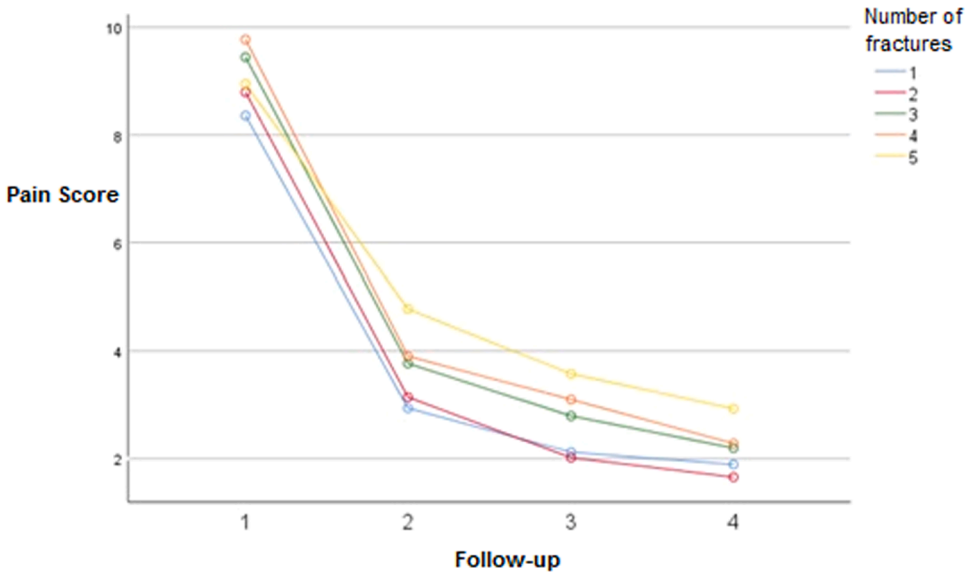

Fig. 3. Association between the number of fractures and the pain score during the follow up.

effective in the management of pain caused by bone fractures; however, intravenous ketamine may be preferable in acute cases due to its speed and greater effectiveness [14,25,26]. Furthermore, the utilization of opioids may be constrained in circumstances where patients may experience hemodynamic instability [27]. Conversely, ketamine, whether administered intravenously or intranasally, has been shown to be a safer and more effective option as an anesthetic and pain reliever [7, 28]. The pharmacodynamics of ketamine ensure that it effectively provides pain relief without severe adverse effects on the patient's hemodynamics [29,30]. The main side effect of ketamine is the experiencing perturbing dissociative symptoms in some patients that may occur at low doses (i.e., 0.1–0.4 mg/kg) [29]. Other side effects include hyper-salivation, hyperreflexia, dizziness, nausea and vomiting [29,30]. These symptom are dose dependent and usually resolve without treatment [29,30]. On the other hand, in animals, ketamine has a higher safety ratio—the ratio of the usual lethal dose to the typical effective dose—compared to morphine, indicating that ketamine is the safer option. In humans, ketamine also exhibits a broader safety margin, with lethal outcomes rarely reported [31,32].

This study examined the efficacy of intranasal and intravenous ketamine and morphine in alleviating pain in patients with bone fractures. The findings revealed that the analgesic efficacy of ketamine, irrespective of its administration method, was comparable to that of intravenous morphine. Intranasal ketamine emerged as a promising alternative due to its minimal and manageable adverse effects and ease of administration.

Strengths and limitations

The main strengths of this study were randomization and a low drop out**.** A significant limitation of the present study was the relatively brief follow-up period for patients. Consequently, it is recommended that subsequent studies assess the efficacy of the drug over extended follow-up periods. Furthermore, the employment of varied administration regimens, such as continuous infusion or intermittent use, and the augmentation of solution concentration to reduce usage frequency, should be appraised in subsequent studies. One significant limitation of our study was the absence of economic analysis. Additionally, a major challenge we encountered was the exceptionally high rate of participant refusal. The primary reason for this reluctance stemmed from concerns about potential side effects of the medication, as many patients feared adverse outcomes.

Conclusion

The results of this study showed significant effects of intranasal ketamine and intravenous ketamine in reducing pain in patients with bone fractures. The findings further suggest that the analgesic effect of intranasal ketamine is comparable to that of intravenous ketamine and morphine, with no significant adverse effects observed.

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Statements and declarations

The authors declare that they have no known financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethic

This study was approved by the Institutional Review Board (IRB) of Tabriz University of Medical Sciences, Tabriz with the ethics code "IR.TBZMED.REC.1401.953." The study protocol was registered in the Iranian registry of clinical trials with ID: IRCT20140524017812N4N1.

CRediT authorship contribution statement

Morteza Zavvar: Data curation, Conceptualization. **Mahboub Pouraghaei:** Supervision, Conceptualization. **Saeid Safiri:** Methodology. **Gholamreza Faridaalaee:** Writing – review & editing, Writing – original draft, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing interests.

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