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ORIGINAL ARTICLE

Efficacy of nebulized fentanyl and low dose ketamine for pain control of patients with long bone fractures: A randomized, double-blind, clinical trial

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ABSTRACT

Introduction: Fentanyl is a lipid soluble, highly potent opioid. The lipid solubility of fentanyl makes it an ideal opioid to be administrated by inhalation. The current study compared ketamine infusion and nebulized fentanyl in bone fracture pain relief.

Methods: In this double-blind, randomized clinical trial, patients aged 18 to 55 years who were admitted to the emergency department (ED) with limb fracture were recruited. A total of 127 patients were included in the study, 51.1% (65) of whom were male and 48.9% (62) of whom were female. The patients were divided equally into two groups: Group I received 100 cm^3 IV infusion of normal saline and 4 μg/kg of 50 μg/ml nebulized fentanyl; Group II received 0.4 mg/kg ketamine in 10 min and 5 cm^3 nebulized normal saline. Pain was assessed using a visual analog scale just before treatment and 5, 10, 15, 30, and 60 min post-treatment.

Results: Before intervention, the pain scores of both groups showed no significant difference. However, log linear analysis in both groups showed a significantly decrement during the follow up (60 min) ($p < 0.0001$). Multiple comparison analysis showed that pain scores were significantly higher in the patients of Group I. Moreover, patients in Group I required additional treatment.

Conclusion: Ketamine can be used as an alternative non-invasive treatment to successfully relieve pain in patients with limb fractures.

African Relevance

- Attention to pain reduction in emergency centres is a priority
- Nebulised fentanyl could be used as an acceptable alternative to intravenous drug administration

Introduction

Bone fractures affect millions of people all over the world and have been a menace to the health of patients for many years [2]. The treatment of priority in emergency departments (EDs) for patients suffer from limb fracture is pain reduction. The control of pain is related to patient gratification [3]. In fact, one of the most common causes for pursuing emergency care is acute pain. It has been reported that nearly 32% of patients admitted to an ED complain of pain; yet, one common problem in EDs is the under treatment of pain [4].

Ketamine was introduced into clinical use in the 1970s [5]. It is an intravenous (IV) anesthetic drug that shows a broad range of pharmacological effects, including catalepsy, sedation, bronchodilation, and somatic analgesia [6]. The effect of ketamine is produced by the non-competitive antagonism of the *N*-methyl D-aspartic acid (NMDA) receptors. Moreover, it cooperates with monoamine, purinergic, cholinergic, and adrenoreceptors as well as opioid receptors [7]. Because of its IV administration route, an IV cannula insertion is required, which can cause additional distress to patients. Furthermore, it is usually time-consuming and can even result in unsuccessful infusion. It has been reported that 12 to 26% of IV catheter infusions are unsuccessful [8]. Therefore, more feasible methods for the administration of analgesic medication are needed.

Analgesic medications most commonly and frequently used in EDs are opioids, the most potent drugs for alleviating pain. Opioids act by suppressing the pain center in the central nervous system (CNS) through μ and δ receptor stimulation [9]. Fentanyl is a lipid soluble, highly potent opioid. The lipid solubility of fentanyl makes it an ideal opioid that can be administrated by inhalation. It is believed that nebulized fentanyl can feasibly be used for effective pain relief. The aim of this study was to compare ketamine infusion and nebulized fentanyl in bone fracture pain relief.

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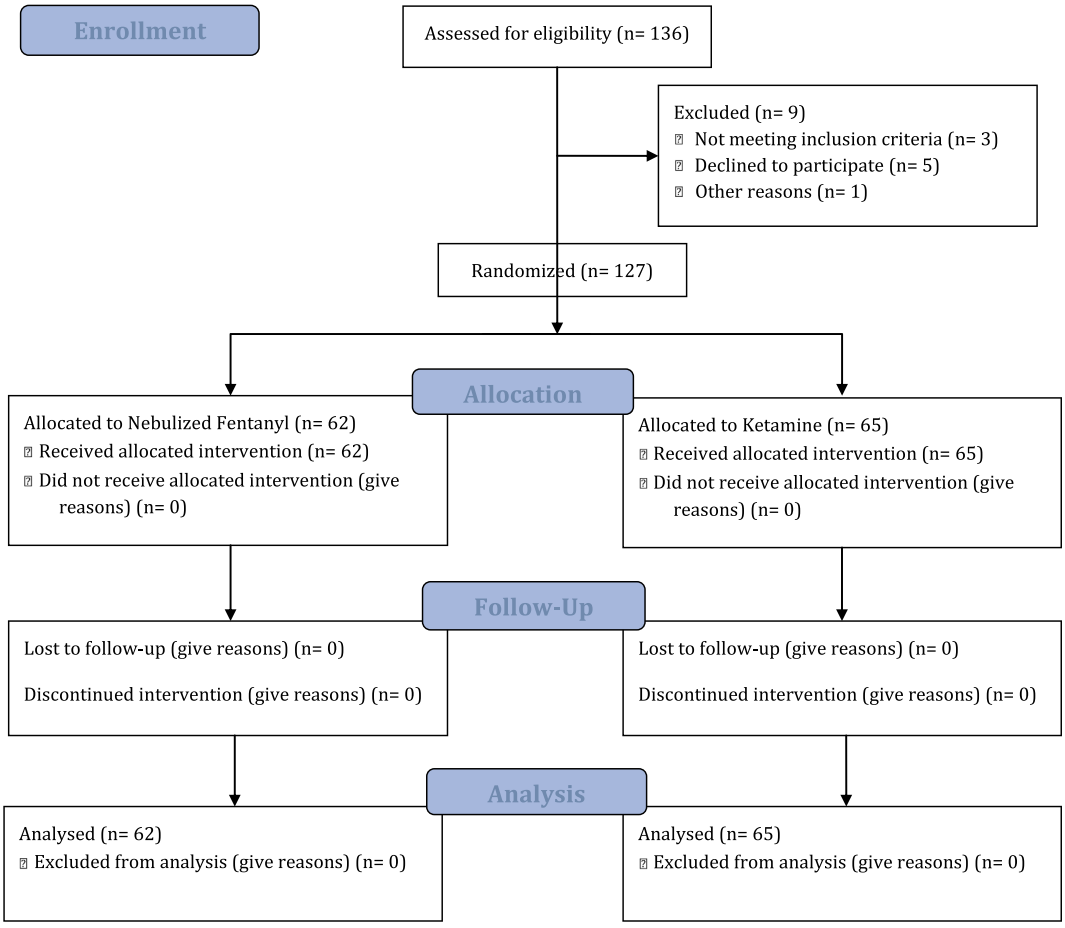

Fig. 1. Study flow diagram.

Table 1
Patient's characteristics.

Variables	Ketamine (N = 65)	Nebulized fentanyl (N = 62)	*p* value
Ages (years)	36.28 ± 10.73	34.5 ± 11.97	0.3
Sex F (%)	22 (33.8)	17 (27.4)	0.43
Limb fracture N (%)			
Upper	23 (35.4)	17 (27.4)	0.21
Lower	42 (64.6)	45 (72.6)	

Table 2
Comparison of drug efficacy in Group I and II.

Variables		Nebulized fentanyl (N = 62)	Ketamine (N = 65)	*p* value
Pain score	Before intervention	7.59 ± 1.8	7.38 ± 2.5	0.69
	5 min	7.23 ± 1.9	6.17 ± 1.7	0.001
	10 min	5.62 ± 2.1	4.76 ± 3.3	0.001
	15 min	3.96 ± 1.1	3.14 ± 1.6	0.001
	30 min	3.66 ± 2.8	2.14 ± 1.4	0.001
	60 min	3.11 ± 1.3	2.33 ± 0.84	0.001
Need to additional therapy	Yes	44 (71%)	0	0.001
	No	18 (29%)	65 (100%)	

Methods

This double-blind, randomized clinical trial (RCT) study recruited patients 18 to 55 years of age with limb fracture who were admitted to the ED of Golestan Hospital, Ahvaz. An ethics code was obtained for this study from the Ethics Committee of Jundishapur University of Ahvaz, and the clinical trial code was received in 2017. This trial was also registered with the Iranian Registry of Clinical Trials' clinical trial registry: 201703129801N2 (http://www.irct.ir, ethic code: IR.AJUMS.REC1395.553). Pain score as a primary outcome was determined by the visual analog scale (VAS), and patients with a VAS score higher than 3 were included in the study. Patients who had consumed anti-psychotic, sedative, TCA, MAOI, SSRI drugs, opioid addicts, patients with underlying acute or chronic renal and hepatic disease, cardiac disease, upper and/or lower respiratory infection, asthma, COPD, or allergies, pregnant or breast-feeding women, fentanyl-prohibited patients, those with multiple myeloma, a history of convulsion, ketamine allergy, head injury, or avulsion fractures, and patients with unstable hemodynamic factors were excluded from the study. Additional therapy for secondary outcome was measured.

The patients were divided equally into two groups using the block randomization method in order to eliminate confounding factors. The drugs were administrated by nurses; neither the patients nor the nurses were aware of the type of drug. Patients in Group I received 100 cm^3 IV infusion of normal saline and 4 μg/kg of 50 μg/ml nebulized fentanyl through a DeVILBISS atomizer. Patients in group II received 0.4 mg/kg ketamine in 10 min and 5 cm^3 nebulized normal saline. Pain was assessed by VAS just before treatment and 5, 10, 15, 30, and 60 min after treatment. Non-responding patients (VAS score higher than 3 after 60 min) were further treated with 0.1 mg/kg IV morphine after the 60 minute period was past.

In order to achieve 90% power and a correlation as small as 0.25 with a 0.05 Type I error rate, the sample size was calculated to be 125 patients. At first, data was analyzed in terms of descriptive statistics;

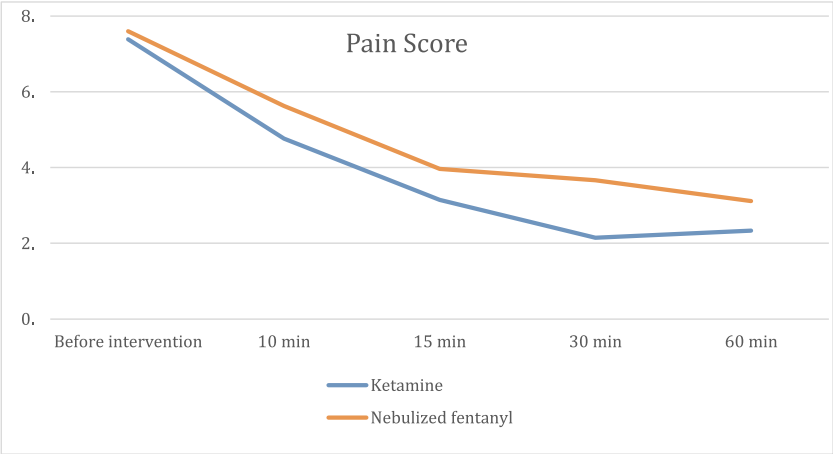

Fig. 2. Pain score trend during the study follow up.

then, to assess data normality, the Kolmogorov-Smirnov test was carried out. Based on data normality, the *t*-test or Mann-Whitney test was used to compare quantities between the two groups, and the chi-square test was used to compare categorical factors. All statistical analyses were performed using SPSS software. A p-value < 0.05 was considered significant.

Results

This study included 127 patients admitted to the ED (Fig. 1). Out of the 127 patients 51.1% (65) were male and 48.9% were female. Demographic factors are shown in Table 1.

The median age of patients in Group I and Group II was 36 and 34.5 years, respectively. The difference was not statistically significant. Upper limb fractures were seen in 6% of patients in Group 1 and in 35.4% of patients in Group II, but the difference was not significant. Thus, the patients in both groups were homogenous based on age, gender, and fracture type.

Before intervention, the pain scores in both groups showed no significant differences; however, log linear analyses in both groups showed a significant decrement during the follow up (60 min) ($p < 0.0001$). Multiple comparison analysis showed that pain scores were significantly higher in Group I patients, and more patients in Group I than Group II required additional treatment (Table 2, Fig. 2).

Discussion

The findings of the current study indicated that ketamine is effective in reducing the pain of limb fractures; VAS scores decreased from 7.5 (before the study) to 3.1 (60 min after treatment) in patients treated with ketamine. While patients in Group II (those who received ketamine) reported a significantly higher level of pain relief than those in Group I, pain specialists have shown that a reduction in pain of 1.3 points on the VAS scale can be clinically significant. Thus, nebulized fentanyl, similar to ketamine, can be used for pain relief in patients with limb fractures. Previous RCT studies have also reported that the nebulized form of opioids has a significant effect on post-operative pain [10]. This evidence provokes interest in using alternative routes of opioid administration, especially in prehospital situations and EDs [11,12]. Attempts are mainly made to seek an administration route with priority over IV infusions of analgesics.

To the best of the authors' knowledge, this is the first study to evaluate the effects of nebulized fentanyl in comparison with IV ketamine in reducing the pain of patients with limb fractures. Many reports have shown that nebulized fentanyl can affect pain control. Farahmand et al. conducted an RCT study in which they compared the effects of nebulized fentanyl and IV morphine on pain reduction in patients with limb fractures. They reported that nebulized fentanyl successfully reduced pain to approximately 3 on the VAS measuring system [13]. Moreover, in a study conducted by Furyk et al., nebulized fentanyl was compared to IV morphine in children with limb fractures. Seventy-three patients were evaluated, and the findings indicated that nebulized fentanyl could reduce the mean VAS score to 3 [14]. Some other authors have studied the analgesic effects of fentanyl administered through different routes. Artfield et al. studied 50 patients with abdominal pain and compared the analgesic effects of 1.5 μg/kg fentanyl administered through nebulized and IV routes. They reported that the IV route led to faster analgesic effects, but after 30 min the pain scores showed no significant difference between the groups [15]. Similarly, the current study showed a delay in the analgesic effect of nebulized fentanyl compared with IV ketamine. In another RCT study, Miner et al. compared the analgesic effects of nebulized fentanyl citrate and IV fentanyl citrate in children admitted to EDs with painful conditions to assess nebulized fentanyl as a feasible alternative to IV fentanyl for relieving acute pain [16]. Compared with previous studies, the current study used different doses of both fentanyl and ketamine. Many efforts have been made by investigators to find a transmucosal delivery route of opioids, especially fentanyl. Intranasal fentanyl has been evaluated for immediate pain relief in patients with breakthrough pain. The results have shown that intranasal fentanyl is briskly absorbed by mucosal membranes and reaches maximum concentrations in plasma in approximately 2 min [17]. Nebulized fentanyl, however, is inhaled into the lungs and then absorbed into the blood through circulation via the pulmonary system. Mather et al. evaluated the pharmacokinetics of nebulized fentanyl on 15 healthy participants and compared concentrations of the drug administered intravenously and through a nebulizer. They showed that a longer time is needed for the drug in nebulized form to reach maximum concentrations in plasma (4 to 9 min in the nebulized route vs. 2 to 4 min in the IV route). The differences were statistically significant [18].

A limitation of this study was the short follow-up period, which precluded determining the side effects of the drugs; thus, the side effects of the drugs were not compared between the groups.

Conclusion

Collectively, the current findings which have shown that both methods provided effective analgesia, but ketamine was somewhat superior to fentanyl. The use of fentanyl needed to be supplemented with longer-acting agents after 60 min. Both agents could be considered in the ED and nebulizer fentanyl could be used if an IV is not available. Moreover patients who received ketamine reported lower pain scores

and needed less additional treatment than those patients who received nebulized fentanyl.

Conflict of interest

The authors declare no conflict of interest.

Dissemination of Results

The findings from this paper has not been disseminated beyond this publication.

Author Contribution

All authors contributed equally to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

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