Original Article

Comparison of the Effect of Intravenous Fentanyl with Low-Dose Ketamine on Pain Relief in Patients Taking Methadone and Suffering from Limb Fractures

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Abstract

Background: Given the significance of pain control in addicted patients and the prominence of not using opioids due to patient's drug dependence, the present study aimed at comparing and evaluating the effect of intravenous fentanyl with low-dose ketamine on pain relief in patients taking methadone and suffering from limb fractures.

Materials and Methods: The present double-blind randomized clinical trial was performed on 100 patients taking methadone and suffering from limb fractures. The patients were divided into two groups receiving 1 μg/kg single dose of fentanyl and 0.3 mg/kg single dose of ketamine (low-dose ketamine). Patients' pain scores and the incidence rate of complications were recorded before the intervention, and 15, 30, and 60 min after drug administration and were then compared between the two groups.

Results: The mean pain score of patients 15 min after the intervention was significantly lower in the low-dose ketamine group with a mean of 2.50 ± 1.34 as compared with the fentanyl group with a mean of 7.10 ± 1.43 ($P < 0.001$). However, the mean pain score was not significantly different between the two groups 30 and 60 min after the intervention ($P > 0.05$). In addition, the incidence rate of complications was not significantly different between the two groups ($P > 0.05$).

Conclusion: According to the results of this study, low-dose ketamine as compared with fentanyl relieves pain in the mentioned patients with a faster effect and in a shorter time although no difference can be found between the pain scores of the two groups 30 and 60 min after the intervention.

Keywords: Addict, Drug, fentanyl, fracture, ketamine, pain

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Introduction

Pain is one of the most common complaints of 70% of patients referring to emergency departments (EDs) and intensive care units; thereby, its control is of special importance in all patients, especially those with traumatic injuries such as limb fractures.[1]

According to the standards of the Joint Commission accreditation of Healthcare Organizations, pain is considered as the fifth vital sign that should be examined regularly from the time of admission to discharge.[2] Hence, the selection and prescription of appropriate and effective analgesics have been extensively attended to by physicians because proper prescription will lead to a higher cooperation on the part of the patient with the physician, a more rapid decision-making procedure, and an increased patient satisfaction with the quality of services provided in the ED.[1,3-5]

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Common treatments include the administration of nonopioid and opioid analgesics. One of the most widely used drugs for controlling pain is opioids, which can be effective in controlling patients' pain. However, this issue is controversial in patients with long-term drug abuse and raises various challenges such as dependence, tolerance, complexity of distinguishing and tackling with drug-seeking behaviors, failure in prescription of adequate medication to patients due to concerns about the complications of drugs, inability to accurately estimate the patient's pain level, and lack of attention to other aspects including psychological issues.[6]

Hence, emergency physicians are faced with limited options in choosing analgesics for this category of patients. Fentanyl can be mentioned as one of the drugs used to relieve patients' pain. Fentanyl is the best recognized synthetic opioid drug and is widely exploited in pain control.[7,8] However, due to the adverse effects of opioids and the possibility of the addicted patients' resistance, the use of alternative drugs to control or prevent pain has been considered as a goal by researchers.[9,10]

In this regard, ketamine is an N-methyl-D-aspartate receptor antagonist, is one of the dissociative anesthetics, and belongs to the family of phencyclidines. It has been characterized by induction of the states of immobility, amnesia (no memory of events while under the influence of the drug), and relief from pain.[11,12] Ketamine has induced more analgesia than placebo in 58% of randomized clinical trials by 2004.[13] Some of these studies have prescribed low doses of ketamine (<2 mg if given intramuscularly and <1 mg if given intravenously) and some have prescribed high doses of ketamine.[14] In the meantime, very limited studies have been devoted to the dose of 0.5 mg/kg.[15-17] As ketamine is considered a phencyclidine analog, its high doses can cause some unintended complications such as hallucinations,[18] dysphoria, nightmares, increased secretion of saliva, and increased intracranial or pulmonary pressure.[19] Therefore, it seems that the use of low doses can probably be associated with earlier discharge and lower incidence rate of airway complications in patients.[20]

In this regard, some previous studies have evaluated the effect of these two drugs (ketamine and fentanyl) in controlling patients' pain and have reported various results;[21-23] however, few studies have addressed and compared the effect of these two drugs on addicts.

Therefore, paying due attention to the control of pain in addicted patients and evaluation of the appropriate treatment in these patients can be very imperative considering the presented literature and the following significant statements: (a) drug-addicted patients often complain of pain control, (b) prominent scientific authorities including the American Pain Association have stated that pain control and treatment in addicted patients should be performed with the same respect and quality as they are performed for other patients,[24] and (c) substance abuse is an important social and public health problem in the Islamic Republic of Iran;[25] dealing with patients with such problems cannot be occasional. In addition, as patients with a history of drug abuse are among a special group of patients whose response to opioids is poor in pain control, the type of prescribed drug in these patients should be dealt with caution. Moreover, due to the fact that fentanyl is a synthetic drug more potent than morphine and is associated with some complications, the use of nonopioid drugs such as ketamine has attracted the consideration of researchers, and some studies have recommended the use of low-dose ketamine for this purpose.[19,23] Finally, considering the emphasis on additional research on low-dose ketamine[14] and its comparison with other drugs, the present study addressed the effect of intravenous fentanyl with low-dose ketamine on pain relief in patients taking methadone and suffering from limb fractures.

Materials and Methods

The present study is a double-blind randomized clinical trial. The population was all patients taking methadone and suffering from limb fractures (lower or upper). The patients referred to the EDs of Al-Zahra and Kashani hospitals in Isfahan during 2018–2019. Following a confidence interval of 95%, a test power of 80%, and considering the standard deviation (SD) of pain scores in the two groups in previous studies[22] to be equal to 0.7 and 0.6, respectively, and the error level of 0.4 ($[\mu_1-\mu_2] = [2.9–2.5]$) obtained due to the difference in the mean pain score in two groups, the sample size of 50 patients was considered for each group.

Inclusion criteria were patients taking methadone, suffering from limb fractures (such as ulnar and radial fractures [forearm fractures], tibial, and fibular), not being pregnant, and being within the age range of 18–65 years. Moreover, satisfaction to participate in the study, lack of insensitivity to fentanyl and ketamine, lack of jaw or facial bone fracture, lack of severe head trauma and decreased level of consciousness, lack of serious trauma in the chest and abdomen, lack of instability in terms of vital signs, lack of psychotropic drug use, and lack of neuropsychiatric disorder history, and visual impairment were the other inclusion criteria. Patients were excluded from the study in the case of severe hypoxia or severe hypotension while receiving the drug. However, none of the patients had these complications; thereby, the sample size was not reduced.

After obtaining a code of ethics from the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.043), a clinical trial code (IRCT20171030037093N25), and a written consent from eligible patients, 100 patients were randomly selected and entered the study. The patients were then divided into two groups receiving intravenous fentanyl and ketamine using random allocation software [Figure 1].

To meet the conditions of blindness, two drugs were prepared in advance by an emergency medicine specialist and put into ready-made packages with codes A and B so that the person prescribing the drug as well as the person recording the clinical and basic information of the patients were blinded by not being informed of the type of intervention.

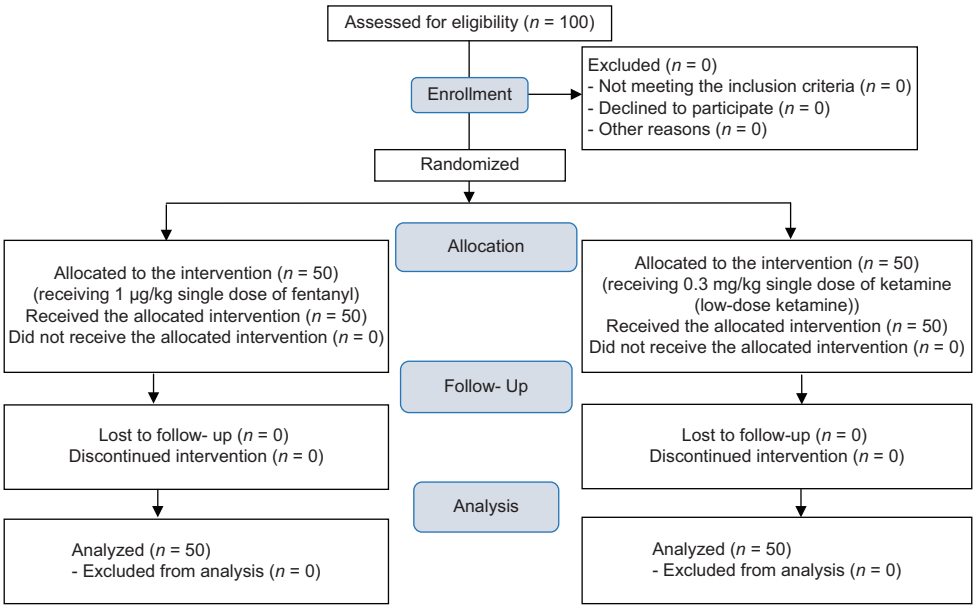

Figure 1: Consort flowchart of patients

Therefore, the drug was prescribed by a resident that had no information about the type of the selected drug and the study groups. The administration of 1 µg/kg single dose of fentanyl and 0.3 mg/kg single dose of ketamine was performed.

Demographic information, the type of limb fracture, and the patients' pain score (based on Visual Analog Scale ranging from 0 to 10) were recorded before drug administration (at the beginning of the study), and 15, 30, and 60 min after drug administration.

If the patients' pain score did not decrease to <5 within 30 min, morphine was prescribed at a dose of 0.5–1 mg/kg and those who needed a higher dose of analgesia were excluded from the study.

Possible complications such as nausea, vomiting, loss of consciousness (LOC), decreased oxygen saturation (SpO_2), and blood pressure (BP) were also recorded within 60 min of follow-up.

Finally, the collected information was entered into the SPSS software (version 23; SPSS Inc., Chicago, Ill., USA). Data were presented as means ± SD or frequency (percentage). At the level of inferential statistics, given the result of Kolmogorov–Smirnov test indicating the normal distribution of data, an independent samples *t*-test, univariate analysis, repeated measures ANOVA, and Chi-square test were used to compare the mean of quantitative data between the two groups; compare the mean pain score between the two groups by adjusting for confounding variables such as age, sex, the amount of methadone use, and the prescription of additional analgesics; evaluate the trend of changes in pain scores in each of the two groups; and compare qualitative data between the two groups. A significance level of <0.05 was considered in all analyses.

Results

The present study was performed on 100 male patients using methadone and suffering from limb fractures in two groups receiving intravenous fentanyl with a mean age of 35.26 ± 6.65 years and the intravenous low-dose ketamine with a mean age of 37.70 ± 6.99 years ($P = 0.077$) [Table 1].

The mean pain score of these patients before the intervention was not significantly different between the two groups ($P = 0.914$); however, 15 min after the intervention, the mean pain score in the ketamine group with a mean of 2.50 ± 1.34 was significantly less than that of the fentanyl group with a mean of 7.10 ± 1.43 ($P < 0.001$). Furthermore, the mean pain score was not significantly different between the two groups 30 and 60 min after the intervention ($P > 0.05$). In addition, each of the two groups had a significant decrease in pain score over time from the time of admission to 60 min after the intervention ($P < 0.001$) [Table 2].

In addition, one case (2%) of nausea and vomiting, four cases (8%) of decreased SpO_2, and seven cases (14%) of hypotension were observed in the fentanyl group. Moreover, one case (2%) of decreased SpO_2 and three cases (6%) of hypotension were observed in the ketamine group. Although the frequency of the incidence of complications was lower in the ketamine group, there was no statistically significant difference between the two groups ($P > 0.05$) [Table 3].

Discussion

The results of the present study revealed that the administration of low-dose ketamine (0.3 mg/kg) significantly reduced patients' pain in a short period of time as the pain score of addicted patients with limb fractures in the ketamine group was significantly lower than that of the fentanyl group 15 min

Table 1: Basic characteristics of patients in two groups

Characteristics	Fentanyl	Ketamine	*P*
Sex; male (%)	50 (100)	50 (100)	-
Age (years)	35.26±6.65	37.70±6.99	0.077
Weight (kg)	69.92±8.37	66.28±11.24	0.061
Methadone	20.50±7.78	21.32±9.09	0.629
Limb fracture (%)			
Upper	23 (46)	18 (36)	0.416
Lower	27 (54)	32 (64)	

Table 2: Comparison of the mean pain score of patients at different times between two groups

Variables	Fentanyl	Ketamine	P^a	P^b
Pain score				
Before intervention	8.94±0.86	8.96±0.97	0.914	0.823
15 min	7.10±1.43	2.50±1.34	<0.001	<0.001
30 min	3.86±1.63	3.24±1.88	0.081	0.211
60 min	3.18±1.17	3.32±1.90	0.658	0.420
P^c	<0.001	<0.001		

[a]Use of independent samples *t*-test, [b]Use of univariate analysis by adjusted sex, age, using methadone and additional drug, [c]Use of repeated measures test

Table 3: Comparison of the frequency distribution of complications between the two groups

Complication	Fentanyl (%)	Ketamine (%)	*P*
Nausea and vomiting	1 (2)	0	1.00
Decreased SpO_2	4 (8)	1 (2)	0.362
LOC	0	0	-
Hypotension	7 (14)	3 (6)	0.318

LOC: Loss of consciousness, SpO_2: Oxygen saturation

after the drug administration. However, the effect of this drug was short and its effect disappeared a little over time up to 60 min after the administration. In contrast, the effect of fentanyl was longer as was observed, and although its effect was significantly different from that of ketamine 15 min after the intervention, the mean pain scores of the two groups were not significantly different from each other 30 and 60 min after the intervention. In fact, it can be stated that fentanyl and ketamine had a longer and shorter effect, respectively. However, as compared to the effect of fentanyl, the reduced effect of ketamine 30–60 min after the intervention could not make a significant difference.

Consistent with the present study, a meta-analysis study by Lee *et al*. indicated that low-dose ketamine can be a key factor in controlling pain in ED as it is associated with minimal complications. Moreover, it may also help reduce drug complications.[23]

The results of another study demonstrated that the pain score in patients with limb fractures in the nebulized fentanyl group was significantly higher than that of the low-dose ketamine group (0.4 mg/kg). Moreover, patients receiving nebulized fentanyl required additional treatment. In addition, the mentioned study concluded that ketamine could be used as a noninvasive treatment to successfully reduce pain in patients with limb fractures.[26]

In previous studies, various doses of ketamine have been used via different routes including intravenously, orally, intramuscularly, intranasally, subcutaneously, rectally, or epidurally, and it has been prescribed with morphine in some cases. In addition, its rapid effect and the least incidence rate of complications have been reported, as well.[18,27-29]

In fact, ketamine rapidly increases in cerebral blood flow and reaches its maximum activity 1 min after the administration due to its low molecular weight, a Pka value close to the physiological pH, and its high lipid solubility.[11] The mentioned properties may explain the reason behind the reported rapid effect of low doses of this drug (0.2–0.5 mg/kg) in our study and many other pilot studies.

It is of great significance to consider the use of low-dose ketamine instead of opioids for addicted patients while it has received little attention in the literature. In this regard, the available evidence revealed that the administration of ketamine may be beneficial for opioid-tolerant surgical patients and may play a role in preventing persistent pain following the surgery.[30]

In another study, low-dose ketamine was used as an adjunct for parenteral opioids in highly tolerant patients with severe cancer pain and as balanced analgesia for the management of pain associated with multiple fractured ribs in an opioid addict.[31,32]

In addition, many studies have reported the administration of a low-dose bolus of ketamine followed by a low-dose infusion (2–4 μg/kg/min) or a single low-dose bolus of ketamine (0.15–0.5 mg/kg) in opioid-naive patients undergoing abdominal,[33] rectal,[34,35] orthopedic,[36] inguinal hernia,[37] and laparoscopic[35] surgeries. Majority of the mentioned studies have revealed the reduced postoperative opioid requirements and pain level.

Another study showed that the administration of low-dose ketamine along with fentanyl could significantly reduce the pain score of post-Nuss procedure in children and the incidence rate of nausea and vomiting without increasing the incidence rate of other complications.[38]

Therefore, it can be stated that in any prescription of analgesics, what is of special importance for the physician, in addition to reducing pain, is to minimize the occurrence of drug complications and adverse effects on the patient. The results of the present study indicated that the effect of low-dose ketamine can be much more successful than fentanyl in reducing pain in these patients in a short time; however, no significant difference could be observed between the mentioned drugs in the long term, i.e., within 60 min. It is imperative to note that although the percentage of complications did not differ significantly between the two groups, the incidence rate of complications was lower in low-dose ketamine as compared with fentanyl.

In line with the findings of the present study, Shackelford *et al*. showed that patients receiving fentanyl and ketamine were not significantly different in terms of respiratory status, and it can be generally concluded that ketamine and fentanyl were sufficiently safe in prehospital administration.[39]

Imani *et al*.'s study indicated that the incidence rate of nausea and vomiting after abdominal surgery was significantly lower in the ketamine group as compared with that of the fentanyl group.[22] Although the incidence rate of complications was lower in the low-dose ketamine group as compared to that of the fentanyl group in our study, the observed difference was not significant.

Some studies have mentioned that fentanyl, as compared with analgesics such as morphine sulfate, sufentanil, and alfentanil, is more effective in terms of analgesia and is associated with fewer respiratory complications and cardiopulmonary changes.[8] Therefore, it should not affect BP based on the physiology of this drug. Hence, fentanyl is preferred in the population of severe trauma patients that may have poor cardiovascular status.[7]

In addition, due to the fact that ketamine is a phencyclidine analog, its high doses can be associated with some complications such as hallucinations,[18] dysphoria, nightmares, increased secretion or saliva, and increased intracranial or pulmonary pressure.[19] It has been suggested that the use of low doses may be associated with earlier discharge and lower incidence rate of airway complications in patients.[20]

Therefore, it can be stated that the preference can be with a drug that, in addition to satisfactory reduction of the pain score, also has few complications. In this study, the efficacy of low-dose ketamine was equivalent to that of fentanyl. Moreover, as the patients in this study were addicted patients with fractured limbs, it may be conceivable to recommend the use of ketamine, even in low doses, to avoid prescribing opioids such as fentanyl. Administration of low-dose ketamine and fentanyl as the best-known synthetic opioids for patients using methadone and suffering from limb fractures in this study can be regarded as one of the strengths of our study. However, small sample size and lack of examination of female patients can be considered as the limitations of this study. In addition, it is suggested that future studies should examine the simultaneous administration of these two drugs or evaluate various doses of ketamine to figure out the most effective dose in this group of patients.

Conclusion

According to the results of the present study, the reduction in patients' pain score 15 min after the administration of low-dose ketamine (0.3 mg/kg) was significantly less than that of the fentanyl group. There was no significant difference in pain scores between the two groups 30 and 60 min after the intervention. Moreover, although the incidence rate of complications in the ketamine group was lower than that of the fentanyl group, this difference was not statistically significant. Therefore, considering the lower incidence rate of complications at low doses of ketamine, we suggest using this dose of ketamine to relieve pain in these patients; however, further studies are required to shed more light on this issue.

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Conflicts of interest

There are no conflicts of interest.

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