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The effectiveness of adding low dose of ketamine to the injected morphine in opioid-addicted patients admitted to emergency ward with acute fracture: A double-blind clinical trial

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ABSTRACT

Introduction: Patients with fractures are among the patients visiting the emergency ward the most. Pain control in these patients has many advantages both ethically and scientifically (physiologically and psychologically) both for the patient and the health system. Many studies have shown that the addition of low doses of ketamine to morphine, which is the standard painkiller of the emergency ward, can reduce the severity of acute pain in patients and the adverse events of morphine. The study tried to examine the effectiveness and the safety of the addition of low doses of ketamine to injected morphine in opioid-addicted patients admitted to emergency ward with acute fractures. *Methodology:* The study was a double-blind clinical trial where 128 patients, who were addicted to different types of opioids based on their self-report and admitted to the emergency ward with acute fractures of the long bones of each of the four limbs, were randomly assigned to two groups: receiving morphine / placebo and morphine/low dose of ketamine. The severity of pain and adverse events of the injectable medication were measured and recorded before receiving the pain medication and 15, 30, 60 and 90 minutes after and compared at the end of the study. The data was analyzed in SPSS16 using descriptive and inferential statistical tests at the significance level of $P<0.05$. *Results:* The severity of pain was similar in both groups before pain medication and 15, 30, 60 and 90 minutes after with no significant difference between the two groups. The incidence of adverse events in the morphine / ketamine group was significantly higher than that of the morphine / placebo group. *Conclusion:* The addition of intravenous low ketamine dose to injectable morphine sulfate cannot increase the effectiveness of pain control in opioid addicted patients with acute fractures. Significant increase in adverse events in the group receiving low dose of ketamine besides morphine sulfate questioned the safety of this medication for patients.

Keywords: Ketamine, morphine, fractures, pain

1. INTRODUCTION

Pain is an unpleasant experience many patients suffer from in the hospitals. Different types of pain, both chronic and acute, impose some costs and discomforts on the individual. Moreover, it affects human resources use and reduces productivity (Fry et al., 2011). Pain has been introduced as the most common cause of patients being admitted to health care centers and receiving medications and 75% of the patients in the emergency wards have experienced a level of pain (Bergman et al., 2012). As whatever the pain cause is, it bothers the patient, its control is so significant in any circumstance and of any type and is among the duties of the physicians. As the emergency ward is the main place where the patients with acute pain meet, pain management and control in this ward is of the biggest challenges and highest priorities for the ones dealing with patients' treatment. The attempts to reduce pain in emergency ward patients used to be mostly for human reasons and to reduce the patient's physical and mental suffering. However, with the progress in other sciences like health economics, a more general view started to rule the management of patients in the emergency ward and hospitals that tried to consider the hospital and its benefits besides dealing with the patients and the efforts to reduce their suffering. Since then many studies and examinations have been done regarding pain control in the emergency ward following surgery and diagnostic and therapeutic interventions and its effects on the length of hospital stay. Most of these studies showed that the lower the patient's pain, the shorter their stay in the emergency ward will be (Schulte, 2004 & Stubhaug et al., 1997). Hemodynamic disorders, including the increase in blood pressure or its severe reduction abnormalities, and the changes in heart rate coupled with changes in cardiac output are among the life-threatening mechanisms because of severe pain (Stucky et al., 2001). Among the effective cellular mechanisms creating tolerance to morphine effects regulating to increase or decrease the number of opioid receptors, the changes in intracellular peaks like adenylyl cyclase, protein kinase C, and the interference of post-synaptic receptors, especially glutamate/aspartate receptors, gamma aminobutyric acid, and monoamine neurotransmitters of central serotonergic nerves can be cited (Blednov et al., 2003). Because of the poor response of the patients with history of using opioids, combining medication to enhance the effects has been of interest to the researchers (Imani et al., 2015). As an anesthetic medication, ketamine applies its analgesic effect by non-competitive inhibition of N-methyl-D-aspartate (NMDA) receptor (Imani et al., 2015). Many studies have been done concerning combining ketamine with different opioids like remifentanil, pethidine and fentanyl, reporting ketamine-induced reduction in hyperalgesia (Guifeng et al., 2009 & Nourozi et al., 2010 & Ndoye et al., 2008). Some studies have shown that combining morphine with ketamine can bring about more analgesic effects (Suraci Nicholas & Grandhi K Ravi, 2016); i.e., these studies claim that morphine sulfate and ketamine can have synergistic or cumulative effects. One of these studies is the one in Sweden where the researchers have concluded that the positive interaction between the analgesia caused by antagonistic effects of NMDA receptor by ketamine and morphine have cumulative and amplifying effects on the patients' pains (Schulte, 2004). Using the low dose of ketamine reduced adverse effects as hallucination (Elia et al., 2005), and also reduced using

opioids during operations by 40 % (Jouguelet-Lacoste et al., 2015). In a study in Australia, morphine 1 mg/kg was used alone or in combination with ketamine 1 mg/kg where low dose of ketamine with PCA in patients with major abdominal surgery was not effective not significantly reducing the patients' need for opioids (Reeves, 2001).

What has made the control and management of pain in the emergency ward so significant for us is the awareness of its different human, practical and operational aspects. Knowing the benefits that proper and effective pain control in the emergency ward can have for the patient, his family, emergency ward personnel and the whole hospital is a great incentive for trying to manage it better. Unfortunately, few doctors are aware of the mechanism of the effect of opioid and non-opioid analgesics in the body. Thus, in most of the cases where pain is not controlled well in the patients, the lack of adequate administration of the medicine dose by the doctor has been a major factor. In most cases, these doctors estimate the analgesic dose of these medications less than what they should and their adverse events more than what they are. Therefore, according to studies conducted in this regard, the lack of effective and adequate administration of analgesic remains as the main cause of the lack of pain control in the emergency ward (Stubhaug et al., 1997 & Stucky et al., 2001 & Reeves, 2001). Hence, the study was conducted to evaluate the effectiveness of adding low dose of ketamine to the morphine injected in opioid addicted patients admitted to emergency ward with acute fractures.

2. METHODOLOGY

The study was a randomized double-blind clinical trial (IR.IUMS.REC.1398.054) comparing the standard usual treatment for controlling severe and mild acute caused by fractures in emergency wards (injectable morphine) with a new treatment regimen (low dose injectable ketamine plus morphine). The selecting of the patients and dividing them into two treatment groups was random and randomized using a random numbers table (Figure 1).

Research place: emergency wards of Rasoul-e-Akram Hospital and Sina Hospital

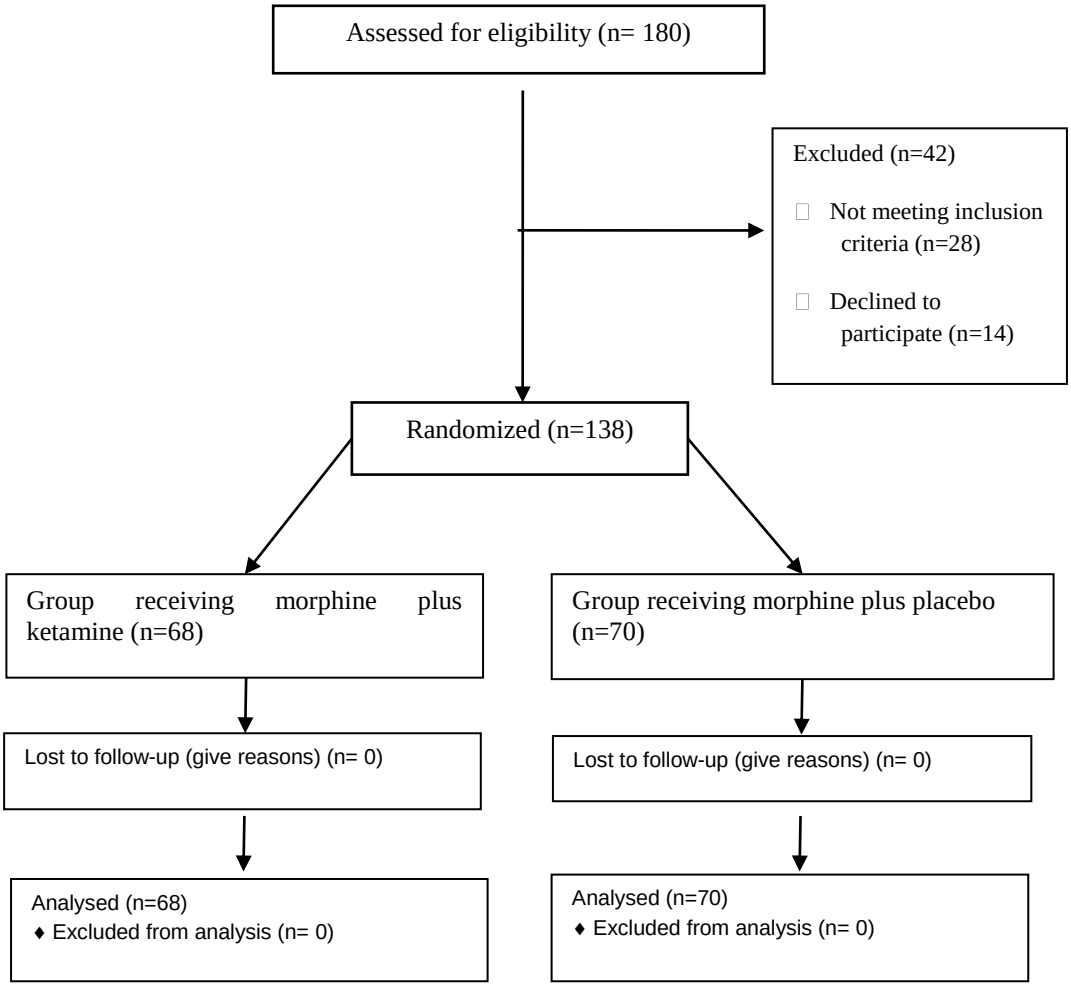

Figure 1 CONSORT Flow Diagram

The inclusion criteria were:

1. Being over 18 years of age
2. Drug addiction (regardless of drug type) and according to the patient's statement
3. Limb trauma causing acute fractures

Exclusion criteria were:

1. Alcohol and psychedelic drug abuse
2. The history of psychological disorders
3. Reduction in consciousness for any reason
4. Moderate to severe head trauma
5. Seizure disorders
6. Chronic hepatic, renal, and coronary artery diseases
7. Pregnancy

Study protocol

The type of study, its significance, the types of medication, their effects, possible adverse events, how they are used, the significance of determining better and more effective medication, following up the effects of the medication and measuring the pain with visual analogue scale (VAS), the importance of the numbers on the ruler and so on were described to the patients with the inclusion criteria. In case of consent, the patient was enrolled and informed consent was received to enter the study.

In patients entering the study, the severity of pain was measured using VAS and recorded as number by patient's self-statement.

Besides the pain severity, the patient's vital signs and cognitive function were measured and recorded. Mini mental state (MMS) system with 0-30 scores was used to check the patients' mental status. The mood status of the patients was measured by profile of mood state (POMS) and dissociative status of the patients by clinician administered dissociative state (CADS).

Then, the patients were into two groups using random numbers table:

1- Group 1: The group receiving morphine at a dose of 50 µg/kg plus placebo (distilled water)

2- Group 2: The group receiving 50 µg/kg of morphine plus 100mg / kg of ketamine

Fifteen minutes after injection, all the mentioned factors were measured again and the possible adverse events were recorded.

The severity of pain and adverse events were measured every 15 minutes to one hour and in case of the patients' need for re-analgesic, he was excluded and the standard analgesic (rescue analgesic) was done with 0.1 mg/kg doses of morphine.

Observing ethical points

First of all, we explained these 2 study methods and after accepting from participants written informed constant form completed by patients. The patients were not charged any fees for medication. The patients' information was confidential. This study was approved by the Ethical committee of Tehran University of medical sciences (IR.IUMS.REC.1398.054). The authors declare that there is no conflicts of interest regarding the publication of this manuscript

Data analysis

The data was analyzed using different statistical tests such as t-test, chi-square, ANOVA and so on in SPSS16. Excel was used to draw the graphs.

3. RESULTS

After excluding the patients with one or more exclusion criteria, 128 patients were enrolled and randomly assigned to two groups: receiving morphine / placebo and morphine / ketamine. Sixty-five patients were in the first and 63 in the second group.

Age

The mean age of the patients in the study was 40.66 ± 17.65 years, with the youngest patient 18 and the oldest 89 years of age. The mean age of the patients in the morphine / placebo group was 38.54 ± 15.75 and the mean age in the morphine / ketamine group 42.17 ± 19.22 years. Statistical analysis using student t-test in two independent groups showed that the mean age in the two groups had no statistically significant differences (P value = 0.18).

Gender

Of the 26 female patients enrolled in the study, 13 (50%) were in the morphine / placebo group and 13 (50%) in the morphine / ketamine. Of the 102 male patients in the study, 52 (50.89%) were in the morphine / placebo group and 50 (49.1%) in the morphine / ketamine. The gender distribution of the patients was similar in both medication groups with no significant statistical differences.

Race

Of the 128 patients examined, 121 (94.5%) were Iranians and 7 (5.5%) were Afghans. Of the 7 Afghan patients, 4 (57.14%) were in the morphine / placebo group and 3 (42.85%) in the morphine / ketamine. Thus, the racial distribution of the patients was similar just as the gender and age distribution with no statistically significant differences.

The profile of the fractures

Overall, of the patients involved in the study, 43 (33.6%) had fractures in the upper extremities and 85 (66.4%) in the lower. Of the 43 patients with upper extremities fracture, 21 (48.9%) were in the morphine / placebo group and 22 (51.1%) in the morphine / ketamine. Of the 85 patients with fractures in the lower extremities, 44 (51.8%) were in the morphine / placebo group and 41 patients (48.2%) in the morphine / ketamine group.

Distribution of the patients according to location of fracture was similar in two medication groups with no statistically significant differences.

Information on the pain control; Severity of the pain before prescribing medications

The mean score of pain in the patients before taking the medication in the morphine / placebo group was 7.84+1.60.
The mean pain score of the patients before receiving the medication in the morphine / ketamine group was 8.07+1.50.
Statistical analysis by student t-test in two independent samples showed that the mean scores of pains in two medication groups before receiving the medication did not differ significantly (P value = 0.39).

Thus, one can conclude that random distribution of the patients in the medication groups was suitable and the patients had similar distribution in terms of demographic characteristics, race, fracture place and pain score before receiving the medication.

As the present study was randomized clinical trial, the analysis of the data on pain intensity was first done using intention-to-treat method; i.e., all the patients in the study (128 patients) were analyzed. In the next stage, as the duration of the analgesic and adverse events of the medications was considered 90 minutes, the patients requesting rescue analgesic in this 90 minute time were excluded from the study and the re-analysis was only on those not requesting or receiving any other painkillers during the 90-minute study and received only morphine / placebo or morphine / ketamine. Doing intention-to-treat increases the accuracy of the interpretation of the results since it includes all the patients in the study.

Intention to Treat Analysis

Pain intensity 15 minutes after medication administration
The mean pain score of patients was 15 minutes after receiving the medication in the morphine / placebo group was 4.76+2.08.
The mean pain score of patients was 15 minutes after receiving the medication in the morphine / ketamine group was 4.39+1.78.
The statistical analysis using student t-test in the two independent samples indicated that the mean score of pain in the two groups of medications was not statistically significant 15 minutes after receiving the medications (P value = 0.28).

Severity of pain 30 minutes after medication administration

The mean pain score of the patients 30 minutes after receiving the medication in the morphine / placebo group was 3.96+2.08.
The mean pain score of the patients 30 minutes after receiving the medication in the morphine / ketamine group was 3.53+1.90.
The statistical analysis by student t-test in the two independent samples showed that the mean score of pain in the two medications groups was not statistically significant 30 minutes after receiving the medications (P value = 0.16).

Severity of pain 60 minutes after medication administration

The mean pain score of the patients 60 minutes after receiving the medication in the morphine / placebo group was 4.33+1.86.
The mean pain score of the patients 60 minutes after receiving the medication in the morphine / ketamine group was 3.90+1.96.
The statistical analysis by student t-test in the two independent samples showed that the mean score of pain in the two medications groups was not statistically significant 60 minutes after receiving the medications (P value = 0.20).

Severity of pain 90 minutes after medication administration

The mean pain score of the patients 90 minutes after receiving the medication in the morphine / placebo group was 3.64+1.57.
The mean pain score of the patients 90 minutes after receiving the medication in the morphine / ketamine group was 3.88+1.89.
The statistical analysis by student t-test in the two independent samples showed that the mean score of pain in the two medications groups was not statistically significant 90 minutes after receiving the medications (P value = 0.43).

The time to request and the prescription of the next analgesic

The mean time for the patient's next analgesic request was 124.92 ± 129.29 minutes in the morphine / placebo group.
The mean time for the patient's next analgesic request was 168.33 ± 142.91 minutes in the morphine / ketamine group.
The statistical analysis with student t-test showed that although the mean time interval of receiving medication in the morphine / ketamine group was more than that of the morphine / placebo group, this difference was not statistically significant (P value = 0.07).
In the first 30 minutes after receiving the medications, 20 out of 65 patients in the morphine / placebo group and in 8 out of 63 patients in the morphine / ketamine requested analgesic again.
At 60 minutes after the administration of medications, 36 out of 65 patients in the morphine / placebo group and 26 out of 63 patients in the morphine / ketamine group requested analgesic again.
At 90 minutes after the administration of medications, 45 out of 65 patients in the morphine / placebo group and 39 out of 63 patients in the morphine / ketamine group requested analgesic again.

The mean pain intensity of patients at 15, 30, 60 and 90 minutes after receiving the medication is given in Table 1.

Table 1 Comparison of pain intensity in the two treatment groups 15, 30, 60 and 90 minutes after receiving medications (Intention-to-treat analysis)

Std. Deviation	Std. Error Mean	Mean	Number	Drug regimen	Scoring time
2.08993	.25922	4.7692	65	Morphine- Placebo	15 minutes
1.78289	.22462	4.3968	63	Morphine- ketamine	
1.59069	.19730	3.9692	65	Morphine- Placebo	30 minutes
1.90775	.24035	3.5397	63	Morphine- ketamine	
1.86478	.23130	4.3385	65	Morphine- Placebo	60 minutes
1.96513	.24758	3.9048	63	Morphine- ketamine	
1.57550	.19542	3.6462	65	Morphine- Placebo	90 minutes
1.89321	.23852	3.8889	63	Morphine- ketamine	

Information on adverse events

Table 2 shows the incidence of complications in the morphine / placebo group and morphine / ketamine group.
Of the 65 patients in the morphine / placebo group, 35 (53.8%) did not show any serious adverse events.
Of the 63 patients in the morphine / ketamine group, 11 (17.4%) did not showed no adverse events.
The incidence of adverse events in the group receiving morphine / ketamine was significantly (P value = 0.000) more than that of the morphine / placebo group.

Table 2 Adverse events of two treatment regimens (Intention-to-treat analysis)

Medicinal diet				Type of complication
Morphine- ketamine (N=63)		Morphine- Placebo(N=65)		
percent	Number	percent	Number	
6.3	4	0	0	Diplopia
1.5	1	0	0	Nystagmus
11.1	7	0	0	Hallucination
3.1	2	0	0	Agitation

Medicinal diet				Type of complication
Morphine- ketamine (N=63)		Morphine- Placebo(N=65)		
percent	Number	percent	Number	
6.3	4	0	0	Diplopia
1.5	1	0	0	Nystagmus
11.1	7	0	0	Hallucination
3.1	2	0	0	Agitation
33.3	21	10.7	7	Loss of consciousness
3.1	2	16.9	11	Nausea / vomiting
23.8	15	18.4	12	Confusion
17.4	11	53.8	35	There is no complication

The analysis of the remaining patients in the study

As the duration of the study was 90 minutes, the patients requesting additional analgesic during the 90 minutes were excluded and the rest of the patients were compared again.

Of the 65 patients in the morphine / placebo group, 38 (58.4%) patients asked for additional analgesic in the first 90 minutes after receiving the medication.

Of the 63 patients in the morphine / placebo group, 29 (46.0%) patients asked for additional analgesic in the first 90 minutes after receiving the medication.

Therefore, the demand for additional analgesic in the morphine / placebo group was about 12% higher than the morphine / ketamine group. However, as already stated, the mean time for requesting additional analgesic in the morphine / placebo group was shorter than that of the morphine / ketamine; i.e., the patients in the morphine / placebo group had requested additional analgesic more and sooner.

Accordingly, 27 patients remained in the morphine / placebo group and 34 in the morphine / ketamine group, who had not requested additional analgesic by the end of the 90 minutes. Comparisons of these two groups were showed.

Severity of pain before medications administration

The mean score of pain in patients before taking the medication in the morphine / placebo group was 6.88 ± 1.50 with a standard deviation. The mean score of pain in the patients before taking the medication in the morphine / ketamine group was 7.85 ± 1.67.

Statistical analysis using student t-test in two independent samples showed that the mean scores of pain in the two medication groups were significantly different before taking the medications (P value = 0.02).

Pain intensity 15 minutes after medication administration

The mean pain score of the patients was 15 minutes after receiving the medication in the morphine / placebo group was 3.65+1.57. The mean pain score of the patients was 15 minutes after receiving the medication in the morphine / ketamine group was 3.88+1.89.

Statistical analysis using student t-test in two independent groups showed that the mean score of pain in the two medication groups was not statistically significant 15 minutes after receiving the medications (P value = 0.43).

Pain intensity 15 minutes after medication administration

The mean pain score of the patients was 15 minutes after receiving the medication in the morphine / placebo group was 3.66+1.70. The mean pain score of the patients was 15 minutes after receiving the medication in the morphine / ketamine group was 4.17+1.94.

Statistical analysis using student t-test in two independent groups showed that the mean score of pain in the two medication groups was not statistically significant 15 minutes after receiving the medications (P value = 0.28).

Pain intensity 30 minutes after medication administration

The mean pain score of the patients was 15 minutes after receiving the medication in the morphine / placebo group was 3.00+1.07.

The mean pain score of the patients was 15 minutes after receiving the medication in the morphine / ketamine group was 2.85+1.35.

Statistical analysis using student t-test in two independent groups showed that the mean score of pain in the two medication groups was not statistically significant 30 minutes after receiving the medications (P value = 0.64).

Pain intensity 60 minutes after medication administration

The mean pain score of the patients was 60 minutes after receiving the medication in the morphine / placebo group was 3.48+1.84.
The mean pain score of the patients was 60 minutes after receiving the medication in the morphine / ketamine group was 2.73+1.18.

Statistical analysis using student t-test in two independent groups showed that the mean score of pain in the two medication groups was not statistically significant 60 minutes after receiving the medications (P value = 0.06).

Pain intensity 90 minutes after medication administration

The mean pain score of the patients was 90 minutes after receiving the medication in the morphine / placebo group was 3.51+1.84.
The mean pain score of the patients was 90 minutes after receiving the medication in the morphine / ketamine group was 3.52+1.76.

Statistical analysis using student t-test in two independent groups showed that the mean score of pain in the two medication groups was not statistically significant 90 minutes after receiving the medications (P value = 0.98).

Table 3 shows the comparison of the pain scores at different times after receiving the medication in two groups.

Table 3 Comparison of pain intensity in the two treatment groups 15, 30, 60 and 90 minutes after receiving medications (Analysis of the patients not requesting any medication within 90 minutes after taking the medication regimen)

Std. Deviation	Std. Error Mean	Mean	Number	Drug regimen	Scoring time
1.50214	.28909	6.8889	27	Morphine- Placebo	Before taking medications
1.67209	.28676	7.8529	34	Morphine- ketamine	
1.70970	.32903	3.6667	27	Morphine- Placebo	15 minutes
1.94579	.33370	4.1765	34	Morphine- ketamine	
1.07417	.20672	3.0000	27	Morphine- Placebo	30 minutes
1.35137	.23176	2.8529	34	Morphine- ketamine	
1.84746	.35554	3.4815	27	Morphine- Placebo	60 minutes
1.18855	.20383	2.7353	34	Morphine- ketamine	
1.84746	.35554	3.5185	27	Morphine- Placebo	90 minutes
1.76215	.30221	3.5294	34	Morphine- ketamine	

Information on adverse events

Table 4 shows the adverse events in patients not requesting analgesic during the first 90 minutes after receiving medication. Statistical analysis using student t-test showed that the adverse events in the morphine / ketamine group was significantly higher than that of the morphine / placebo group (P value <0.005)

Table 4 The prevalence of adverse events in the two treatment regimens (Analysis of the patients not requesting any analgesic within 90 minutes after taking the medication regimen)

Medicinal diet				Type of complication
Morphine- ketamine (N=34)		Morphine- Placebo(N=27)		
percent	Number	percent	Number	
11.7	4	0	0	Hallucination
59.2	16	7.4	2	Loss of consciousness

Medicinal diet				Type of complication
Morphine- ketamine (N=34)		Morphine- Placebo(N=27)		
percent	Number	percent	Number	
11.7	4	0	0	Hallucination
3.7	1	7.4	2	Nausea / vomiting
20.5	7	25.9	7	Confusion
17.6	6	59.2	16	There is no complication

Comparison of the results of two types of analyses

Comparison of the results of two analyses performed on all patients included in the study completing the course and not requiring additional analgesic during the first 90 minutes showed that:

The mean pain score in the 15, 30, 60 and 90 minutes in both groups was similar in both analyses not showing any significant statistical differences; i.e., the effectiveness of both medication regimens in controlling pain in opioid addicted patients with limb fracture was the same.

The incidence of adverse events in both analyses in the morphine / ketamine group was significantly higher than that of the morphine / placebo group.

4. DISCUSSION

The addicted patients, including those who are addicted to opium and opioid use, form a special category of patients admitted to emergency wards and hospitals. Biological changes because of substance abuse change the physiological characteristics of these people, so that according to some studies, the patients addicted to opium or opioid will have short-term and long-term adverse events than others f they undergo surgery. This could be due to weakening of the immune system in these people. One of the studies in this area is the one by Malvia et al., in India, conducted as a prospective cohort study, comparing surgical complications in 71 opium-addicted patients with 50 non-addicted patients. The results indicated that the total need for analgesic and the overall hospital stay in opium-addicted patients were higher than the other patients were and the dependent and non-dependent morbidity was higher in these patients (Weinbroum, 2003). In controlling the pain in addicted patients, there has always been a tendency to use another medication as a supplement to morphine sulfate to avoid morphine doses to dangerous levels to control the patient's pain. One of these supplements is ketamine (Lee et al., 2000). Various studies have examined the analgesic effects of ketamine in the recent years. In a study in Korea, 40 patients undergoing surgery, with analgesic infusion started for them, were included in the study and divided into two groups. The first group received a combination of fentanyl and placebo, and the second group a combination of fentanyl and ketamine. In both groups, before the onset of infusion, a bolus analgesic was given using automatic pumps. The study showed that the addition of ketamine to fentanyl in the postoperative period could enhance pain control in patients without causing any significant adverse events. Ketamine could not reduce the patient's need for opioid (fentanyl), but the overall pain severity significant reduced in the patients (Marhofer et al., 2000). In study by Borstall on patients undergoing abdominal hysterectomy, 70 patients were divided into two groups of 33 (morphine alone) and 37 (combination of ketamine and morphine). The results indicated that the severity of pain and the duration of patient use of self-control pumps of analgesic injection in the group with combination of ketamine and morphine were lower than that of the morphine-only group. In addition, these patients experienced less cough, dysphoria, itching and nausea. However, there were no significant differences in the overall level of need for analgesic in the two groups (Yeom et al., 2012). Despite the existence of the studies where ketamine has shown good effectiveness in controlling pain in the patients and in some cases reduced adverse events of the patient, the present study found that pain intensity control in groups receiving morphine / placebo or morphine / ketamine was the same, and morphine / ketamine shows more adverse events.

According to the results of the present study, the number of patients requesting more analgesic after receiving the initial regimen was more in the morphine / placebo group than in the morphine / ketamine group. Additionally, the median time interval between receiving the primary medication regimen and the subsequent application of the next dose was lower in the morphine / placebo group compared to the morphine / ketamine group. However, the rates of the patients who received the medication at different minutes after the medication in both groups - morphine / placebo and morphine / ketamine - were equal with no significant differences. Thus, one can conclude that morphine / placebo has controlled the pain of addicted patients with acute fractures the same as morphine / ketamine; i.e., the effectiveness of the morphine / ketamine medication regimen in controlling pain

in patients was not more than the morphine / placebo. One of the interesting results of the study was that patients in the morphine / ketamine group despite reporting similar pains to that of the morphine / placebo group requested additional analgesic later than the morphine / placebo group. Perhaps this is due to the effects of central ketamine on the nervous system and changes made in the level of pain tolerance. The results showed that ketamine could not be used as an adjunct to morphine sulfate to control pain in addicted patients with fractures. In another study efficacy of morphine versus low dose ketamine in long bone fractures compared and this study showed successful pain controlling in these patients (Jahanian et al., 2018). Regarding the adverse events of the regimens examined in this study, it was seen that the morphine / ketamine medication regimen imposes more complications on patients, so that so that the incidence of adverse events in the morphine / ketamine group was significantly higher than that of the group morphine / placebo. All the patients suffering diplopia, nystagmus, hallucinations and agitation were in the morphine / ketamine group, and none of the patients in the morphine / placebo group showed these complications. Sleep loss was one of the complications significantly higher in the morphine / ketamine group compared to the morphine / placebo group. This shows that co-administration of ketamine and morphine can amplify and exacerbate the effects of morphine depressant on the central nervous system. This might be due to the cumulative effect of ketamine and morphine on the central nervous system as well.

Another common adverse effect of morphine / ketamine was dizziness. This adverse event had more prevalence in the morphine / placebo group, but was more common in the morphine / ketamine group. The justification for this could be similar to justifying an increase in the level of consciousness loss in the morphine / ketamine group. Unlike the complications mentioned, some of the adverse events were lower in the morphine / ketamine group. One of these adverse events was vomiting. The prevalence of nausea and vomiting was higher in morphine / placebo group, so that in the morphine / ketamine group, only two patients suffered nausea. None of these patients needed medication to control nausea, whereas in the morphine / placebo group, 11 patients had severe nausea and vomiting, five of whom had to receive venous antiviral medicine. Similar study shows the patients in the morphine / ketamine group experienced less cough, dysphoria, itching and nausea compared to those receiving morphine alone (Burstal et al., 2001).

Overall, the number of patients in the morphine / placebo group with no serious adverse events was more than those in the morphine / ketamine group (35 versus 11). This finding was similar to the study that compared the use of automated pumps with morphine infusion of ketamine with morphine infusion, where the adverse events of ketamine were significantly higher than morphine (Burstal et al., 2001). As various studies have found different results concerning the effectiveness and safety of ketamine alone or in combination with morphine in controlling acute pain in different patients, citing review studies in this regard can prove helpful. A review study published in 2010, which was a randomized, double-blind clinical trial on adding different doses of ketamine to morphine and other opioids given to the patient with patient-controlled pumps, compare the effectiveness (the ability to control pain) and safety (the incidence of adverse events) of the combination of ketamine and opioids with opioid alone. Finally, this review study selected 11 studies conducted on 887 patients and compared their results. In all the studies selected, pain intensity was measured using VAS and the patients with a severity of pain over 4.5 were enrolled in the study. Out of the 11 studies selected in this review study, six studies showed that the addition of ketamine to morphine has a significant effect on postoperative pain relief in the patients and five studies showed that the addition of ketamine to morphine or other opioids creates no significant clinical effect. This review study has stressed that ketamine has significant analgesic effects in the surgeries on thorax and can be used as a supplement to the opioids in self-control pumps that the patient regulates. Though this systematic review has concluded that co-administration of ketamine decreases the adverse events, such as reduced arterial oxygen saturation, and reduces total analgesic need in the patient, considering that out of the 11 studies 5 studies have shown that the addition of ketamine does not increase the effectiveness of pain control the study calls for more studies for a conclusion in this regard (Carstensen et al., 2010).

5. CONCLUSION

The results showed that adding low dose of ketamine to injectable morphine sulfate not only has no significant clinical effects on reducing the pain intensity of patients, but also increases the adverse events imposed on them. Thus, morphine / ketamine combination compared to morphine / placebo does not result in more effectiveness and immunity and cannot be considered as a substitute for it.

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