

## Effect of Intravenous Morphine and Ketorolac on Pain Control in Long Bones Fractures

### Abstract

**Background:** According to the lack of adequate studies on comparing the analgesic effect and complications of ketorolac with morphine in long bone fractures, this study aimed to compare the efficacy of ketorolac with morphine in patients referring to the Emergency Department with long bones damage and fracture. **Materials and Methods:** In this clinical trial study, 88 patients with long bone fracture were selected randomly and divided into two groups. To scale the intensity of pain, visual analog scale (VAS) were used. Intravenous ketorolac and morphine with the loading dose of 10 mg and 5 mg, respectively was administered to a group, followed by 5 mg and 2.5 mg every 5–20 min, if necessary ( $VAS \geq 4$ ). The pain scores before injection and at 5 min, half an hour and 1-h after the injection were measured and recorded for all patients. **Results:** The mean age of the ketorolac and morphine groups was  $29.1 \pm 12.5$  and  $33.2 \pm 11.4$ , respectively. In the groups, there was 63.6% and 70.5% of male patients respectively. The mean  $\pm$  SD of pain score before the injection was  $7.59 \pm 1$  and  $7.93 \pm 1.09$  ( $P = 0.13$ ). One hour after the injection, the mean  $\pm$  SD of pain in the both groups was  $1.41 \pm 0.9$  and  $1.61 \pm 1.17$  and the mean pain score has no significant difference in the two groups before the injection. Repeated measures ANOVA test also showed that the trend of changes in pain score had no significant difference in both groups ( $P = 0.08$ ). **Conclusion:** According to the fewer side effects of ketorolac and effective pain release versus morphine, ketorolac could be suggested to use.

**Keywords:** Ketorolac, long bone fracture, morphine

### Introduction

Pain is one of the major causes of referring to Emergency Department with a remarkable number of main complaints. Although pain is the most common complaint of patients in Emergency Department, few studies have been conducted on the prevalence of the issue. In the previous studies, the study populations were heterogeneous, and we do not have enough information on the prevalence of patients with long bone fractures referring to Emergency Department.<sup>[1-4]</sup>

One of the major causes of pain is trauma, which is defined as the damage caused by external or internal forces of the body and can be associated with either the loss of continuity of structures or not.<sup>[2,5-8]</sup> Studying and treatment of pain has for a long time been one of the grounds neglected by the modern medicine. Several studies have shown that a lot of people referring to Emergency Department, especially children, and trauma victims received treatment

less than what is needed for the pain. There are many barriers including racial and ethnic issues, pain tolerance, and the inadequate knowledge of emergency medical personnel on the adequate and appropriate pain management in Emergency Department.<sup>[1,4,9,10]</sup>

Morphine is the most common analgesic used for pain control in these patients. Although such analgesics are cheap, the risk of dependency is existed; therefore, they are regarded as dangerous drugs. Divided and repeated doses of morphine results in dependency and it's unite do can result in serious complications, so it increases the need for monitoring the patient by medical staff and personnel. Another problem of morphine and other opioids is to have the sedative property that makes the patient completely unconscious. In addition to better pain relief, high doses of opioids have more side complications and, in fact, they are like a double-edged sword.<sup>[10-12]</sup> Ketorolac as a nonsteroidal anti-inflammatory injected drug (NSAID)

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**Babak Masoumi,  
Behdad Farzaneh,  
Omid Ahmadi,  
Farhad Heidari**

*From the Department of  
Emergency Medicine, Medical  
School, Isfahan University of  
Medical Sciences, Isfahan, Iran*

### Address for correspondence:

*Dr. Behdad Farzaneh,  
Department of Emergency  
Medicine, Medical School,  
Isfahan University of Medical  
Sciences, Isfahan, Iran.  
E-mail: [behdadfarzane@yahoo.com](mailto:behdadfarzane@yahoo.com)*

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has analgesic and anti-inflammatory properties. Also, it does not have sedative property. It is only as an injectable NSAID allow to control the pain as a rapid intravenous injection in North America, UK and other parts of Europe and Hong Kong. Several studies have suggested that ketorolac can be compared in the treatment of acute pain with opioids.<sup>[12]</sup>

Given the properties of ketorolac, as an NSAID, and the lack of enough studies regarding the comparison between analgesic effect and complications of ketorolac with morphine in long bone fractures, the present study aimed to compare the efficacy of ketorolac with morphine in patients referring to the Emergency Department due to the long bones damage and fracture.

## Materials and Methods

This is a double-blind clinical trial study conducted in June 2013 to September 2014 on patients referring to Emergency Department of Al-Zahra Hospital due to long bone fractures. This study was approved by Local Ethic Committee of Isfahan University of Medical Sciences, and all patients signed a consent form.

Eighty-eight patients were randomly divided into two groups (morphine and ketorolac group) by block randomization in a way that the first patient was luckily put in the morphine group and the others were successively and alternatively distributed in the ketorolac and morphine groups. Inclusion criteria were age over 18 years, patient's consent to participate in the study, patients with long bones fractures, and without asthma, chronic obstructive pulmonary disease, rheumatoid fever, peptic ulcer disease, gastrointestinal bleeding (GIB), and known hypersensitivity to drugs. It should be noted that patients with other problems except long bone fractures, patients without complete consciousness, as well as patients with hemodynamic instability and symptoms of respiratory depression and GIB during the pain relief injection, were excluded from the study.

The required sample size was calculated using estimating sample size formula as a total of 44 patients assigned to each group, to compare two means and considering 95% of confidence level, test power of 80, postoperative pain score of 1.33 and 0.8 as minimal significant difference between the two groups (See flow digram).

The blind method was in a way that patients were unaware of the type of drug and injection was performed by the physician of project manager while the pain score assessment was done by a nurse in the Emergency Department who was not aware about the study.

At first the patients were evaluated in terms of inclusion and exclusion criteria and then, interviewed by emergency medicine resident; their pain score was assessed by visual analog scale (VAS) scale too.<sup>[13,14]</sup> In the procedure,

intravenous ketorolac with the loading dose of 10 mg was administered to a group within 60 s, followed by 5 mg every 5 min to 20 min, if necessary (VAS  $\geq 4$ ) and intravenous morphine with the loading dose 5 mg was administered to another group, followed by 2.5 mg every 5 min to 20 min, if necessary (VAS  $\geq 4$ ).<sup>[8]</sup> The pain scores before the injection and at 5 min, half and 1 h after the injection were measured and recorded for all patients.

Finally, the obtained data were analyzed by SPSS software version 22 (SPSS Inc, Chicago, IL, USA) using statistical Chi-square for comparing the individual and nominal variables between groups and Student's *t*-tests in order to compare the ordinal variables.

## Results

In this study, 88 patients with regard to the inclusion criteria of the study were distributed and studied in two groups of 44 individuals.

The mean of age in the two groups receiving morphine and ketorolac was  $33.18 \pm 11.4$  and  $29.1 \pm 12.5$ , respectively and according to *t*-test, there was no significant difference between the two groups ( $P = 0.11$ ). The sex ratio (female/male) was 31.13 and 28.16, respectively in the two groups of receiving morphine and ketorolac and according to Chi-square test there was no significant difference between the two groups ( $P = 0.5$ ). Generally, the most common type of fracture was radius bone fracture and no significant difference was observed between the two groups ( $P = 0.91$ ). The distribution of demographic variables and the type of fractures in the two groups are given in Table 1.

The mean and standard deviation of pain score before the injection until 1-h after injection in both groups of morphine and ketorolac have been shown in Table 2. According to the *t*-test, the mean pain score has no significant difference in the two groups before the injection. The pain score did not differ at 5, 30, and 60 min after injection in both groups too. Repeated ANOVA also showed that the trend

**Table 1: Distribution of frequency of age, sex, and type of fracture in both groups**

Variables	Morphine	Ketorolac	<i>P</i>
Mean age	33.2±11.4	29.1±12.5	0.11
Sex <i>n</i> (%)			
Male	31 (70.5)	28 (63.6)	0.65
Female	13 (29.5)	16 (36.4)	
Location of fracture <i>n</i> (%)			
Humeros	6 (13.6)	5 (11.4)	0.91
Tibia	2 (4.5)	4 (9.1)	
Femor	4 (9.1)	2 (45.5)	
Tibia	4 (9.1)	5 (11.4)	
Ulna	3 (6.8)	5 (11.4)	
Radius	22 (50)	21 (47.7)	
Fibulla	3 (6.8)	2 (4.5)	

of changes in pain score had no significant difference in both groups ( $P = 0.08$ ).

During the study, 22 patients received the additional dose of drug wherein 14 individuals belonged to the morphine group and 8 ones to the ketorolac group (31.8% vs. 18.2%); however, according to Chi-square test, the receipt of additional dose of analgesic was not significantly different in the two groups ( $P = 0.11$ ).

The frequency of receiving additional dose of analgesic in the both groups has been shown in Figure 1. In the following of Table 2, the receipt frequency of additional dose of analgesic has been shown for the two groups from 5 to 20 min. According to Chi-square test, the frequency of additional dose of analgesic had a significant difference just at 10<sup>th</sup> min between the two groups ( $P = 0.021$ ). Also, 20 min later, no patient has received an additional dose of analgesics.

During the study, 22 patients suffered from postoperative complications as 18 cases were in the control group and 4 ones in the ketorolac group [Figure 2] (40.9% vs. 9.1%) and according to Chi-square test, incidence of complications had a significant difference in both groups ( $P = 0.001$ ). The observed complications in patients included nausea, vomiting, dyspnea, and hypotension in 11, 3, 2, and 3 cases, respectively that according to the Fisher's exact test, the incidence of nausea had a significant difference in both groups ( $P = 0.024$ ) [Table 3].

## Discussion

The overall objective of this study was to compare the effect of intravenous ketorolac and morphine on the control of pain in patients with long bone fractures admitted to Al-Zahra Hospital Emergency Department in Isfahan. In the present study, 44 patients with fractures in the mentioned parts received intravenous morphine and ketorolac injections and the pain relief, need to receive additional analgesic and the incidence of side complications from taking drug were compared in both groups.

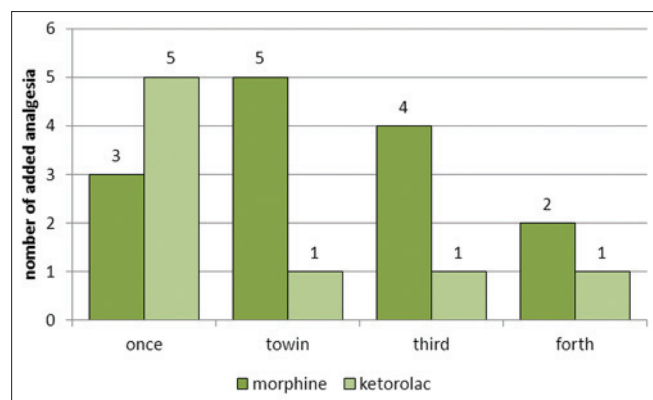


Figure 1: Distribution of the frequency of additional dose of analgesic in the two groups

Patients are receiving morphine and ketorolac had no significant difference in terms of age, sex and location of the fracture, and no distortive effect of these factors was found in both groups. According to the obtained results, with the intravenous injection of the first dose of the drug, the pain score was significantly reduced in both groups; however, pain reduction rate was the same in the two groups and no advantage was observed in the comparison between morphine and ketorolac. During the study, the morphine and ketorolac groups received 31.8% and 18.2% additional dose of analgesic, respectively; however, no statistically significant difference was observed between the two groups. Also, the total number of receiving analgesic times was not different in the two groups; however, at 10<sup>th</sup> min, more patients in the morphine group received additional analgesic. Therefore, taking morphine and ketorolac is equally effective in fracture pain reduction in patients with long bone fractures; however, the incidence rate of side complications was significantly higher in

**Table 2: Mean and SD of pain score and the number of patients received additional dose of analgesics in the two groups**

Variables	Time	Groups		P
		Morphine	Ketorolac	
Pain intensity (mean±SD)	Before injection	7.93±1.09	7.59±1	0.13
	5 min later	3.84±1.7	3.34±1.38	0.13
	30 min later	2.64±1.28	2.39±0.81	0.28
	60 min later	1.61±1.17	1.41±0.9	0.36
Added injection n (%)	5 <sup>th</sup> min	10 (2.3)	8 (18.2)	0.59
	10 <sup>th</sup> min	12 (27.3)	3 (6.8)	0.021
	15 <sup>th</sup> min	7 (15.9)	2 (4.5)	0.08
	20 <sup>th</sup> min	4 (9.1)	1 (2.3)	0.18

SD: Standard deviation

**Table 3: Frequency distribution of incidence of side complications in both groups**

Complications	Groups		P	
	Morphine	Ketorolac		
Nausea n (%)	No	35 (79.5)	42 (95.5)	0.024
	Yes	9 (20.5)	2 (4.5)	
Vomiting n (%)	No	42 (95.5)	43 (97.7)	0.99
	Yes	2 (4.5)	1 (2.3)	
Depression n (%)	No	42 (95.5)	44 (100)	0.49
	Yes	2 (4.5)	0 (0)	
Hypotension n (%)	No	41 (93.2)	44 (100)	0.24
	Yes	3 (6.8)	0 (0)	
Drowsiness	Yes	4	1	
	No	40	43	

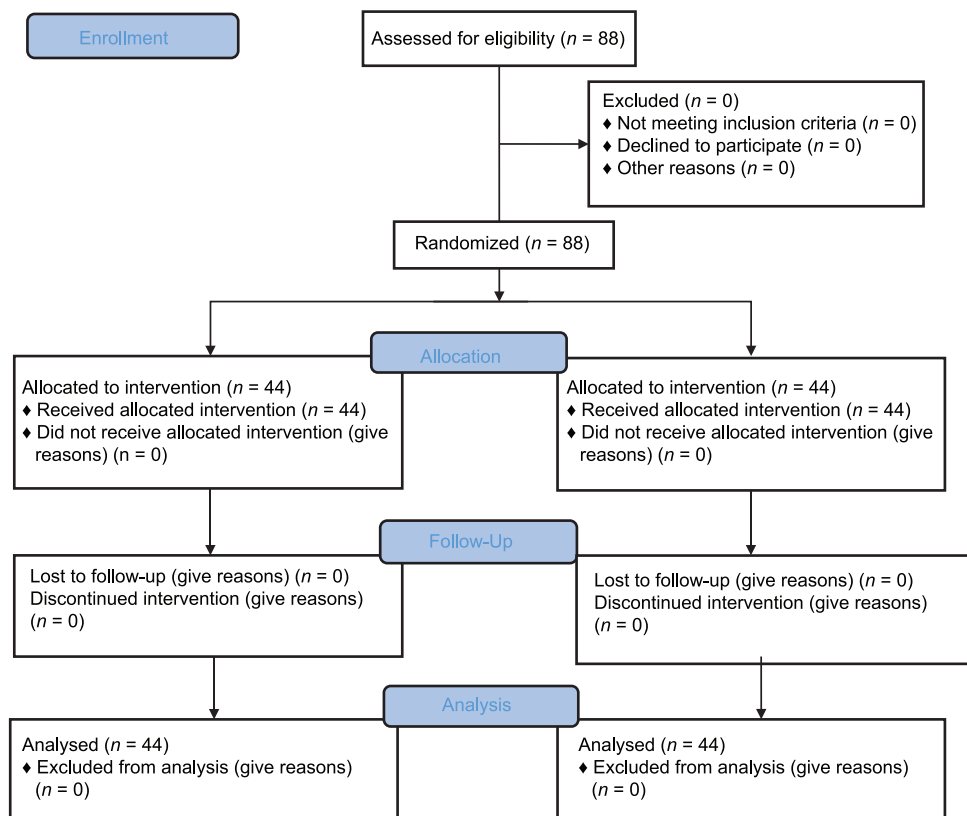


Figure 2: Consort flowchart of the study

patients receiving morphine that the major difference was in the incidence of nausea after the intravenous injection of the drug.

In several studies, ketorolac has been compared with other analgesics. In the study conducted by Veenema *et al.*, a single dose of ketorolac could be equal to meperidine while the side complications of ketorolac were less than that of meperidine.<sup>[12]</sup> The study by Innes *et al.* which aimed to examine the side complications and effectiveness of ketorolac in the treatment of a low backache compared with acetaminophen-codeine concluded that ketorolac was the superior drug than acetaminophen codeine.<sup>[6]</sup> In a study by Etches *et al.* with the aim of investigate the relief effect of ketorolac after the orthopedic surgeries, they concluded that an intravenous dose of ketorolac causes the reduction of morphine consumption and better relief in comparison with placebo.<sup>[2]</sup> In a study by Rainer *et al.*,<sup>[8]</sup> the cost-effectiveness of intravenous ketorolac was compared with that of intravenous morphine in the treatment of pain in organ damage. The results revealed that compared to morphine, ketorolac is more cost-effective in pain relief in organ damage. However, in the study by Cepeda *et al.*, in abdominal surgeries, the intravenous ketorolac alone had no sufficient performance in the pain relief despite the good tolerance by patients.<sup>[5]</sup> Therefore, considering the important role of inflammatory mediators in the creation of pain and a lot of side complications of opioids, with appropriate anti-inflammatory properties and fewer side complications,

ketorolac is an appropriate choice for pain reduction in patients with long bone fractures. This study had small sample size due to the inclusion criteria and unsatisfied patients refusing to participate and not including to the study samples which should be considered as a limitation.

Especially, in cases where taking opioids has the possibility to create complications, ketorolac is an appropriate analgesic and can be used depending on the physician discretion and patient's condition.

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### Conflicts of interest

There are no conflicts of interest.

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