

# Analgesic Response to Fentanyl in Comparison to Morphine among Adult Traumatic Patients in Emergency Departments: A Randomized Clinical Trial

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## Abstract

**Background:** Several studies have been performed to evaluate the efficacy of different pain management techniques in patients with trauma, using different methods.

**Objectives:** To compare Intravenous (IV) morphine vs. fentanyl for analgesic response, the time to reach lowest pain score, and adverse effects in patients with trauma who were referred to Emergency Department (ED) was investigated.

**Methods:** This double-blind randomized controlled trial (June-December 2017) was performed on adult traumatic patients, who were referred to the EDs of two main trauma centers (Affiliated to Shiraz University of Medical Sciences), in southern Iran. The inclusion criteria were acute pain >4 on a Numeric Rating Scale (NRS) 0-10 upon presentation. The patients were randomly allocated to receive a single dose of IV morphine (0.1 mg/kg) or IV fentanyl (2 µg/kg). The pain score was recorded at baseline, 5, 10, 30, and 120 minutes after administration of either morphine or fentanyl, as well as adverse effects. Then, the data were analyzed.

**Results:** In order to carry out this study, 167 patients were enrolled. The initial NRS in both groups were similar. The mean ± SD of NRS at all times was higher in the fentanyl group, except in 10 minutes, but only in 120 minutes, this difference was statistically significant ( $P = 0.01$ ). The mean ± SD of pain reduction in all times was similar in both groups. The incidence of adverse effects in both groups were not different ( $P = 0.18$ ).

**Conclusion:** According to findings, IV fentanyl had a similar analgesic effect to IV morphine in traumatic patients with acute pain. Also, there was no significant difference in terms of adverse effects between groups.

**Keywords:** Acute Pain, Pain Management, Emergency Department, Morphine, Fentanyl

## 1. Background

Pain control is critical and challenging when managing patients with trauma,<sup>1</sup> especially in Emergency Departments (ED).<sup>2</sup> Pain control has ethical, legal, and clinical dimensions, which has been described as a primary goal in emergency medical services.<sup>3,4</sup> Although providing a suitable and timely pain control is not only a patient's right, there is a lack of standardized protocols for analgesia prescription for acute pain control in hospitals.<sup>5</sup> For example, guidelines for Advanced Trauma Life Support (ATLS) does not describe any recommendations with respect to selection and dosing of analgesics,<sup>6</sup> and there is an obvious mishandling in pain control among traumatic patients.<sup>7</sup> Uncontrolled pain has harmful effects on physiological cycles, e.g., unstable hemodynamic status,

mydriasis, fatigue, insomnia, and disturbance in the immune system function. In addition, it has several psychosocial effects, containing anxiety, posttraumatic stress disorder, and disorientation, as well as increasing patient's stress response.<sup>5,8</sup>

Several studies were performed to evaluate the efficacy of different pain management techniques in patients with trauma, using different methods such as non-pharmacologic technique like splinting the fractures or prescribing a range of pharmacological medications including opioids, lidocaine, and non-steroidal anti-inflammatory drugs (NSAIDs).<sup>3,10,11</sup> Moderate to severe pain is often cared pharmacologically with Intravenous (IV) opioids that morphine is by far the most popular in comparison to

others. However, opioids have several complications such as; dizziness, sedation, constipation, nausea/vomiting tolerance, physical dependency, addiction, respiratory depression, and hemodynamic instability, which makes them a clinical concern and prevent physicians to prescribe proper and adequate dosage in pain management.<sup>11</sup> There is huge interest in the administer of fentanyl (one of opioids) in traumatic patients due to its rapid onset of analgesia, little effect on blood pressure, and potential for less nausea/vomiting in comparison with morphine.<sup>12</sup>

The effect of fentanyl vs. morphine has been evaluated in the pre-hospital situation in previous studies,<sup>13,14</sup> but there is no sufficient evidence to use it in hospital settings for pain management among traumatic patients.<sup>15</sup>

## 2. Objectives

The goal of this trial was to compare IV morphine with fentanyl for analgesic response, the time to reach lowest pain score, and adverse effects in patients with trauma who were referred to EDs.

## 3. Methods

### 3.1. Study Design

The present study was designed as a double-blind Randomized Controlled Trial (RCT), which was conducted to compare IV morphine with IV fentanyl for pain control in adult patients with trauma between June and December 2017, who were referred to the EDs of Shiraz Namazi and Rajaei hospitals (Affiliated with Shiraz University of Medical Sciences), the two main trauma centers in Shiraz, southern Iran.

### 3.2. Participants

Traumatic patients with Glasgow Coma Score (GCS) of 15, age more than 18 years, who had an initial acute pain score of 4 or more (0 = no pain and 10 = worst possible pain) on the Numerical Rating Scale (NRS) upon presentation, and initial oxygen saturation greater than 95%, were enrolled in this study. The exclusion criteria included patients with systolic blood pressure less than 90 mmHg, patients with asthma, alcohol or other drug intoxication, judged by the attending physician, use of other opioids within the last 7 days, known pregnancy, and cognitive impairment. In addition, patients with chronic pain syndromes such as sickle cell disease or fibromyalgia and known allergy to either fentanyl or morphine were excluded from the study, as well as all patients who received any types of the analgesics. Also, all patients with limb trauma who had been transferred to the EDs, had not received analgesics by EMS, and only immobilization were performed for them were excluded from this study.

### 3.3. Sample Size and Sampling Method

Using Medcalc software version 13.0 for Windows, a

sample size of 180 patients were calculated (90 in each group) to detect a 1.3 point or greater difference on the NRS, assuming a 2-tailed  $\alpha$  of 0.05, 80% power and Standard Deviation (SD) of 3.<sup>16</sup>

### 3.4. Randomization

In the current study, we used the block randomization method. Each block size was 2 by 2, and in total 45 blocks were considered. The acceptable sequences for packages within each block were: 1) AABB, 2) ABAB, 3) BBAA, 4) BABA, 5) ABBA, and 6) BAAB. Then each were marked from 1 to 6 as above. The packages within blocks were then sequentially numbered from 1 to 180. Participants were consecutively numbered from 1 to 180, based on the time of admission and hospital registration code.<sup>10</sup>

Allocation was performed by blindly matching the patients' number and package. The randomization sequence and concealment were performed by an emergency medicine attending physician who was an Iranian board-certified in emergency medicine, and a faculty member [NZ]. Allocation and matching of the participants' number to the package number in order to receive the intervention was performed by an emergency medicine resident [MJA].

### 3.5. Blinding

Two sets of 90 sterile, colorless, similar and ready to inject 10 cm<sup>3</sup> syringes were prepared and were labeled A (morphine 0.1 mg/kg) and B (fentanyl 2 µg/kg) before concealment. Both drugs were diluted with normal saline. This means the amount of drug in each syringe was the same. According to block randomization, each patient received either treatment A or B. The patients and the nurses who administrated were blinded. In addition, the physicians did not know which patients received drug A or B. Hence, the patients, nurses, as well as data analyzer were blinded to the type of analgesic.

### 3.6. Study Interventions

The patients were first triaged and admitted in the ED, and standard ED's management were performed. Parallel to that the purpose and process of the study were explained to eligible patients by the researchers [NZ, MJA] according to the inclusion and exclusion criteria. The participants were then selected and were asked to sign the written informed consent. Then, they were randomly allocated to receive a single dose of IV morphine (0.1 mg/kg) [MORPHINE SULFATE DP 10MG/1ML AMP, Darou Pakhsh company, Iran] or IV fentanyl (2 µg/kg) [FENTANYLE DP 0.1MG/2ML Amp, Darou Pakhsh company, Iran] over 2-3 minutes [NZ, MJA].

### 3.7. Outcomes Evaluation

The pain score was recorded by stopwatch at baseline, 5,

10, 30, and 120 minutes after the beginning of administration in both groups, using the NRS (with minimum of 0, as no pain, to maximum of 10, as the worst pain). The pain reduction on the NRS after administration of IV morphine or IV fentanyl was calculated as the difference between the baseline pain score, and 5, 10, 30, and 120 minutes after the beginning of administration. The vital signs were measured and recorded in several stages: 5, 10, 30, and 120 minutes after the intervention. The adverse events of the systolic blood pressure <90 mmHg and O<sub>2</sub> saturation <90% were assessed according to these measures. The time related to the lowest pain score was recorded, and the drugs adverse effects (including nausea, vomiting, systolic blood pressure <90 mmHg, and O<sub>2</sub> saturation <90%) were also assessed, which was considered as the secondary outcome. These data were recorded by an emergency medicine specialist [MJA], supervised by the emergency medicine attending physician [NZ].

### 3.8. Data Gathering

All data were collected using a data gathering form, which included the patients' demographic information such as age, gender, weight, and type of trauma (blunt or penetrating), injury mechanism, injury location, as well as clinical findings (blood pressure, heart rate, respiratory rate, oxygen saturation, GCS, and pain score) were recorded. In addition, adverse events such as respiratory depression (<12 breaths per minute), O<sub>2</sub> desaturation

<90%, hypotension (systolic blood pressure <90 mmHg), nausea, emesis, and reduced level of consciousness were recorded for two hours post baseline. Patients were asked to rate their pain on a NRS, where 0 is no pain and 10 is the most severe pain. Pain scores and vital signs were recorded at baseline, at 5, 10, and 30 minutes, and 2 hours post baseline.

### 3.9. Statistical Analysis

All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 22 for Windows through descriptive and analytical tests, such as independent sample *t*-test, Chi-square, repeated measurement of the analysis of variance (rANOVA), and nonparametric tests. The distribution of variables was assessed with Kolmogorov-Smirnov test. Results have been presented as mean  $\pm$  SD for continuous variables, and were summarized in number (percentage) for categorical ones. Two-sided *P*-value < 0.05 was considered to be statistically significant.

### 4. Results

Out of the 234 patients assessed for eligibility, 41 patients did not meet the inclusion criteria and 13 individuals refused to participate. Thus, the final number of patients being randomized into two study groups was 180 (90 patients in each group). Data of eight patients in the morphine group and five patients in the fentanyl group

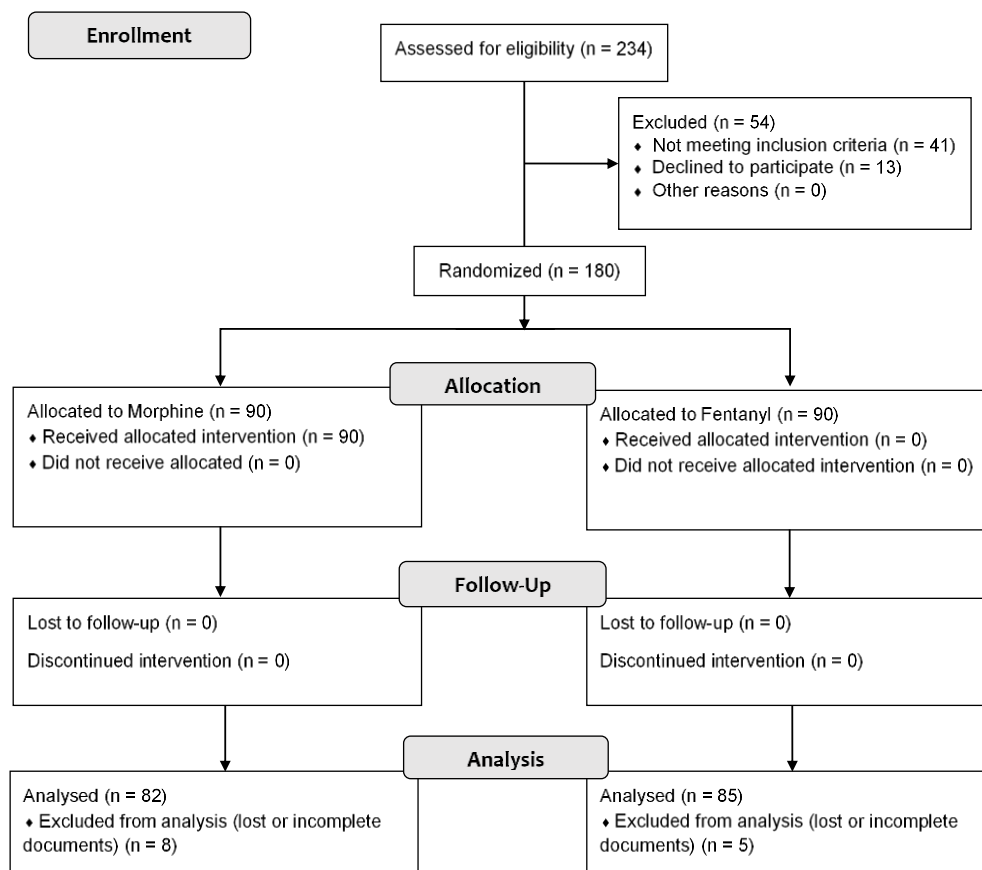


Figure 1. CONSORT Flow Diagram.

**Table 1.** Baseline Characteristics of the Patients

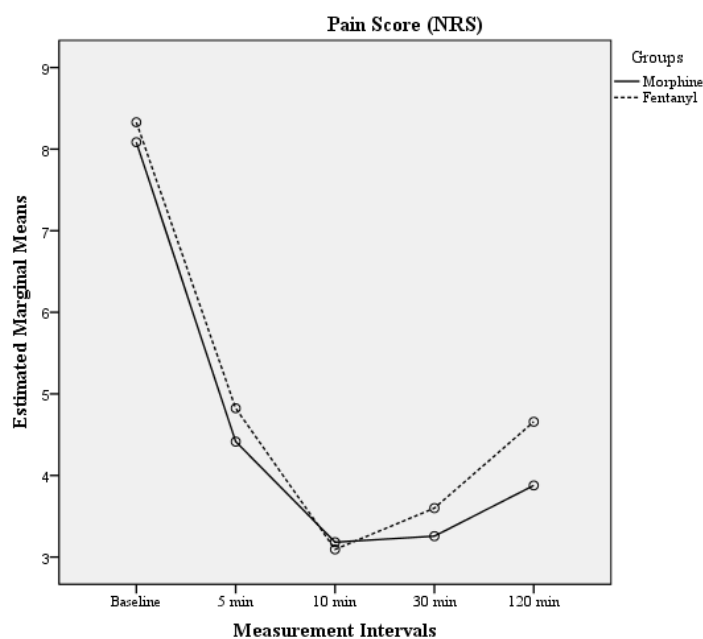
Baseline characteristics	Total (n = 167)	Morphine group (n = 82)	Fentanyl group (n = 85)	Pvalue
Demographics				
Age (year)	39.63±17.49	39.94±19.38	39.34±15.56	0.82
Wight (Kg)	70.28±10.05	68.59±11.41	71.66±8.09	0.05
Male (%)	132 (79)	63 (76.8)	69 (81.2)	0.49
Female (%)	25 (21)	19 (213.2)	16 (18.8)	
Vital signs before the intervention				
Systolic blood pressure (mm Hg)	120.49±11.04	119.43±8.08	121.52±13.25	0.22
Diastolic blood pressure (mm Hg)	76.57±7.05	77.12±7.44	76.12±6.67	0.36
Respiratory rate (per min)	19.85±1.59	19.84±1.51	19.85±1.69	0.96
Heart rate (per min)	80.83±5.75	81.23±6.68	80.20±4.22	0.23
O <sub>2</sub> saturation (%)	94.61±0.77	94.76±0.71	94.45±0.81	0.81
Type of trauma (%)				
Blunt	155 (92.8)	74 (90.2)	81 (95.3)	0.21
Penetrating	12 (7.2)	8 (9.8)	4 (4.7)	
Mechanisms of injury (%)				
Motor vehicle collision	67 (40.1)	30 (36.6)	37 (43.5)	0.13
Falling down	85 (50.9)	41 (50)	44 (51.8)	
Gunshot wound	15 (9)	11 (13.4)	4 (4.7)	
Injury location (%)				
Head/neck	4 (2.4)	1 (1.2)	3 (3.5)	0.36
Face	5 (3)	1 (1.2)	4 (4.7)	0.22
Chest	36 (21.6)	16 (19.5)	20 (23.5)	0.51
Abdomen/pelvic	22 (13.2)	15 (18.3)	7 (8.2)	0.10
Extremity	100 (59.9)	49 (59.8)	51 (60)	0.80
Pain score (NRS)				
Baseline	8.21±1.76	8.09±1.65	8.33±1.85	0.37
5 minutes	4.62±1.75	4.41±1.99	4.82±1.47	0.13
10 minutes	3.14±1.78	3.18±1.50	3.09±2.02	0.75
30 minutes	3.43±2.07	3.26±2.18	3.60±1.96	0.29
120 minutes	4.28±2.01	3.88±1.95	4.66±1.99	0.01*

\* Statistically significant. NRS = numeric rating scale, SD = standard deviation

were lost or incomplete. Finally, 167 patients were enrolled, 82 were randomly assigned to the morphine group and 85 to the fentanyl group. Figure 1 shows the CONSORT flowchart of the studied patients. It should be considered that all the patients received only one dose of drug, and all of them responded to it. It is worth mentioning that there was no need for dose maintenance.

Totally, the mean ± SD of age was 39.63 ± 17.49, which 79% were male and the reason for trauma was falling down (50.9%). The mean ± SD of age was 39.94 ±

19.38 (range 19-48) years in the morphine group, and 39.34 ± 15.56 (range 19-51) years in the fentanyl group ( $P = 0.82$ ). There was no statistically significant difference in gender distribution (male/female ratio), weight, vital signs, type of trauma, mechanism of injury, and injury location between the two groups. The initial NRS in the morphine and fentanyl group were not statistically different ( $8.09 ± 1.65$  vs.  $8.33 ± 1.85$ ,  $P = 0.37$ ), and all of them had initial pain score  $\geq 4$  (as inclusion criteria), and totally 60 (35.9%) patients had an initial pain score equal to 10.



**Figure 2.** Pain Score Changes in Morphine and Fentanyl Groups.

The median of initial pain score in the morphine and fentanyl group was 8 and 9, respectively. The mean  $\pm$  SD of NRS at 5, 10, 30, and 120 minutes are shown in Table 1. It should be noted that the mean  $\pm$  SD of NRS at all times was higher in the fentanyl group, except in 10 minutes, but it was not statistically significant. In the time of 120 minutes, this difference was statistically significant (morphine group:  $3.88 \pm 1.95$  vs. fentanyl group:  $4.66 \pm 1.99$ ,  $P = 0.01$ ) (Figure 2). The partial effect size was equal to 0.907 ( $P < 0.001$ ).

The analysis showed that the mean  $\pm$  SD of lowest NRS was recorded earlier in the fentanyl group compared to the morphine group ( $13.12 \pm 9.03$  vs.  $15.49 \pm 15.08$  minutes); however, this difference was not statistically significant ( $P = 0.21$ ). Table 2 shows the NRS changes from baseline to 5, 10, 30, and 120 minutes after intervention in both groups. The mean  $\pm$  SD of pain reduction from baseline to 5, 30, and 120 minutes in the morphine group was greater than the fentanyl group, but

the mean  $\pm$  SD of pain reduction from baseline to 10 minutes in the fentanyl group was slightly more than the morphine group. However, these differences were not statistically significant.

The rANOVA was used to evaluate NRS changes in each group and during 120 minutes all patients had NRS reduction until 10 minutes, which was statistically significant (from  $8.09 \pm 1.65$  to  $3.18 \pm 1.50$  in the morphine group and from  $8.33 \pm 1.85$  to  $3.09 \pm 2.02$  in the fentanyl group), and after that the pain score increased in both groups until 120 minutes. However, when comparing both groups, there was no statistically significant difference in NRS changes at 5, 10, 30, and 120 minutes.

The incidence of life-threatening adverse effects in the fentanyl group was lower than the morphine group, but this difference was not statistically significant (12 [14.17%] vs. 18 [21.95%];  $P = 0.18$ ) (Table 3), and no patient in either group had to use naloxone and intubation.

**Table 2.** Numeric Rating Scale (NRS) Changes (from baseline to 5, 10, 30, and 120 minutes after intervention in both groups)

Mean change from	Morphine group (n = 82)	Fentanyl group (n = 85)	P value
Baseline	8.09 $\pm$ 1.65	8.33 $\pm$ 1.85	0.37
Baseline to 5 minutes	-3.66 $\pm$ 2.22	-3.51 $\pm$ 1.66	0.61
Baseline to 10 minutes	-4.89 $\pm$ 1.56	-5.24 $\pm$ 2.01	0.21
Baseline to 30 minutes	-4.82 $\pm$ 1.79	-4.73 $\pm$ 2.06	0.77
Baseline to 120 minutes	-4.21 $\pm$ 1.73	-3.67 $\pm$ 2.04	0.07

**Table 3.** Comparing the Incidence of Adverse Events between Morphine and Fentanyl Groups

Adverse effects	Total	Morphine group (n = 82)	Fentanyl group (n = 85)	P value
Total number of patients affected with adverse effects	30 (18)	18 (21.95)	12 (14.17)	0.18
Nausea	19 (11.4)	11 (13.51)	8 (9.41)	0.41
Vomiting	11 (6.6)	6 (7.31)	5 (5.88)	0.71
Systolic blood pressure <90mm Hg	4 (2.4)	1 (1.21)	3 (3.52)	0.32
O <sub>2</sub> saturation <90%	4 (2.4)	2 (2.43)	2 (2.35)	0.91

## 5. Discussion

We hypothesized that IV fentanyl (2  $\mu$ g/kg) could produce a better analgesic response than IV morphine (0.1 mg/kg) in patients with trauma in ED. This was due to rapid onset of effect, preventing further escalation in pain that could be more refractory to treatment, with lower side effects.<sup>12</sup>

Concordant with the results of previous studies, our results showed that morphine and fentanyl had similar effects on pain reduction in adult traumatic patients 5, 10, 30, and 120 minutes after the initiation of administration. It was observed that the lowest NRS was recorded earlier in the fentanyl group compared to the morphine group; however, this difference was not statistically significant. Statistically, we found that NRS was reduced until 10 minutes in both groups, and after that moment the pain score increased in both groups until 120 minutes. However, when comparing both groups, there was no statistically significant difference in NRS changes at 5, 10, 30, and 120 minutes.

To the best of our knowledge, just one retrospective

cohort study had compared the analgesic response and safety of IV morphine vs. fentanyl for adult patients with trauma who were admitted to the ED. Wenderoth et al. found that IV morphine (4 mg) and fentanyl (50  $\mu$ g) had a similar effect on pain control. Also, they stated that the lowest post dose pain score was observed earlier in the fentanyl group, but similar to our study, this difference was not statistically significant.<sup>17</sup>

Moreover, the results of the Galinski et al. study was in line with ours, comparing IV morphine (0.1 mg/kg, then 3 mg every 5 minutes) and fentanyl (1  $\mu$ g/kg, then of 30  $\mu$ g every 5 minutes) during the first 30 minutes on patients with severe acute pain in the pre-hospital situation in a double-blind RCT. They found that the analgesic effect of both drugs was the same, as well as the rate of adverse effects.<sup>13</sup> Also, Smith et al. found no significant difference between IV morphine (4 mg) and fentanyl (50  $\mu$ g) in analgesic response in traumatic patients during transport *via* a physician-staffed air medical service.<sup>15</sup> In Iran, Vahedi et al. compared the pain reduction between IV fentanyl (1  $\mu$ g/kg) vs. morphine

(0.1 mg/kg) in opioid addicted patients with acute traumatic limb injuries in a double-blind RCT, and reported that the effectiveness and safety of fentanyl was the same as morphine.<sup>18</sup>

However, it must be noted that standard protocols must contain titration and repeated doses to reach sufficient pain relief for the duration of the patients ED stay. Curtis et al., reported that using fentanyl in pain management amongst patients with trauma can reduce the time to initial analgesia. Also, they found no adverse events attributable to the analgesia protocol despite cumulative doses of fentanyl up to 150 µg.<sup>19</sup> However, this was a non-comparative study, and it did not assess the rate of other side effects such as nausea or vomiting.

The incidence of adverse effects in the fentanyl group was lower than the morphine group, but we found no statistically difference in the adverse event profiles between two groups. Theoretically, morphine has more histamine reaction and could lead to a higher rate of hypotension and itching,<sup>20</sup> but the overall incidence of histamine-related adverse effects was low in our study. Also, no patient in either group required naloxone or intubation. In line with our study, Wenderoth et al. and Vahedi et al. did not find any difference in adverse effects between both groups in their studies.<sup>17,18</sup> Moreover, Galinski et al. in pre-hospital setting reported that the incidence of side effects was similar in morphine and fentanyl groups. However, they stated that the comparatively short transport times (approximately 40 minutes) did not allow accurate valuation of adverse effects such as nausea, vomiting or itching that might have happened after arriving at the hospital.<sup>13</sup>

### 5.1. Limitations and Suggestions

As we designed, got approve, and did this research before the publishing any meta-analysis about this issue (June to December 2017), and the related meta-analysis was published in November 2017,<sup>15</sup> and until that time, we did not find any related meta-analysis and clinical guideline about this topic, and only 2 RCTs were published in comparing IV fentanyl and IV morphine in prehospital traumatic patients not in ED,<sup>13,14</sup> we thought that there is not enough evidence, so we designed and performed this study. Therefore, we should publish our results. However, our results confirmed previous studies.

The current study had some limiting factors, which diminished the impact of the results. This study was conducted on adult patients, and the effects on pediatric population were not investigated. Also, NRS was not evaluated in the time of 60 minutes, while the peak plasma times of morphine and fentanyl are 30-60 minutes. Consequently, the NRS trend was elevated in the time of 120 minutes. It should be considered that this change was not significant for morphine unlike fentanyl. Moreover, in this study we could not assess the adverse

effects at 5, 10, and 30 minutes, separately, and evaluated them holistically. Hence, we recommend larger studies to determine all the aspects of these interventions on traumatic patients in EDs, as well as systematic review and meta-analysis.

## 6. Conclusion

Fentanyl had a similar analgesic effect in comparison with morphine in traumatic patients who referred to EDs with acute pain. There was no significant difference in drug-induced side effects among the study groups. Fentanyl showed a similar but more rapid analgesic response in comparison with morphine in trauma case; however, this difference was not statistically significant. Thus, it can be recommended to administer IV fentanyl as a feasible alternative to IV morphine for the treatment of acute pain in traumatic patients in ED.

### Research Highlights

#### What Is Already Known?

- Several studies were performed to evaluate the efficacy of different pain management techniques in patients with trauma, using different methods.
- Moderate to severe pain is often cared pharmacologically with intravenous (IV) opioids that morphine is by far the most popular in comparison to others. However, opioids have several complications.

#### What Does This Study Add?

In this study, it was found that fentanyl had a similar analgesic effect in comparison with morphine in traumatic patients who referred to EDs with acute pain.

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### Author Contributions

NZJ contributed as the main author with the concept of planning the study. NZJ, AD and MJA contributed in the study design, patient selection and also the follow ups. RSM and MJA performed the statistical analysis and interpreted the data. RSM and MJA wrote the manuscript. NZJ, AD and FF contributed in revising the manuscript. All authors approved the final revision.

### Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

### Ethical Approval

The current study was approved and supported by Shiraz

University of Medical Sciences (grant No. 96.01.01.14253), which was conducted in accordance with the Declaration of Helsinki and its later amendments, which was approved by the vice-chancellor of research and technology, as well as the local Ethics Committee (IR.SUMS.MED.REC.1397.133) of Shiraz University of Medical Sciences. Also, it was registered and approved by the Iranian Registry of Clinical Trials (IRCT) (IRCT20180608040013N1 at <http://www.irct.ir>). To consider ethical issues, the collected data were not revealed to anyone, except for the researchers. All participants signed a written informed consent.

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