

# Acute pain management with intravenous 0.10 mg/kg vs. 0.15 mg/kg morphine sulfate in limb traumatized patients: a randomized double-blinded placebo-controlled trial

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## ABSTRACT

**BACKGROUND:** We aimed to compare pain relief and safety of two doses of morphine in adult emergency department (ED) patients with acute limb trauma pain.

**METHODS:** A total of 200 adult ED patients over 20 years of age requiring opioid analgesia were randomly allocated to two groups. Following a first dose of intravenous morphine sulfate at 0.10 mg/kg, a randomized double-blind placebo-controlled trial of intravenous morphine sulfate at 0.05 mg/kg versus the same amount of placebo was performed. Measurement of visual analogue scale pain intensity and assessment of adverse effects were performed at baseline (before morphine at 0.10 mg/kg), 30 minutes from baseline (just before study drug administration), and at 60 minutes from baseline (30 minutes after study drug).

**RESULTS:** No significant difference was found between groups at 30 minutes from baseline. There was significant reduction in final pain after 1 hour in the 0.15 mg/kg compared to 0.10 mg/kg group ( $p < 0.05$ ). In addition, there was a significant improvement in the mean score of pain in the same group ( $p < 0.05$ ). The percent of pain reduction in the intervention and control group relative to the basic measures was 52.70% and 35.82%, respectively. Adverse effects were present in both groups; however, there was no statistically significant difference between groups.

**CONCLUSION:** Using two doses of morphine instead of one is a safe and effective method for pain reduction in isolated limb trauma. We recommend performing a second injection of 0.05 mg/kg morphine 30 minutes after the initial standard dose of 0.10 mg/kg to decrease pain in these patients.

**Key words:** Acute pain, emergency medicine, randomized controlled trial.

## INTRODUCTION

Up to 70% of all patients presenting to emergency departments (EDs) experience varying degrees of pain, and if the insult is trauma, management could be challenging because

different systems could be involved.<sup>[1]</sup> After a primary survey including vital survey of the respiratory and cardiovascular systems, pain management is a key step in the ED.<sup>[2]</sup>

Opioids are a mainstay of moderate to severe pain management in acute events such as trauma and chronic pain due to malignancies.<sup>[3,4]</sup> The prototype of opioids in the ED is morphine. It is the most frequent drug for acute pain control because it has few side effects and provides acceptable analgesia with different dosage protocols.<sup>[5]</sup> Various doses for morphine administration have been recommended. Nevertheless, previous studies have reported inadequate pain control in the ED.<sup>[6-9]</sup> A study conducted by Bijur et al.<sup>[10]</sup> suggested that the common 0.10 mg/kg starting dose of morphine may be too low to adequately control acute severe pain.

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The aim of this study was to define a minimum effective dose of morphine for obtaining maximum analgesia in limb trauma. We compared the pain relief and safety of two doses of morphine in adult ED patients with acute limb trauma pain.

## MATERIALS AND METHODS

### Study Design

Following the first intravenous morphine sulfate at 0.10 mg/kg, a prospective randomized double-blind placebo-controlled trial of intravenous morphine sulfate at 0.05 mg/kg versus the same amount of distilled water as a placebo was performed in adult ED patients over 20 years of age with acute limb trauma pain requiring opioid analgesia.

### Setting

The study was conducted in the ED of an academic large trauma center from 20 March 2009 to 19 March 2011. Data collection was performed by four emergency medicine residents available 24 hours per day, 7 days per week. They were trained and blinded to the study protocol. They assessed the pain score at baseline and 30 and 60 minutes afterwards.

### Selection of Participants

Patients over 20 years of age presenting to the ED with pain following acute limb trauma of less than three days' duration, and considered by the ED attending professors to require opioid analgesia, were suitable for inclusion. Exclusion criteria were: requirement of rescue analgesia, death of patients in

less than one hour, referral of patients to the operating room in less than one hour, multiple trauma patients for whom the ED attending professor ordered naloxone or more opioids, unwillingness to provide informed consent or to receive a second dose of analgesic, serious life-threatening complications such as respiratory depression after the first dose injection, previous adverse reaction to morphine, cognition problems, or disoriented patients who were unable to cooperate.

Emergency medicine residents ordered the morphine injection for those patients whose triage assessment indicated pain and for whom opioid analgesia was deemed to be warranted by the ED attending physician. Written informed consent was obtained from all participants. The study protocol was approved by the ethical committee of Tehran University of Medical Sciences.

### Interventions

Patients were randomly allocated to two pain management groups that were assigned to receive morphine sulfate at either 0.10 mg/kg or 0.15 mg/kg (Fig. 1). After initial assessment of baseline pain, all participants received an initial dose of morphine sulfate at 0.10 mg/kg. Reassessment of pain was performed at 30 minutes from baseline, followed immediately by intravenous administration of morphine at 0.05 mg/kg or placebo during two minutes. Patients received either a second dose of morphine sulfate at 0.05 mg/kg or the same amount of purified water solution as placebo in the form of clear, colorless fluid. Final pain assessment was performed at 60 minutes from baseline (equal to 30 minutes after the sec-

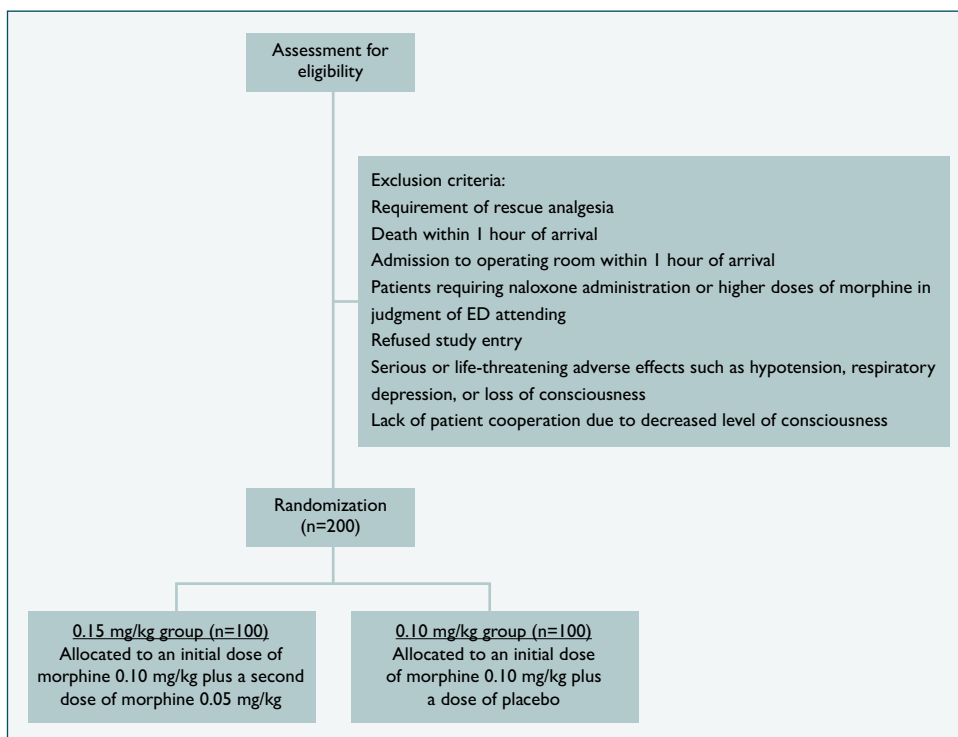


Figure 1. Enrollment, randomization, and treatment protocols.

ond injection). The patient and ED resident both remained blinded to the group assignments during the entire study.

All medications were administered by an ED nurse who was blinded to the study. Safety was monitored by continuous pulse oximetry, monitoring of respiratory rate and pulse rate, and blood pressure monitoring every 10 minutes. Oxygen was to be administered for an oxygen saturation of less than 95%. Normal saline solution was administered for a systolic blood pressure less than 100 mmHg, and naloxone was considered for a pulse oximeter reading less than 95% after oxygen administration, a pulse rate less than 60 beats/min, or a systolic blood pressure less than 100 mmHg after administration of a saline solution bolus.

## Methods of Measurement

Patients were asked by one of the four trained emergency medicine residents to rate their pain intensity on 10-point visual analogue scale (VAS), ranging from 0, equivalent to “no pain”, to 10, equivalent to “worst possible pain.” The VAS pain score is the most commonly used tool to assess pain, is sensitive to small changes, and provides a continuous variable suitable for statistical analysis.<sup>[11]</sup> It has been widely accepted due to its ease and brevity of administration, minimal intrusiveness, and conceptual simplicity.<sup>[12]</sup> The VAS pain intensity measurement was administered at baseline (before morphine at 0.10 mg/kg), 30 minutes from baseline (just before study drug administration), and at 60 minutes from baseline (30 minutes after the study drug). Based on the pharmacokinetics of morphine, 30 minutes following morphine injection was chosen as a practical time within which adequate analgesia is achieved in patients with severe pain without missing an analgesic effect.<sup>[13]</sup> Morphine side effects including vomiting, hypotension, tachycardia, respiratory depression, decreased level of consciousness (Glasgow Coma Scale (GCS) score), and urinary retention were documented after each injection in both groups. Hypotension was defined as a drop of systolic pressure below 90 mmHg after morphine administration. Tachycardia was defined as a heart rate above 100/min, and respiratory depression was defined as a respiratory rate below 10/min associated with an oxygen saturation of rate less than 90%. For all of the mentioned adverse effects, underlying conditions such as hemorrhage or head trauma were ruled out.

## Data Entry

Data were entered into a Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS, Inc., Chicago, IL) database. Patients with acute isolated limb trauma, who referred to the referral university hospital in Tehran, the capital of Iran, were included in the study. Two hundred patients over 20 years of age were divided into two equal groups to receive one or two doses of morphine as a controlled clinical trial. Randomization was performed based on simple block randomization. Both patients and physicians were double-blinded to the one-dose and two-dose groups, and there was a code over each

syringe injection; the executive manager was aware of the presence of water versus morphine.

Visual analogue scale (VAS) of pain for all patients was documented three times: at the entrance time, at 30 minutes after injecting a dose of 0.10 mg/kg morphine, and at 30 minutes after the second injection, which was 0.05 mg/kg morphine in the intervention (two-dose) group and water as placebo in the control (one-dose) group. Morphine side effects, including vomiting, hypotension, tachycardia, respiratory depression, decreased consciousness, and urinary retention, were documented after each injection in both the one-dose and two-dose groups.

## Primary Data Analysis

Descriptive statistics are reported as frequency and percent for categorical data and as mean and SD for continuous data. Means were compared using a t test for normally distributed data or the nonparametric Mann-Whitney U or Wilcoxon signed-ranks tests for data not fitting the assumptions of parametric testing. The data were tested for normality using the Kolmogorov-Smirnov normality test. Covariate analysis was used to assess the effect of possible confounding variables such as age, sex, and initial pain score.

A sample size of 100 was calculated a priori for each treatment group to detect differences with 90% power with an  $\alpha$  level of 0.05. Statistical analysis was conducted using the SPSS 16.0 software (SPSS, Inc., Chicago, IL).

## Outcome Measures

The primary outcome measure, the between-group difference in mean before-after change in pain score at 30 and 60 minutes among patients randomized to receive either morphine at 0.05 mg/kg or placebo, was calculated as follows: The change in VAS from 30 to 60 minutes was calculated for each subject. The mean change in VAS was calculated for each treatment group. The difference between the mean changes in VAS for the two groups was calculated with 95% CI. A minimum clinically significant change in patient pain severity was defined a priori as a change of 40% on the VAS. Secondary outcome measures included adverse events, which were defined a priori as respiratory depression, hypotension, tachycardia, vomiting, decreased consciousness, and urinary retention.

## RESULTS

Two hundred patients were enrolled in our study. Random allocation resulted in 100 patients assigned to the 0.10 mg/kg morphine group and 100 assigned to the 0.15 (0.10 + 0.05) mg/kg group. All patients received the initial morphine dose of 0.10 mg/kg, and all the patients allocated to the 0.15 mg/kg group received the second bolus of the study drug. Baseline characteristics of the study groups are described in Table 1;

**Table 1.** Baseline characteristics of the study group

| Characteristics     | 0.10 mg/kg group (n=100) | 0.15 mg/kg group (n=100) |
|---------------------|--------------------------|--------------------------|
| Mean age, y (range) | 32.8 (30.4-35.2)         | 33.1 (30.3-35.9)         |
| Sex, n (%)          |                          |                          |
| Male                | 82 (82)                  | 76 (76)                  |
| Female              | 18 (18)                  | 24 (24)                  |

these characteristics were balanced among the two treatment protocols.

The VAS scores at the three time points at which pain was assessed and between the two doses of morphine are demonstrated in Table 2. No significant difference was found between the two groups at 30 minutes, indicating the same effect of the 0.10 mg/kg initial bolus administered to both groups. Statistical analysis of pain score revealed a significant reduction in final pain after 1 hour in the 0.15 mg/kg compared to the 0.10 mg/kg group ( $p<0.05$ ). In other words, injection of half a dose of the first injection (0.05 mg) morphine compared with the water 30 minutes after the initial standard dose of 0.10 mg/kg morphine significantly decreased pain in patients with acute limb trauma.

In addition, there was a significant improvement in the mean pain score in the same group ( $p<0.05$ ). The percent of pain reduction in the intervention and control groups relative to the basic measures was 52.70% and 35.82%, respectively.

Adverse effects were present in both groups; however, there was no significant difference between the two groups (Table 3). None of the patients in either group received naloxone for reversal of opioid effects. Hypotension occurred in 12 patients, half of which were males. Eighteen patients had one episode of vomiting, 12 of which occurred in males. Nine patients had a fall in consciousness level indicated by a GCS score of 14/15, and 7 of these cases were males. We had 22 incidences of tachycardia, 14 of which occurred in males. We observed no cases of respiratory depression or urinary retention. None of our study population required intubation.

## DISCUSSION

This study was conducted to compare the safety and analgesic efficacy of two morphine sulfate dosages (0.10 mg/kg versus 0.15 mg/kg) in adult patients with acute limb trauma. We were able to demonstrate a significant ( $p<0.05$ ) decrease in pain scores in patients receiving 0.15 mg/kg, 30 minutes after administering the extra 0.05 mg/kg dose. Additionally, comparing the VAS scores at 30 and 60 minutes after baseline in each group showed significant pain reduction in the intervention group ( $p<0.05$ ) and no significant difference in the control group.

There have been few studies on the ideal dosage of opioids for management of acute pain. One such study determining the best intravenous morphine titration protocol by comparing two methods showed that receiving 0.10 mg/kg morphine then 0.05 mg/kg every 5 minutes intravenously is associated with more pain relief than receiving half the amount for each dose.<sup>[14]</sup> Another study quantifying the analgesic effect of a 0.10 mg/kg dose of intravenous morphine to ED patients presenting in acute, severe pain suggested that this dosage may be inadequate for pain management.<sup>[10]</sup> The method of morphine administration is also of question. In some studies, a loading dose is administered followed by intravenous morphine titration every 5 minutes.<sup>[10,14,15]</sup> Other studies suggest starting treatment with a titration regimen in order to monitor and minimize adverse effects.<sup>[15,16]</sup>

Morphine and fentanyl are among the most widely used and studied analgesics for trauma patients in the ED. A randomized double-blinded study comparing morphine and fentanyl

**Table 2.** Mean pain score (using visual analogue scale) by group at baseline, 30 minutes, and 60 minutes

| Visual Analogue Scale                              | 0.10 mg/kg group (n=100) | 0.15 mg/kg group (n=100) | p      |
|----------------------------------------------------|--------------------------|--------------------------|--------|
|                                                    | Mean±SD (range)          | Mean±SD (range)          |        |
| Baseline score before first morphine dose          | 8.04±2.238 (7.6-8.48)    | 7.95±2.194 (7.53-8.37)   | >0.05  |
| Score at 30 min (30 min after first morphine dose) | 5.2±2.558 (4.69-5.71)    | 5.69 ± 2.529 (5.19-6.19) | >0.05  |
| Score at 60 min (30 min after study drug)          | 5.16±2.74 (4.62-5.7)     | 3.76±3.198 (3.13-3.39)   | *<0.05 |

SD: Standard deviation; \*Considered statistically significant.

**Table 3.** Comparison of adverse effects in two groups of one- versus two-dose morphine injection for acute pain of limb trauma 60 minutes after baseline (30 minutes after placebo vs. 0.05 mg/kg morphine administration)

| Adverse effect                   | 0.10 mg/kg group (n=100) | 0.15 mg/kg group (n=100) |
|----------------------------------|--------------------------|--------------------------|
| Hypotension                      |                          |                          |
| No                               | 96                       | 92                       |
| Yes                              | 4                        | 8                        |
| Tachycardia                      |                          |                          |
| No                               | 92                       | 86                       |
| Yes                              | 8                        | 14                       |
| Vomiting                         |                          |                          |
| No                               | 92                       | 90                       |
| Yes                              | 8                        | 10                       |
| Decreased level of consciousness |                          |                          |
| No                               | 96                       | 95                       |
| Yes                              | 4                        | 5                        |
| Respiratory depression           |                          |                          |
| No                               | 100                      | 100                      |
| Yes                              | 0                        | 0                        |
| Urinary retention                |                          |                          |
| No                               | 100                      | 100                      |
| Yes                              | 0                        | 0                        |

in a prehospital setting demonstrated the two drugs were comparable in treating severe, acute pain in a prehospital setting during the first 30 minutes in spontaneous breathing patients.<sup>[17]</sup>

The minimum clinically significant difference in pain reduction has been determined for pain scaling methods through extensive studies.<sup>[18-21]</sup> Accordingly, various meaningful percentages or cut-off points for pain reduction scores have been defined ranging from 33%<sup>[22]</sup> to 50%.<sup>[23]</sup> In a study aimed to categorize declines in pain intensity and percent pain reduction, a 20% reduction in pain score corresponded to 'minimal' improvement, a 35% reduction to 'much' improvement, and a 45% reduction corresponded to 'very much' improvement.<sup>[24]</sup> Overall, it can be assumed that a decrease of 40% is an acceptable pain reduction threshold. According to our study, the mean reduction in pain score was 52.7%, which is well above the threshold. The reduction in the control group was 35.82%. It can therefore be concluded that a single 0.10 mg/kg dose of morphine is minimally effective for pain management in patients with acute limb trauma as previously concluded,<sup>[10]</sup> whereas administering a cumulative 0.15 mg/kg morphine dose by adding a second dose of 0.05 mg/kg 30 minutes after the initial dose significantly increases the analgesic efficacy.

In this study, we also attempted to compare the safety and side effects of the two treatment protocols. Administration of 0.15 mg/kg of morphine was not associated with a statistically or clinically significant increase in adverse effects.

We found that a 50% increase in analgesia lead to increased pain relief, without increasing the risk of potential adverse events. Our results support the superior analgesic effect of 0.15 mg/kg morphine over the commonly used 0.10 mg/kg dose. It can be concluded that the maximum potential effect of morphine is exceeded at doses above 0.10 mg/kg, with higher doses providing additional effect, as observed in our study. Our findings are consistent with those of previous studies assessing the relationship between analgesia and the amount of morphine administered.<sup>[25]</sup> It was concluded by Aubrun et al.<sup>[25]</sup> that the VAS score does not markedly change until the morphine dose approaches that dose ultimately needed to obtain pain relief, and abruptly decreases afterwards. According to this hypothesis, acute pain reduction in response to increased administration of opioids may follow a stepwise pattern in which an analgesic threshold must be reached before patients can perceive clinically meaningful additional relief. Patients in severe pain may need to receive a "threshold" amount of morphine before it is possible for them to recognize and report that a minimal clinically important improvement in pain severity has occurred. The finding that a dose of 0.15 mg/kg of morphine provided superior pain relief to a dose of 0.10 mg/kg is consistent with this hypothesis, indicating that 0.15 mg/kg is the analgesic threshold for a further clinically significant decrease in VAS for a substantial number of patients.

On the other hand, there is a similar study that is in discrepancy with our concluded optimal dose. In a randomized controlled trial, the effectiveness of 0.15 mg/kg intravenous morphine was also compared with that of 0.1 mg/kg in adult ED patients with acute pain.<sup>[26]</sup> The 0.15 mg/kg group achieved a statistically superior analgesic response at 60 minutes, with a mean between-group difference of 0.8 on the Numerical Rating Scale (NRS). However, this difference did not reach the 1.3-point threshold for being clinically superior. The authors suggested that a possible next step would be to study even higher doses of morphine. There are several potential explanations for the discrepancies. First of all, the study population in the mentioned study consisted of 280 patients 21-65 years of age, presenting to the ED with pain of less than or equal to seven days' duration with heterogeneous causes. As indicated in the study, it is possible that different conditions involve different pain production and perception pathways and that not all are equally responsive to morphine. We narrowed our study cases to a more homogeneous population consisting of 200 patients with acute limb trauma pain of less than three days' duration. Another influential factor is the different pain measurement scales used in our studies. We used VAS instead of the verbally administered numeric rating scale (VNRS) previously administered. A recent comparison of VAS and VNRS in the assessment of acute pain

in the ED showed a strong correlation between VAS and VNRS ( $r_s=0.93$ ). However, there was not perfect agreement between the two scales. VAS and VNRS were therefore not interchangeable in assessing an individual patient's pain over time in the ED setting, with VNRS having practical advantages over VAS in this setting.<sup>[27]</sup> Nevertheless, the 50% reduction in pain score considered as a threshold was achieved with our study protocol. The possible impact of cultural influences on pain perception and expression may also have contributed to our different results. There was general agreement with previous studies<sup>[14,26]</sup> in terms of safety and adverse effects of our study dosage.

In randomized evaluations of pain management, we must, for ethical reasons, assure that adequate rescue analgesia is available to all patients, regardless of whether they receive the investigative drug. For this reason, we excluded from the study patients who required additional doses of analgesics or rescue analgesia. Use of rescue therapy has been reported to affect visual analogue scores, side effects and discharge times, lead to underestimation of symptom duration and severity, and increase the number of dropouts. There is no general agreement as to the ideal method of assessing pain scores in this context.

The population of our study was limited to adult patients over 20 years of age with limb trauma. As such, our results cannot be extrapolated to the pediatric or elderly population or to patients presenting with other causes of pain.

In conclusion, according to our study, using two doses of morphine instead of one is a safe and effective method for pain reduction in isolated limb trauma. Therefore, it is recommended to perform a second injection of 0.05 mg/kg morphine 30 minutes after the initial standard dose of 0.10 mg/kg to decrease pain in patients with acute limb trauma.

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Conflict of interest: None declared.

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## KLİNİK ÇALIŞMA - ÖZET

### Ekstremitte yaralanması olan hastalarda intravenöz 0.10 mg/kg veya 0.15 mg/kg morfin sülfat ile akut ağrı tedavisi: Randomize çift kör plasebo kontrollü çalışma

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**AMAÇ:** Akut ekstremitte yaralanması olan hastalarda erişkin acil serviste yapılan iki ayrı morfin dozunun ağrı giderimi ve güvenliğini karşılaştırmak.

**GEREÇ VE YÖNTEM:** Opiyoit analjesisine gerek duyan 200 acil servis hastası randomize olarak iki gruba ayrıldı. Bu randomize çift-kör, plasebo kontrollü çalışmada intravenöz yolla 0.10 mg/kg dozda morfin ve daha sonra hastaların bir bölümüne 0.05 mg/kg IV dozda morfin veya aynı miktarda plasebo verildi. Başlangıçta (0.10 mg/kg morfin vermeden önce), 30 (çalışma ilacı verilmeden hemen önce) ve 60 dakika sonra Görsel Analog Ölçekle ağrının şiddet derecesi ve yan etkiler değerlendirildi.

**BULGULAR:** Başlangıça göre 30. dakikada önemli bir farklılık saptanmadı. Morfinin 0.15 mg/kg dozda yapıldığı grupta diğer gruba (0.10 mg/kg doz grubu) göre bir saat sonra ağrı anlamlı derecede azalmıştı ( $p<0.05$ ). Bu grubun ağrı skorunda önemli bir iyileşme vardı ( $p<0.05$ ). Girişim ve kontrol grubunda ağrı sırasıyla %52.70 ve %35.82 oranında azalmıştı. Her iki grupta gözlemlenen yan etkiler açısından istatistiksel açıdan anlamlı bir fark yoktu.

**TARTIŞMA:** İki morfin dozu yerine tek doz morfin uygulaması ekstremitte yaralanmalarında ağrı giderimi açısından güvenli ve etkili bir yöntemdir. Bu hastalarda ağrıyı azaltmak için ilk standart 0.10 mg/kg dozdan 30 dakika sonra 0.05 mg/kg dozda morfin verilmesini önermekteyiz.

**Anahtar sözcükler:** Akut ağrı, acil tıp, randomize kontrollü çalışma.

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