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Original Contribution

Intravenous morphine titration as a rapid and efficient analgesia for adult patients with femoral shaft fractures after injury☆

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ABSTRACT

This study aimed to compare the analgesic effects of intravenous ibuprofen and intravenous morphine titration for femoral shaft fractures in adult patients. In total, 293 participants were enrolled and randomly received intravenous ibuprofen or intravenous morphine titration. Their visual analogue scale (VAS) results were recorded every 5 minutes after the first administration. The VAS scores before and during transport were also measured. Meanwhile, the type and frequency of the adverse effects were also recorded in both groups. Patients treated with morphine showed a faster and greater reduction in the VAS than those in the ibuprofen group within 1 hour after the first administration. Interestingly, intravenous morphine titration provided consistent analgesia even during the further transport. No significant immediate adverse event was observed in all of the participants, except for sedation, which might be beneficial for keeping the patient quiet and might not be arbitrarily attributed to adverse effects. No addiction was noted in the morphine group. This study demonstrated that intravenous morphine titration is a faster and more efficient analgesia for femoral shaft fractures than ibuprofen in adult patients immediately after injury.

Femoral shaft fractures, which are frequently associated with a high-impact trauma mechanism, are becoming an important clinical problem associated with high morbidity and disability rate because of the accelerated pace of life, increasing traffic accidents, and frequent disasters [1,2]. Pain, particularly severe pain, is a more prominent complaint of patients than activity limitations because of the powerful muscle tension. Untreated pain has been reported to cause short-term problems such as anxiety, needle phobia, hyperesthesia, and fear of medical care [3,4]. The most severe pain after injury occurs within the first 24 hours [5]. Regretfully, orthopedists and patients might pay more attention to the operation and ignore pain management immediately after injury [6]. There is no rapid and efficient external fixation to prevent fracture end friction during frequent movements, which further worsen the pain [7]. Although narcotics exert definite analgesic effect, concern has increased regarding the misuse of prescription narcotics in developed countries because of their easy availability. Conversely, access to intravenous narcotics is frequently difficult because of overly bureaucratic restrictions in developing countries [8]. At present, systemic administration of nonsteroidal anti-inflammatory drugs is among the most frequently used by orthopedists for analgesia [9]; however, the analgesic effect and onset time are not satisfactory [10]. A rapid and efficient analgesic method is needed.

Opioids are highly effective drugs for pain controlling. As a strong opioid drug, morphine has been used for centuries to alleviate human pain. Intravenous administration of morphine is widely used for severe pain relief for conditions such as terminal cancer and chest pain with acute myocardial infarction [11-14]. The Centers for Disease Control and Prevention guidelines promote the efficiency of morphine in the remission of severe pain, including that of terminal cancer [15]. The American Heart Association guidelines suggest that intravenous morphine should be routinely used in patients suffering from severe pain from acute myocardial infarction [16]. In addition, morphine is also applied to relieve pain related with a fracture, whether preoperation or postoperation [17,18]. The use of an intravenous morphine titration allows a rapid titration of the dosage needed for quick and complete pain relief [12]. Considering that intravenous morphine titration has been recently advocated for acute and severe pain control [19,20], we consider whether this analgesic method could be applied to fracture patients in orthopedic departments immediately after injury.

The objective of this study was to assess the efficacy of intravenous morphine titration analgesia in adult patients presenting to the orthopedic department with femoral shaft fractures. Our hypothesis was that intravenous morphine titration analgesia would be more rapid and efficacious than intravenous ibuprofen therapy. This study would help to provide a rapid and efficient analgesia for adult femoral shaft fracture patients and improve their medical experience.

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1. Material and methods

The procedures of this randomized controlled clinical trial followed the ethical guidelines of the Helsinki Declaration of 1975 (as revised in 2000) and were approved by the ethics committee of Zhongnan Hospital of Wuhan University. We recruited participants from the orthopedic department of Zhongnan Hospital, Wuhan University, Wuhan, China. Approximately 5000 surgical procedures are performed in this department each year, of which more than 300 are femoral shaft fractures. All of the participants were fully informed regarding our procedures and the possible adverse effects, and each patients signed informed consent forms. The time period for the case collection was from September 2012 to February 2014.

1.1. Participants

A convenience sample of adults between 20 and 60 years of age was eligible for enrollment when they presented at the orthopedic department with femoral shaft fractures (*International Classification of Diseases, 10th Revision* = S72.301) secondary to an injury of less than 24 hours. The inclusion criteria were as follows: with body weight more than 50 kg, with adequate venous access, and with the ability to perform a pain intensity report. The exclusion criteria were as follows: pregnancy or lactation, contraindications of ibuprofen or morphine such as digestive ulcer, coagulation defect and severe hepatic and renal dysfunction, with a prior history of allergy or contraindications to opioid or ibuprofen, already taken an opioid containing an analgesic, with other specified injuries, open fracture, with unstable hemodynamics after major trauma, with delirium or dementia, and could not understand the pain scales.

1.2. Study protocol

Patients were randomized to receive either ibuprofen or morphine titration randomly. All subjects were equipped with an intravenous access multifunctional monitor immediately upon arrival at the department. The clinical monitoring included arterial blood pressure, heart rate, respiratory rate, pulse oxygen saturation, and sedation. Patients were questioned by the orthopedist regarding the presence of pain and asked to rate the pain intensity. The pain level was recorded on a visual analogue scale (VAS) from 1 to 100 (best to worst) [21]. For the ibuprofen group, when the VAS was greater than 70, patients received 800 mg of intravenous ibuprofen once after hospitalization [22]. For the morphine group, when the VAS was greater than 70, intravenous morphine was titrated every 5 minutes by 3-mg increments, and pain was assessed every 5 minutes until *relief*, which was defined as a VAS score of 30 or lower [12]. Morphine titration was stopped if the patient had a respiratory rate lower than 12 per minute, had a pulse oxygen saturation lower than 95%, and/or experienced a serious adverse event related to morphine administration (allergy with cutaneous rash and/or hypotension, vomiting, severe pruritus). In cases of severe ventilator depression (a respiratory rate <10 per minute), naloxone (an intravenous bolus of 0.04 mg) was administered until the respiratory rate was greater than 12 per minute. Pain assessments were performed every 5 minutes after the first injection. In addition, adverse effects occurring within 24 hours of the first dose were also recorded, including nausea and vomiting, respiratory depression, urinary retention, itching, sedation, allergy, and dizziness [23]. The baseline demographic (eg, age, sex) and clinical data (eg, fracture classification, medical history, current medications) were collected by an independent investigator.

1.3. Outcome measures

The primary outcome was the difference in the pain scale scores at different time points after the first analgesics dose, including the transport during the radiographic examination. The secondary outcomes included the type and frequency of adverse effects.

1.4. Data analysis

We expected that the incidence of morphine-induced adverse effects should be less than 20% and the incidence of severe morphine adverse effects should be less than 2%. Thus, we calculated that at least 300 patients would be needed to maintain a 95% confidence interval (CI) of the incidence within these limits. The data are expressed as the mean ± SEM or median and 95% CI. Student *t* test was used to compare the 2 means, and a Pearson χ^2 test was used to compare the 2 proportions. Data analysis was performed using SPSS 17.0 (SPSS Inc, Chicago, IL). *P* values of less than .05 were considered to be statistically significant.

2. Results

2.1. Participants

The general characteristics of the participants are shown in Table 1, and the study subject flow is shown in Fig. 1. Of the 314 participants who underwent randomization, 293 (93.3%) received at least 1 dose of the intervention and were included in our analysis. In total, the study included 144 participants from the ibuprofen group and 149 from the morphine group. All of the participants who did not take any of the analgesic reported that they did not feel the pain severe enough to require an analgesic. There was no statistical significance between enrollment with respect to age (43.6 ± 9.3 vs 45.4 ± 8.4), sex (31 female [21.5%] vs 36 female [24.2%]), and weight (66 ± 6.5 vs 63 ± 5.9). The initial pain scores ranged from 83 to 100. The mean (SD) initial VAS scores were not significantly different between the 2 groups (89 ± 5.4 for ibuprofen vs 90±5.2 for morphine, $P = .11$).

2.2. Efficacy

The primary objective of this study was to determine the efficacy of intravenous ibuprofen compared with an intravenous morphine titration in femoral shaft fracture patients immediately after arriving at the orthopedic by patient self-assessment of pain using VAS scores. The results are shown in Fig. 2. There was no statistical significance in the median pain scores between the groups on arrival at the orthopedic department. For the primary outcome measurement, patients treated with an intravenous morphine titration had a greater reduction in their VAS scores than those in the ibuprofen group in the first 30 minutes after titration ($P < .01$ or $P < .05$). There was no difference between the 2 groups 1 hour after titration, which indicated that morphine might bring a much faster pain relief.

The extruding of fracture ends always aggravated the pain. So, we recorded the VAS scores before and during the transfer from the stretcher to the radiographic examination table. As shown in Fig. 3, the VAS scores increased remarkably during transfer in the ibuprofen group ($P < .01$), whereas there was no significant increase in the VAS score of the morphine group, which indicated that the efficiency of morphine in the early analgesia was higher than ibuprofen and that intravenous morphine titration could well manage the pain generated from the friction

Table 1
General characteristics of participants.

Characteristic	Ibuprofen n = 144	Morphine n = 149
Age, y, mean ± SD	43.6 ± 9.3	45.4 ± 8.4
Female sex, n (%)	31(21.5)	36(24.2)
Weight, kg, mean ± SD	66 ± 6.5	63 ± 5.9
Initial VAS, mean ± SD	89 ± 5.4	90 ± 5.2

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