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Original Contribution

# Efficacy and safety of nebulized morphine given at 2 different doses compared to IV titrated morphine in trauma pain☆,☆☆

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ABSTRACT

*Background:* Our aim was to compare the efficacy and safety of intravenous (IV) titrated morphine with nebulized morphine given at 2 different doses in severe traumatic pain.
*Methods:* In a prospective, randomized, controlled double-blind study, we included 300 patients with severe traumatic pain. They were assigned to 3 groups: Neb10 group received 1 nebulization of 10-mg morphine; Neb20 group received 1 nebulization of 20-mg morphine, repeated every 10 minutes with a maximum of 3 nebulizations; and the IV morphine group received 2-mg IV morphine repeated every 5 minutes until pain relief. Visual analog scale was monitored at baseline, 5, 10, 15, 20, 25, 30, and 60 minutes after the start of drug administration. Treatment success was defined by the percentage of patients in whom visual analog scale decreased greater than or equal to 50% of its baseline value. When this end point was not reached, rescue morphine was administered. Pain resolution time was defined by the elapsed time between the start of the protocol and the reach of treatment success criteria.
*Results:* Success rate was significantly better at 97% (95% confidence interval [CI], 93-100) for Neb20 group compared to Neb10 group (81% [95% CI, 73-89]) and IV morphine group (79% [95% CI, 67-84]). The lowest resolution time was observed in Neb20 group (20 minutes [95% CI, 18-21]). Side effects were minor and significantly lower in both nebulization groups compared to IV morphine group.
*Conclusions:* Nebulized morphine using boluses of 10 mg has similar efficacy and better safety than IV titrated morphine in patients with severe posttraumatic pain. Increasing nebulized boluses to 20 mg increases the effectiveness without increasing side effects.



## 1. Introduction

Pain is a common cause of emergency department (ED) visits. Its control remains a challenge and health priority worldwide [1]. Several international recommendations [2,3] have been developed to optimize analgesic treatment in particular in busy and crowded care settings like the ED [4-6]. However, poor quality of care in patients with severe pain is frequent, and there are still barriers to prescribing opioids in the ED [7,8]. The major factors precluding the optimal use of opioids in the treatment of severe pain are the fear of serious side effects and the necessity to have an intravenous (IV) access requiring an additional nursing availability and workload [9-11]. With the emergence of easier and potentially safer methods of morphine administration such as inhalation and nebulization, the approach to analgesia in the ED may improve the willingness of ED nurses and physicians to use opioid analgesics [12-16]. It has been demonstrated in some studies [14,15,17] that nebulized morphine has the same efficiency as IV route in the treatment of acute pain. However, this issue has not been fully documented in adult patients [13,16,17]. In addition, the optimal dose of morphine via nebulization is unknown. Considering that analgesic effect of nebulized morphine could result both from systemic and local effects, it could be expected that increasing the dose of morphine by nebulization route would increase the magnitude of analgesia without increasing side effect rate.

The purpose of our study was to evaluate the efficacy and safety of nebulized morphine using 2 different doses compared to IV morphine in management of posttraumatic acute pain in adult ED patients.

☆ Conflict of interest: None.
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## 2. Methods

### 2.1. Patients

This is a prospective, randomized, controlled double-blind study performed between April 2012 and March 2014 at Fattouma Bourguiba University Hospital (Monastir, Tunisia), which is a large tertiary care hospital with approximately 110000 ED patient visits per year. Patients were screened for inclusion except during the night shift and weekend. We included in this study patients older than 18 years admitted to the ED for severe acute pain after a recent trauma (within <12 hours). Severe pain is defined by visual analog scale (VAS) greater than or equal to 70 on a scale from 0 to 100 (none to worst pain). Exclusion criteria included known allergy to morphine, nausea or vomiting at admission, Glasgow Coma Scale less than 15, inability of the patient to cooperate (alcohol consumption or abnormal mental status), hypotension with systolic blood pressure less than 110 mm Hg, bradypnea less than 12 breaths per minute, $SaO_2$ less than 95% while breathing room air, facial trauma, presence of rhinitis, nasal obstruction, or allergy to opioids. We also excluded all patients who received analgesics within 6 hours before ED admission. Of note, in usual practice, most of our trauma patients do not receive analgesia before the ED visit. The protocol was approved by the ethics committee of our institution.

### 2.2. Protocol

After inclusion and obtaining written patient informed consent, randomization was performed using computerized random number generation and sealed envelopes before the start of enrollment in the study. Patients were assigned to 3 groups: the Neb10 group including patients who received 1 nebulization of 10-mg (1 mL) morphine (Lab Renaudin France) diluted in 4 mL of normal saline associated with IV bolus of 5-mL normal saline (placebo), the Neb20 group including patients who received one nebulization of 20-mg (2 mL) morphine diluted in 3 mL of normal saline and IV bolus of 5-mL normal saline as in the first group, and the IV morphine group including patients who received a bolus of 2 mg of IV morphine (0.2 mL) diluted in 4.8 mL of normal saline associated with 1 nebulization of 5-mL normal saline (placebo). Protocol treatments (morphine or placebo) were repeated every 5 minutes for IV route and every 10 minutes for nebulization route until reaching the end point of the protocol. Each nebulization was performed with a compressed air nebulizer (CPS 23, SYSTEM Villeneuve-Sur-Lot France) using 8 L/min of airflow during approximately 10 minutes. The pharmacist was responsible for preparation and dispensing the study drug. The investigators, treating physicians, nurses, and patients were blinded to the treatment. No medication that might alter the pain sensorium and/or mental status of the patient was allowed to be administered during the study period. For all patients included in the study, demographic data and clinical characteristics were collected and stored on a standard clinical record form. Demographic data included age, sex, comorbidity, injury severity score, and time between injury and randomization. Clinical data included intensity of pain estimated by VAS, cause of trauma, systolic and diastolic blood pressures, heart rate, respiratory rate, oxygen blood saturation ($SaO_2$), and diagnosis at ED discharge. The same investigator performed each assessment. When the patients had difficulties in understanding how to read the VAS, they were allowed to use a numerical rating scale (from 0 to 100). The following parameters: VAS, blood pressure, heart rate, respiratory rate, and $SaO_2$ were measured at baseline, 5, 10, 15, 20, 25, 30, and 60 minutes after the start of protocol treatments. Occurrence of side effects such as hypotension, somnolence, decrease in respiratory rate (<12 cycles per minute), allergic reactions, vomiting, nausea, and dizziness was monitored during all the protocol period. Patients were specifically queried about all of these potential side effects. Primary end point included the treatment success rate and pain resolution time. Treatment success rate was defined by the percentage of patients in whom the decrease in VAS was greater than or equal to 50% of its baseline value. Pain resolution time was defined by the elapsed time between the start of the protocol and the decrease of baseline VAS by at least 50%. In case of treatment failure, defined as the inability of the protocol treatment to reduce baseline VAS by at least 50% within the protocol period, rescue IV morphine was allowed to be administered. Side effects were continuously monitored during the protocol, and immediate discontinuation of the protocol treatment was decided in case of occurrence of serious side effects. Serious side effects included respiratory depression, oxygen desaturation less than 95%, significant hypotension defined by a decrease of baseline arterial pressure by more than 20%, and consciousness disturbance defined by a Glasgow Coma Scale less than 15. Naloxone

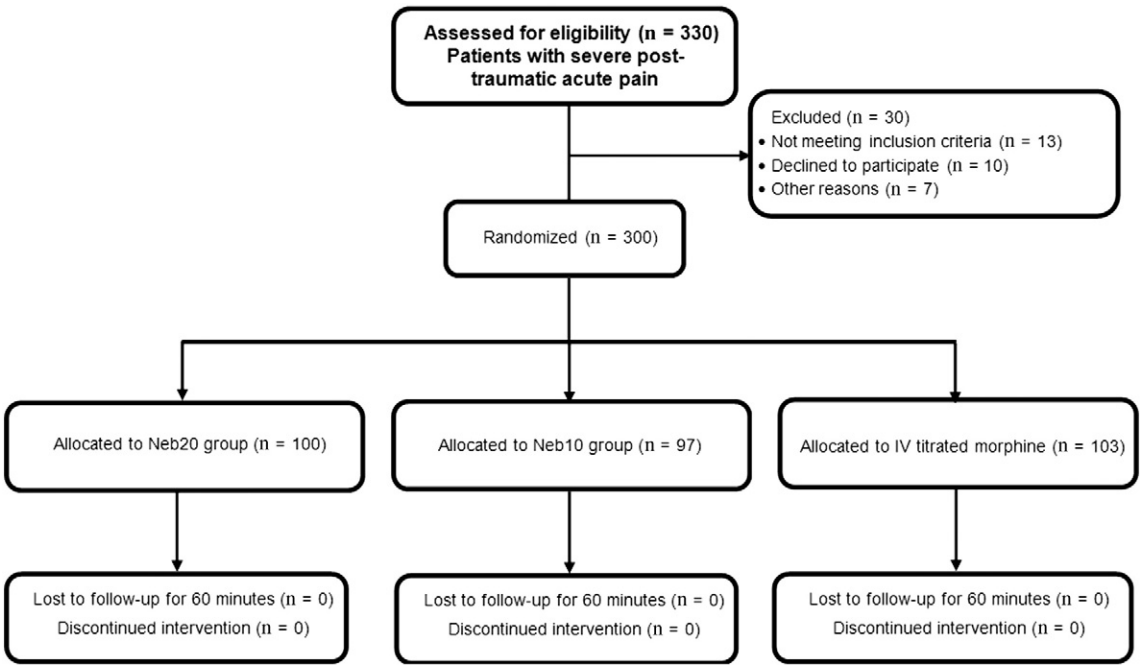


**Fig. 1.** Trial profile.