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Original Contribution

Efficacy and safety of nebulized morphine given at 2 different doses compared to intravenous 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

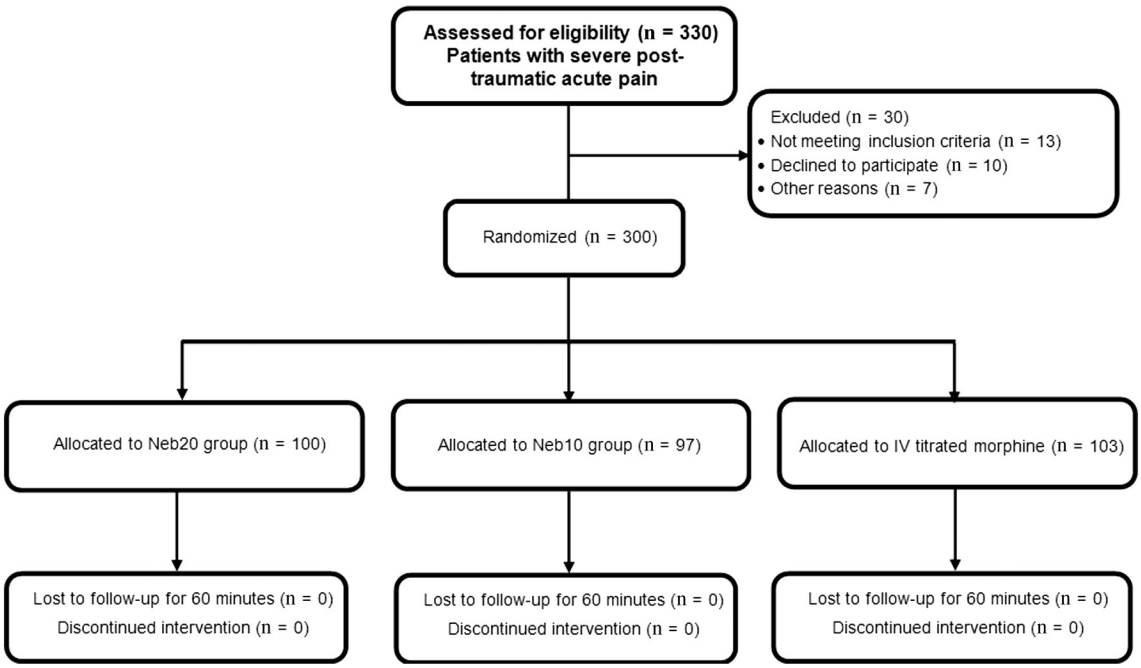

Fig. 1. Trial profile.

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Table 1
Baseline characteristics in the 3 treatment groups

	IV morphine, n = 103	Neb10, n = 97	Neb20, n = 100
Age, y (SD)	30 (9)	29 (8)	28 (8)
Sex male (%)	74	72	82
Weight, kg (SD)	71 (17)	67 (14)	71 (23)
Comorbidity			
Hypertension (n)	1	1	1
Diabetes mellitus (n)	4	2	0
COPD (n)	0	0	0
Trauma localization (%)			
Upper limb	62	65	70*,**
Lower limb	18	20	19
Back	7	4	1†
Pelvic trauma	14	11	10
Injury severity score, mean (SD)	5 (3)	5 (3)	4.5 (2)
Vital signs at ED admission, mean (SD)			
Heart rate, beats/min	81 (13)	83 (17)	89 (13)
Systolic blood pressure, mm Hg	131 (18)	131 (17)	129 (16)
Diastolic blood pressure, mm Hg	78 (14)	78 (13)	74 (11)
Baseline VAS, mean (SD)	78 (11)	79 (10)	77 (9)

Abbreviation: COPD, chronic obstructive pulmonary disease.
* $P < .01$ between Neb20 and Neb10 groups.
** $P < .01$ between Neb20 and IV morphine groups.

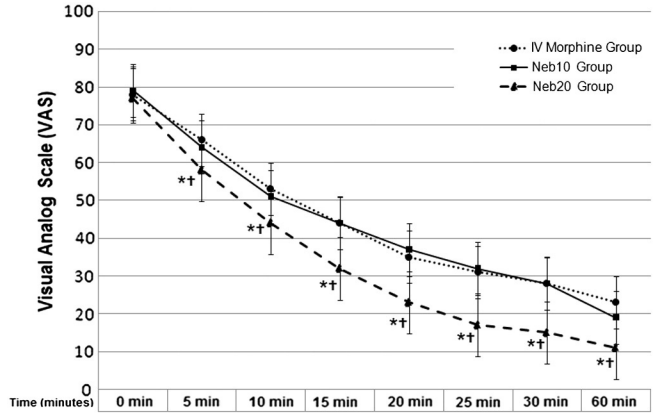

Fig. 2. The VAS changes from baseline at each time point for the 3 groups: IV morphine, Neb10, and Neb20 groups. *$P < .05$ between Neb20 and Neb10 groups. †$P < .05$ between each time point and baseline for the 3 groups.

was immediately available. At the end of the protocol, patients received the care required by the nature of their injury according to the decision of their treating physicians.

2.3. Data analysis

Variables are expressed as mean and SD and median and 25% to 75% interquartile range or 95% confidence interval (CI) as appropriate. Comparisons were made among continuous variables using analysis of variance for independent samples. χ^2 Or Fisher exact test was used for discrete variables. Comparison between the 3 groups was examined using Kruskal-Wallis test. A sample size of 100 per treatment group was calculated to detect a difference of at least 13% in the VAS with 90% power and α level of .05. All tests were 2 tailed, and $P < .05$ was considered statistically significant. Calculations were performed with a software package for windows (version 18; SPSS, Inc, Chicago, IL).

3. Results

During the study period, 330 patients with posttraumatic pain were screened, but 300 patients were finally included: 97 in Neb10 group, 100 in Neb20 group, and 103 in IV morphine. Thirteen patients were withdrawn from Neb10 group, 7 from Neb20 group, and 10 from IV morphine group (Fig. 1). At baseline, the 3 study groups were comparable in terms of demographic characteristics; previous medical history; injury severity score; and clinical presentation at admission including VAS, blood pressure, heart rate, respiratory rate, and SaO_2 (Table 1).

Success rate was not significantly different between Neb10 group and IV morphine group (81% [95% CI, 73-89] vs 79% [95% CI, 75-83]). Success rate was 97% (95% CI, 93-100) in Neb20 group, and the difference was statistically significant compared with the other groups ($P < .01$). Resolution time was similar between Neb10 group and IV morphine group (26 minutes [95% CI, 21-31] and 28 minutes [95% CI, 24-32], respectively). The lowest resolution time was observed in Neb20 group (20 minutes [95% CI, 18-22]); the difference was statistically significant compared with the other groups ($P < .01$) (Table 2). The maximal absolute decrease of VAS was highest in Neb20 group (60 [95% CI, 57-63]) compared with Neb10 group (50 [95% CI, 44-56]) and IV morphine group (46 [95% CI, 40-52]). The VAS change from baseline at each time point in the 3 groups is shown in Fig. 2. There was a significant decrease in the VAS at all time points in the 3 groups. From the 5-minute time point, the Neb20 group had a significant larger decrease in pain compared to the other groups. This difference persisted during all the protocol period. In IV morphine group, the mean total dose of morphine administered was 11.4 mg (95% CI, 8.4-14.4) for IV morphine group, and the median number of boluses required was 4 (95%, CI 3-5) ranging from 1 to 6 boluses (Fig. 3). The mean total dose of nebulized morphine was 21.2 mg (95% CI, 17.1-25.3) for Neb10 group and 36.5 mg (95% CI, 25.9-47.1) for Neb20 group. The median number of nebulizations was 2 (95% CI, 2-3) for Neb10 group and 1 (95% CI, 1-2) in Neb20 group. Rescue dose of morphine was required in 5, 2, and 2 patients, respectively, in Neb10, Neb20, and IV morphine groups. Change of blood pressure, heart rate, respiratory rate, and SaO_2 was not significant in the 3 groups. Overall, 29 patients (9.7%) experienced minor side effects: 19 (18.4%) in the IV morphine group, 5 (5.1%) in the Neb10 group, and 5 (5%) in the Neb20 group; the difference was significant between the IV group and both nebulization groups (Table 3). The most frequent side effect was dizziness (55%). No major side effect was recorded during the study protocol.

4. Discussion

Our study demonstrated that, in patients with severe posttrauma acute pain, nebulized morphine with bolus doses of 10 mg was as potent as IV titrated morphine and that the protocol using repeated bolus doses of 20 mg of nebulized morphine was superior to the protocol using 10 mg. In addition, time resolution of pain was the shortest with boluses of 20 mg compared with 10 mg of nebulized morphine

Table 2
Outcome of patients

	IV morphine, n = 103	Neb10, n = 97	Neb20, n = 100
Success at 60 min, n (%)	78 (79)	79 (81)	97 (97)*,**
Time resolution (min), mean (SD)	28 (17)	26 (18)	20 (9)*,**
VAS difference 0-60 min, mean (SD)	46 (23)	50 (23)	60 (14)*,**
Rescue dose of morphine, n (%)	2 (1.9)	5 (5)	2 (2)

* $P < .01$ between Neb20 and Neb10 groups.
** $P < .01$ between Neb20 and IV morphine groups.

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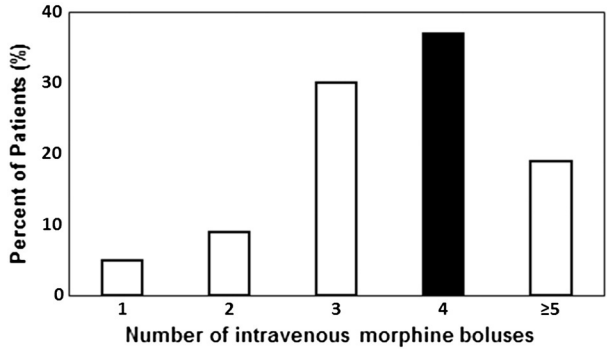

Fig. 3. Distribution of patients according to number of IV morphine boluses. Black bar represents the median number of boluses.

and IV titrated morphine. There were a fewer patients with side effects in both nebulized groups compared with IV morphine group.

Suboptimal pain management in EDs is known to be common. Large studies conducted in ED patients with moderate to severe pain demonstrated that nearly the half received analgesics and the same proportion reported that their pain had not been relieved at discharge from the ED [9]. It is now well proven that inadequate treatment of acute pain increases the risk of acute complications and developing chronic pain, which negatively impacts quality of life [1]. Furthermore, quality of pain treatment is one of the main factors influencing patient satisfaction in the ED [18,19]. Systemic administration of opioid analgesics such as IV morphine are commonly prescribed in the ED to relieve severe pain [8,20]. However, side effects can impede their use and their clinical effectiveness [21,22]; although there is a trend of an increase in prescribing of opioid in the ED, it is still insufficient [7,8]. Alternative analgesic methods with a better efficacy/tolerance ratio have the potential to improve this situation. Pulmonary route of delivery was proposed as one of these methods [23,24]. Most available studies used inhaled or intranasal opioids either as a preinduction anesthesia or as postsurgery analgesia but less often in the ED [25-30]. In our study, we used nebulization, as this method allows provision of great amount of drug and would provide simple and available analgesia without the need for IV access [26-30]. It was demonstrated that this route of opioid administration was as efficient as conventional IV delivery [13,15,31,32]. It was notably demonstrated that onset and duration of analgesic morphine effects were similar between IV administration and inhalation delivery. However, comparison of nebulization and IV administration of morphine was rarely performed except in few pediatric studies [14,15]. In adults, Fulda et al [13] compared nebulized morphine and patient-controlled IV morphine to relieve severe posttraumatic pain. They demonstrated that both treatments provided equivalent efficacy with less sedative effects in patients treated with nebulization. The same findings were reported in the study of Nejmi et al [16] in patients with thoracic trauma comparing nebulized morphine with epidural bupivacaine-fentanyl analgesia. More recently, Farahmand et al [17] designed a study to compare the effectiveness of nebulized fentanyl with IV morphine in 90 ED patients with moderate to severe acute limb pain. They found that both protocols provided similar rate of success and tolerance. These results are in agreement with our findings, but the new information provided by the present study is that the degree of analgesia obtained with nebulized morphine is dose dependent as increasing the unitary dose of morphine from 10 to 20 mg led to a better relief of pain in our patients. We can even suggest that a bolus of 20 mg of nebulized morphine is optimal and that there is no need to further increase the initial dose as analgesic success was obtained in almost all the patients of Neb20 group (97%). Of note, the success rate in our IV titrated morphine group (79%) is similar to the usual success rates observed in the acute care literature [33,34]. The better analgesic effect of higher doses of nebulized morphine compared with IV morphine suggests that pain control with nebulization may be related more to the availability of morphine in the lung than to its concentration in the serum. Although the exact mechanism of analgesia via intrapulmonary route is still unclear, it was suggested that opioids can act directly on specific lung receptors or via anxiolytic effects after systemic absorption [35,36]. It seems unlikely that systemic effect of morphine could explain all the antalgic effects observed in our patients, as it was demonstrated that systemic bioavailability of opioids via pulmonary route is quite low [24]. Although we did not measure serum morphine level in our study to assess the degree of pulmonary systemic absorption of the drug, the fact that 20 mg of morphine did not induce more side effects compared with 10 mg suggests that pulmonary systemic absorption of morphine in our patients was not high. There are very limited published data on the safety of nebulized opioids in the treatment of acute pain. Most of the adverse effects described previously were minor and did not alter the care of the patients [17]. We confirmed these conclusions that support the good safety of morphine nebulization even when high doses are used.

Our study had some limitations that should be discussed. First, the choice of morphine dosing could favor nebulized route with regard to the different dosages used. The rationale for morphine dosing should be explained here. Previous works suggested that mean systemic bioavailability of morphine via pulmonary route ranges from 5% to 35%. If we assume that the mean bioavailability is somewhere between 10% and 20%, then to achieve the equivalent effect of 4-mg IV morphine within 10 minutes, the nebulized dose should be between 10 and 20 mg. In addition, if we compare the total doses of morphine received in each group, we find that a 3:1 and 2:1 nebulized/IV ratios were used, respectively, in Neb20 and Neb10 groups, which would mean that bioavailability of nebulized morphine should be more than 50% to accept that there is likely an underdosing of IV morphine in our study. Second, although this study had a good power to detect difference in efficacy between the 3 treatment strategies, it could be not sufficient to detect difference regarding some rare side effects. Third, our study did not include patients younger than 18 years. However, the good efficacy/safety ratio of nebulized morphine as demonstrated in the present study is encouraging for the widespread application of this needle-free method in children. Fourth, the duration of the protocol in our study was limited to 60 minutes. It might be too short to assure a full comparison between the groups. However, in clinical practice, the first hour of pain treatment in the ED is certainly the most relevant.

Table 3
Side effects

	IV morphine, n = 103	Neb10, n = 97	Neb20, n = 100
Minor (n)			
Sleeping	3	1	0
Dizziness	10	2	4
Vomiting	3	1	1
Nausea	3	1	0
Rash	0	1	0
Total	19*	6	5
Major (n)	0	0	0

* $P < .05$ between IV morphine group and both nebulization groups.

5. Conclusions

In summary, in the treatment of acute posttrauma pain, we found that nebulized morphine given at a bolus dose of 20 mg was more effective than IV titrated morphine with fewer side effects. The use of nebulized unitary dose of 10 mg provided similar analgesic effect than IV morphine titration with fewer side effects. Morphine nebulization is a good substitute to IV route because this method provides a simple and rapid ED analgesia for trauma patients.

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