Journal of Research in Clinical Medicine

J Res Clin Med, 2020, 8: 21
doi: 10.34172/jrcm.2020.021
https://jrcm.tbzmed.ac.ir

TUOMS PRESS

Original Article

Comparing the efficacy of nebulized morphine with intravenous morphine in traumatic musculoskeletal pain management

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Article info

Article History:
Received: 28 Jan. 2020
Accepted: 23 Mar. 2020
e-Published: 2 June 2020

Keywords:
- Intravenous morphine
- Nuebolized morphine
- Pain management
- Traumatic musculoskeletal pain

Abstract

Introduction: This study was designed to compare the effectiveness of intravenous morphine with nebulized morphine in pain relief of patients referring to the emergency setting with traumatic musculoskeletal pain.

Methods: This randomized, placebo-controlled and double-blind clinical study evaluated 160 patients 18 to 65 years of age with acute traumatic pain, who attended the emergency department during 2019. Subjects were assessed with Numerical Rating Scale based on inclusion and exclusion criteria and randomly divided into two groups. In one group, 80 patients received IV morphine (0.1 mg/kg+5 mL normal saline) plus an equivalent volume of IV placebo. In the second group, 80 patients received nebulized morphine (0.2 mg/kg+5 mL normal saline) plus nebulized placebo. Pain score was monitored in all patients with Numerical Rating Scale before and after intervention at baseline, 15, 30, 45, and 60-minute intervals. Patients' vital signs and possible adverse events were evaluated in each observation time points. Finally, all participants were assessed for their satisfaction with pain management. Data were analyzed using repeated measure analysis for continuous variables and Binomial test for categorical variables

Results: There was no significant difference between the demographic characteristics of patients in study groups. Pain relief between the two groups was similar during the observation (0, 15, 30, 45, 60 min) ($P>0.05$). There were no changes in vital signs between two groups, although the nebulized group had lower systolic blood pressure at the time-point of 15 minutes after the treatment initiation ($P=0.03$).

Conclusion: Although Nebulized morphine has similar efficacy in comparison with IV route, nebulization might be considered as the clinically efficacious route of morphine administration with minimal side effects, providing optimal pain relief in patients..

Introduction

The chief reasons for the most of emergency department (ED) visits are related to the pain-related conditions and sever pain management. Currently, pain management is one of the challenging issues with high priority worldwide.[1] Despite significant developments in pain control, there has been chief concern about the adequate and timely treatments of acute pain in busy and overcrowded care settings like the ED.[2] Providing rapid, effective, and safe painkiller therapy for patients with severe pain immediately after triage is the desirable standard requirement for effective clinical practice in EDs. The morphine is an important medication for pain relief in many emergency settings, and its intravenous administration is widely used as the gold standard method.[3] However, there are still barriers to the ED application of this method including a high number of ED admissions, the necessity to additional nursing availability, heavy workload, unsuccessful intravenous catheter insertions, poor quality and continuity of care for patients, lacking sufficient training in pain relief, and concerns about potential opioid-related adverse effects.[4] So, in order for the physicians and ED nurses to more willingly use opioid analgesics, feasible alternatives and potentially safer techniques of morphine administration have been recently addressed; including nebulization and inhalation.5 Although it has been indicated that the efficiency of using nebulized rout for morphine administration is the same as an intravenous route in acute pain relief, the effectiveness of nebulized morphine

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in adult patients has not been elucidated well.[6] Therefore, in this study, we aimed to assess and compare the efficacy of nebulized morphine to IV administration of morphine in patients referred to the emergency ward with traumatic musculoskeletal pain. Moreover, we evaluated the adverse effects and patients' satisfaction in both IV and nebulized morphine routes.

Methods

Study design

This prospective, double-blind, randomized control clinical trial was performed to compare the pain relief achieved with administration either by breath-actuated nebulizer or IV at ED wards of Iran University Hospitals (Tehran, Iran) during 2019. Patients and researchers were blinded.

Patients

A total of 160 patients aged 18 to 65 years attending the ED for acute traumatic pain and meeting inclusion criteria were approached to participate in the study. Male and female patients were considered eligible for enrollment if the pain was of sufficient severity to warrant treatment opioid analgesia (Numerical Rating Scale score ≥ 5 out of 10). According to our exclusion criteria, patients with known allergy to morphine, hypotension (systolic blood pressure less than 90 mm Hg), Glasgow Coma Scale less than 15, pregnancy or breastfeeding, drug addiction, significant hepatic, renal or cardiovascular disease or abnormal mental status and inability to understand the pain scales were excluded from this study.

Protocols

The informed consent form was obtained from all participants. In order to achieve an alpha level of 0.05 and a statistical power of 80% the sample size computation was done by the Cochrane formula, revealing that at least 77 patients per group were required. To ensure the accuracy of the assumptions and calculations, we decided to consider a large margin of error and recruited 80 patients per group. Patients were randomly assigned to two groups. In first group subjects received IV morphine (0.1 mg/kg + 5 mL normal saline) plus an equivalent volume nebulized placebo. In the second group, patients received nebulized morphine (0.2 mg/kg + 5 mL normal saline) plus an equivalent volume of IV placebo for pain management. The placebo in both groups was isotonic sodium chloride solution. The following parameters including pain score and vital signs such as blood pressure, respiratory rate, heart rate, Glasgow Coma Score and oxygen saturation were assessed and recorded at baseline, 15, 30, 45 and 60 minutes after initiation of analgesic drug administration. Moreover, the occurrence of adverse effects such as vomiting, nausea, hypotension, bradycardia, decreased respiratory rate (<12 breaths per minute) and decreased the level of consciousness was constantly monitored by nursing staff during the protocol period. According to pain score assessment and treating physician's preference, additional analgesia dose or rescue dose (5 mg/kg morphine) was available to be administered for both groups if the pain score was five or more and patients did not achieve enough pain relief after 15 minutes. At the end of the study, all subjects were asked to express their satisfaction with pain management. Patients' satisfaction was evaluated using a 5-item rating scale ranging from extremely satisfied to dissatisfied after explaining the possibility of side effects.

Data Analysis

statistical analysis was performed using SPSS version 19 (SPSS Inc., Chicago, IL, USA). Independent t test was used for data analysis instead of analysis of variance with repeated measurements for categorical variables. Data were expressed as mean ± SD. A statistically significant difference was considered to be indicated by P value of less than 0.05.

Results

Among patients referred to the EDs, a total of 180 eligible patients aged 18 to 65 years with acute traumatic musculoskeletal pain were considered for the trial based on inclusion and exclusion criteria. According to sample size calculation patients randomly were divided into two groups, including IV morphine group (n = 80) and nebulized morphine group (n = 80) (Figure 1). Demographic characteristics of the two treatment groups including age, gender and weight, are summarized in Table 1. There was no statistically significant difference comparing sex, age, and weight of the two groups. In this study, the causes of acute pain in both treatment arms were classified into two different groups of wound and soft tissue injuries, and the fractures. These variables similarly distributed in all the groups (Table 2). Moreover, assessment of pain score in IV and nebulized morphine

Table 1. Demographic characteristics of patients in the IV morphine and nebulized morphine groups

Characteristics	IV morphine group	Nebulized morphine group	*P*[a]
Gender, No. (%)	Female, 27 (33.8) Male, 53 (66.3)	Female, 19 (23.8) Male, 61 (76.3)	0.11
Age (y), mean ± SD	41 ± 14.19	39.16 ± 14.06	0.42
Weight (kg), mean ± SD	73.11 ± 9.65	70.71 ± 11.16	0.14

[a] The analysis was performed using binominal χ^2 test for gender and *t* test for age and weight.

Table 2. Causes of pain in the IV morphine and nebulized morphine groups

Causes of pain	IV morphine group	Nebulized morphine group	Total
Wound and soft tissue injuries	34 (42.5%)	43 (53.75%)	77 (48.1%)
Fractures	46 (57.5%)	37 (46.25%)	83 (51.9%)
Total	80	80	160

groups indicated that the groups have the same mean initial pain score (7.33 ± 1.79 vs. 7.80 ± 1.66, respectively). The groups showed no significant pain relief after 15 minutes of the first analgesic administration. However, we observed a total reduction in pain score at the timepoints of 30, 45 and 60 minutes after the first dose administration in both groups, although the differences between the groups were not significant statistically (Table 3 and Figure 2). Despite a remarkable decrease in patients' pain scores with a different cause of acute pain in study groups, the statistical difference was not considerable between treatment groups. During the observation period and at any time-point of study, vital signs including the diastolic blood pressure and heart rate were similar in both groups (Table 4). While patients in both groups had similar systolic blood pressure at baseline, 30, 45 and 60 minutes, patients in the nebulized group had lower systolic blood pressure at the time-point of 15 minutes after the treatment initiation compared with the other group, and there was a statistically significant difference ($P=0.03$). Furthermore, in the intravenous morphine group, patients experienced a slight decrease in oxygen saturation compared with the other group at all time-points of the study protocol. This difference was statistically significant ($P<0.005$). Moreover, respiratory rate reduction in the IV group at any given time interval during the observation was statistically significant in comparison with the other group ($P<0.05$). Given the data tabulated in Table 5, the

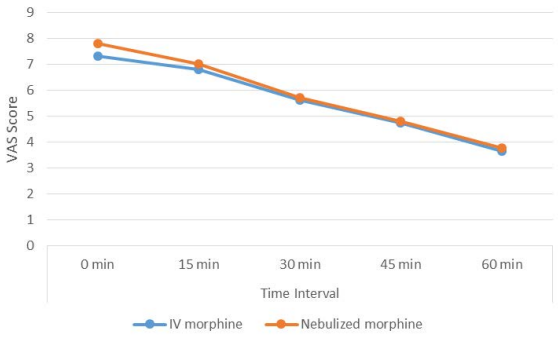

Figure 2. The VAS changes from baseline at each time point for the 2 groups: IV morphine and Nebulized morphine Group.

incidence of nausea and vomiting as the adverse events was observed more in the IV group than the nebulized group (6.3% vs. 0% respectively). However, those adverse events were not life-threatening, and patients were managed conservatively. At the timepoint of 1h after the initiation of analgesic administration, 16 patients (20%) in IV group and 2 (2.5%) patients in the nebulized group needed to receive a rescue dose (Table 5). Patient satisfaction from pain management was similar in both groups ($P=0.34$, Table 6).

Discussion

Acute pain is one of the most common reasons for attendance at hospital EDs. Rapid and appropriate pain management is among the great concerns of ED clinicians (physicians and nursing staff).[1] Delayed onset of pain control may not only lead to detrimental impacts on the patient's conditions and quality of pain treatment in such an overcrowded setting but also increase the risk of potential complications such as cardiovascular events. Pain relief with the administration of analgesics as the first

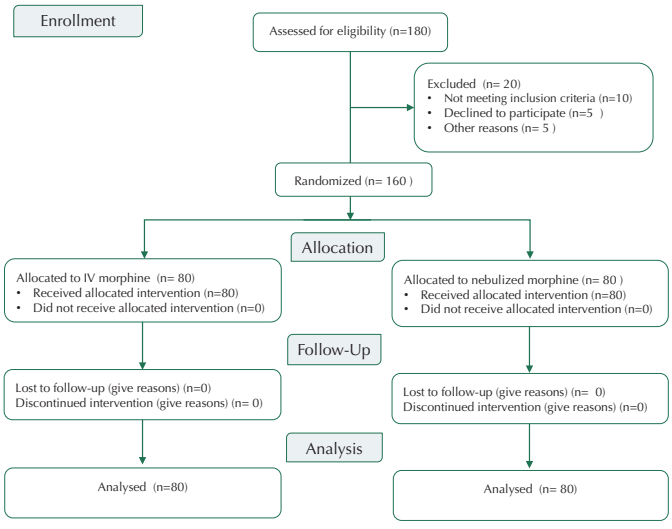

Figure 1. Trial profile.

Table 3. Decrease of pain score from the base in time intervals after drug administration in both groups

Groups	0 min	15 min	30 min	45 min	60 min
IV morphine					
No	80	80	80	80	80
Mean ± SD	7.33 ± 1.79	6.81 ± 1.57	5.63 1.68	4.76 ± 1.82	3.66 ± 2.09
Nebulized morphine					
No	80	80	80	80	80
Mean ± SD	7.80 ± 1.66	7.02 ± 1.99	5.72 ± 1.96	4.80 ± 1.78	3.76 ± 1.99
P	0.09	0.44	0.77	0.89	0.76

Table 4. Vital signs in both groups during the observation period, mean ± SD

Vital Sign	IV morphine group	Nebulized morphine group	*P*
Heart rate, beats/min	81.01±7.71	79.60±7.97	0.35
Systolic blood pressure, mm Hg	129.2±1.87	128.59±1.87	0.41
Diastolic blood pressure, mm Hg	79.80±10.26	80.87±8.70	0.53
Oxygen Saturation, Percentage	95.35±1.48	96.01±1.76	0.005
Respiratory Rate, beats/min	14.77±3.03	15.62±1.79	0.045

Table 5. Number of patients with complications or need for rescue dose (IV morphine 5 mg) in both groups during the observation period.

	IV morphine group	Nebulized morphine group
Nausea, vomiting	5 (6.3%)	0 (0%)
Need for rescue dose	16 (20%)	2 (2.5%)

P=0.0001 for both IV morphine group and Nebulization group.

line of treatment is the first and foremost recommendation of all guidelines for pain management in ED.[7] Morphine, as an effective opioid drug and one of the most favorable analgesics, has been used to initiate management of acute pain in the ED for decades.[2] Providing rapid and optimal pain relief under the lowest effective dose with minimal adverse effects are the remarkable merits of morphine administration for pain control.[3] The present study was designed to compare the efficacy of two different morphine administration routes in pain management among patients referring to EDs. Although administration of morphine intravenously is considered as the gold standard analgesic and common method for management of severe acute pain in the EDs, IV placement as a source of patient anxiety and discomfort can be time-consuming and costly for both clinicians and patients.[3,8] Therefore, given mentioned obstacles, physicians prefer alternative analgesic approaches with better efficacy, safety, and feasibility. Pulmonary opioid delivery provides a promising and non-invasive route for pain management.[9] Although inhaled and nebulized opioid administration has been introduced as a common method in pre-induction or postoperative analgesia, its application is less popular in the ED. In the present study, we used to administer either nebulized and IV morphine for ED patients with acute traumatic pain to compare the safety and efficacy of these methods in pain management. Nebulization is considered as a simple and effective delivery method for the administration analgesia without the need for IV access allowing for rapid delivering a large amount of drug to achieve the desired results. It has been demonstrated in some studies that inhalation delivery as effective as traditional IV morphine administration in acute pain management[8]; however, this issue has not been well elucidated.[10] Patients were monitored in five times an hour (0, 15, 30, 45 and 60 min). Based on our study, administration of both IV morphine (0.1 mg/kg) and nebulized morphine (0.2 mg/kg) have the same effectiveness in pain relief with same onset and duration of activity in both groups. Despite the same rate of satisfaction from pain relief among participants in both groups at the end of the observation, IV group needed to receive a rescue dose during the monitoring. Although there have been numerous studies comparing the efficacy of different analgesic drugs administered intravenously

Table 6. Patients' satisfaction with regard to pain control based on a 5-item Likert rating scale

Groups	Extremely satisfied	Very satisfied	Somewhat satisfied	Satisfied	Dissatisfied
IV morphine group	12 (15%)	21 (26.3%)	27 (33.8%)	18 (22.5%)	2 (2.5%)
Nebulized morphine group	9 (11.3%)	30 (37.5%)	18 (22.5%)	19 (23.8%)	4 (5%)
Total	21 (13.1%)	51 (31.9%)	45 (28.1%)	37 (23.1%)	6 (3.8%)

or via nebulization method, comparison of intravenous and inhalation administration of morphine was rarely performed except in few studies. Grissa et al compared the nebulized morphine with two different doses and IV morphine to relieve trauma pain. They demonstrated nebulized morphine given at a bolus dose of 20 mg was more effective than IV titrated morphine with less sedative effects. However, administration of 10 mg of nebulized morphine provided equivalent efficacy in pain relief than IV morphine titration with fewer side effects.[11] The same findings were reported in a randomized clinical trial of Miner et al in children with acute pain comparing nebulized fentanyl citrate with fentanyl citrate administrated intravenously. They concluded that the pulmonary route of fentanyl administration might be a feasible alternative to the IV method for a variety of painful conditions in patients older than three years.[8] More recently, a study which was designed by Farahmand et al indicated that both nebulized fentanyl citrate and IV morphine were successful methods in pain management of patients with moderate to severe acute limb pain.[10] Regarding the same efficacy of both methods in pain relief, our findings are in agreement with results previously published by these groups. In our study, the incidence of adverse effects in those that received nebulized morphine was lower than IV morphine group. In this regard, these results follow the same line as those obtained in Grissa et al[11] study. Our study was one of the few studies that compared nebulized morphine with IV morphine in patients with traumatic musculoskeletal pain using a controlled double-blind, randomized clinical trial. Moreover, in the current study, all study participants were monitored for an hour for the incidence of any possible complications, which is by far longer than any other studies.

Conclusion

Considering this study and previous studies, delivering opioid analgesics by the pulmonary route could be used as a feasible substitute for rapid, effective, and safe pain relief immediately after triage in different age groups, ranging from children to adults for a variety of painful conditions. According to our study, although nebulized morphine has the similar efficacy in comparison with IV route, nebulization might be considered as the clinically effective route of morphine administration providing optimal pain relief in patients with minimal side effects.

Conflict of Interest

Authors have no conflict of interest.

Ethical approval

The study protocol was approved by the Research Ethics Committee of Iran University of Medical Sciences.

Authors' contribution

Study design, MM; study conduction, HA; data gathering, AD & MR; literature review and critic, NGh; writing, HA.

Acknowledgments

The authors would like to express their gratitude to all of the staffs of emregency department and patients who involved in this study.

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