Comparison of Divided Dose versus Bolus Administration Morphine Sulfate for Management of Acute Pain in Traumatic Fracture in Patients Admitted to Emergency Department

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Abstract Introduction: Pain is one of the most common reasons that patients visit emergency departments. Morphine has been used extensively in pain management but there is no consensus about the effectiveness of method of administration. The aim of this study was to compare the divided dose vs bolus medication form of morphine sulfate for management of acute pain in traumatic fracture. **Methods:** we designed a randomized double-blind clinical trial. On basis of inclusion and exclusion criteria, 160 patients with acute traumatic fracture were enrolled to the study and randomly divided into two groups. The first group (bolus group) received 0.1mg/kg morphine and then 0.1mg/kg normal saline every 5 minutes. The second group (titration group) received 0.1mg/kg of morphine in divided doses every 5 minutes. All injections were intravenously. The primary outcome was pain and before of injection, 15 minutes and 60 minutes after injection were recorded. Data were analyzed using SPSS 19. **Results:** 77 patients included 49 (63.6%) male with mean age of 47.42 ± 13.15 years were in titration group and 83 patients included 47 males (56.6%) with mean age of 52.40 ± 15.62 years were in bolus group. The complication rate was significantly higher in bolus group (75.9% vs 53.2%, $P < 0.0001$). The need to extra morphine injection in bolus and titration group were 62.7% and 28.6%, respectively ($P < 0.0001$). The mean pain score before and at 15 and 60 minutes after injection were 9.56 ± 1.03 , 6.61 ± 1.86 and 1.85 ± 1.13 in titration group and 9.76 ± 0.48 , 6.53 ± 1.59 and 0.61 ± 0.46 in bolus group, respectively. The pain score was significantly lower in titration group at 60 minutes after injection ($P < 0.0001$). **Discussion:** The results of this study showed that titration of morphine are a safe and effective method in compared with bolus administration to

reducing acute pain in traumatic fracture.

Keywords Titration, Morphine Sulfate, Acute Pain Control

1. Introduction

Pain is one of the most common reasons that patients visit the emergency department [1,2,3]. So that more than one-third of patients presenting to the emergency department of teaching hospitals complain of moderate to severe pain [4,5]. Failed to control pain will cause damage to physical health, psychological, social and spiritual [6,7]. Other problems such as increasing the length of treatment, complications and side effects of treatment and decreased concentration, appetite, physical activities and social relationships Sleep disorders and poor quality of life was significantly higher in patients who cannot control their pain [8,9]. One of the drugs used to control pain are opioids, In the meantime the morphine is more often and that is prescribed intramuscular or intravenous injection just one place that each has its own problems [10], but using alternate forms and its titration can be associated with reduced complications and better patient satisfaction [11]. The titration reduced morphine consumption and therefore, reduced the possible complications, However, studies have been conducted with different clinical outcomes [11-13]. It is thought that administration of divided dose and titration have better effects than bolus, But given that such studies are not perfect in this case, is still not accepted as a rule. Therefore, this study aimed to compare the divided doses of morphine and IV bolus administration of morphine in

patients with Traumatic fractures referred for acute pain management in the emergency department of Sari hospital.

2. Methods and Material

This study is a double blind randomized clinical trial on patients with traumatic fractures with acute pain in the age group of 18-60 years was referred to Imam Khomeini hospital in Sari. Inclusion criteria on the basis; VAS (visual analog scale) pain intensity between 10-7 and GCS equal to 15.

Pregnancy or suspected pregnancy, allergy to morphine, mental illness and depression and a history of opiate dependence, Received pain medication in the past six hours, the patient withdrawn to participate in the study and unstable patient was considered as exclusion criteria.

Patients were randomly divided into two groups by random number table. The first group (Group bolus) was injected with 0.1 mg / kg morphine and the next dose as 0.1 mg / kg of normal saline at 5-minute intervals. The second group (Group titration) injected with 0.1 mg / kg of morphine IV in divided doses with an interval of 5 minutes. The study was double-blinded, so that during the study patients, doctors, nurses from all phases of the study were unaware. Preparation and drug injection was performed by two nurses so that nurse who provides the drug was unaware about the patient and the other nurse taking the drug was unaware of the type of drug. All uniform and random drug injection syringes and recording of data by one person (resident of emergency medicine) was conducted.

The primary outcome studied was pain scores less than 3 and pain relief at 15 and 60 minutes after injection was assessed. If needed additional doses in patients 0.1 mg / kg intravenous morphine sulfate at 60 minute administered. Secondary outcome of study was complications in both groups during the study.

3. Ethical Approval

All patients provided informed consent to inclusion in

the study. This study was approved by the Ethics Committee of the Mazandaran University of Medical Sciences, Sari, IRAN.

4. Statistical Analysis

Results were shown as median, mean and standard deviation. The chi square, student t test and Fischer exact test was used for analysis of data. The procedures included were transcription, preliminary data inspection, content analysis and finally interpretation. Statistical analysis was performed with SPSS software (version 20, Chicago, IL, USA). P values less than 0.05 were considered statistically significant.

5. Results

The number of patients enrolled in the study was 160 patients; in the group titration 77 and 83 patients were in the bolus group. Of the 77 patients enrolled in the titration Group 49 patients (63.6%) and from 83 patients enrolled in the bolus group 47 patients (56.6%) were male ($P = 0.366$). The mean age of patients enrolled in the Group titration and bolus, respectively 47.42 ± 13.15 years and 52.40 ± 15.62 years, the difference was statistically significant different ($P = 0.031$). The average height and weight of patients enrolled in the two groups was not statistically significant different ($P > 0.05$).

Type of trauma in the titration group; 45 (58.4%) accidents, 24 cases (31.2%) fall, in 6 cases (7.8%) sports events, and 2 patients (2.6%) were other incidents. Type of trauma in patients with bolus group included; 54 patients (65.1%) accidents, 21 cases (25.3%) fall and 8 (9.6%) was sports events. Type of trauma in both groups had no statistically significant difference ($P = 0.379$).

Fifty patients (64.9%) in titration group and 63 patients (75.9%) in bolus had upper limb fracture and 27 patients (35.1%) in titration group and 20 patients (24.1%) in bolus group had lower extremity fractures bolus group ($P = 0.128$). The number of fractures in the two groups was not statistically significant ($P = 0.917$) table 1.

Table 1. Basic information of patients

P Value	bolus	titration	Patients' data	
0.031	52.40 ± 15.62	47.42 ± 13.15	age	
0.366	47 (56.6%)	49 (63.6%)	Gender (male)	
0.785	168.38±10.21	167.97±8.56	Height (cm)	
0.139	70.98±11.44	68.31±11.32	Weight (kg)	
0.379	54 (65.1%)	45 (58.4%)	accidents	Type of trauma
	21 (25.3%)	24 (31.2%)	fall	
	8 (9.6%)	6 (7.8%)	sport	
	0	2 (2.6%)	other	
0.128	63 (75.9%)	50 (64.9%)	Upper limb	Fracture zone
	20 (24.1%)	27 (35.1%)	Lower limb	
0.917	35 (42.2%)	30 (39%)	1	Number of fractures
	38 (45.8%)	37 (48 %)	2	
	10 (12%)	10 (13%)	3	

Table 2. The incidence of side effects in both groups of patients

P value	Bolus	Titration		
0.125	9.56 ± 1.03	9.76 ± 0.48	Before infusion	VAS score
0.766	6.61 ± 1.86	6.53 ± 1.59	Min 15	
<0.0001	1.85 ± 1.13	0.61 ± 0.46	Min 60	
<0.0001	52 (62.7%)	22 (28.6%)	Additional morphine	
0.709	3.40±0.92	3.31±0.82	Mean of Additional morphine	
0.003	63 (75.9%)	41 (53.2%)	Side effects	
<0.0001	11 (13.3%)	5 (6.5%)	nausea	complications
	16 (19.3%)	10 (13%)	vomiting	
	18 (21.7%)	12 (15.6%)	dizziness	
	10 (12%)	6 (7.8%)	sweating	
	0	8 (10.4%)	itching	
	8 (9.6%)	0	hypotension	

Mean score of patients in titration group before the injection, 15 and 60 minutes after the injection, respectively, 9.76 ± 0.48, 6.53 ± 1.59 and 0.61 ± 0.46.

Mean score of patients in bolus group before the injection, 15 and 60 minutes after the injection, respectively, 9.56 ± 1.03, 6.61 ± 1.86 and 1.85 ± 1.13. VAS score between the two groups before injection (P = 0.125) and 15 min after injection (P = 0.766) were not significantly different.

However, the average VAS score in titration group at 60 minutes was significantly lower (P <0.0001).

The need for additional doses of morphine in 22 patients (28.6%) in titration group and 52 patients (62.7%) in bolus Group was observed.

The effectiveness of morphine was significantly higher in patients titrated so that the need to re-dose bolus of morphine in patients in comparison to titrated patients were 1.94 times. (RR: 1.94, 95%CI: 1.41-2.68, P<0.0001)

The average doses of morphine required additional bolus

were not significantly different between two groups. Respectively, 3.31 ± 0.82 vs. 3.40 ± 0.92, P = 0.709).

The incidence of complications in the titration is 53.2% (41 patients) and 75.9% in the bolus group (63 patients).

The incidence of complications was significantly higher in bolus patients and risk in these patients was 1.69 times more than in titration Group (RR: 1.69, 95%CI: 1.15-2.49, P=0.003).

The most common adverse events in groups are dizziness, vomiting and nausea. However, itching in patients with titration and hypotension was found only in patients bolus group (P <0.0001).

6. Discussion

Our study showed pain severity One hour after injection in patients who received morphine titration method was significantly lower than bolus group. The effectiveness of

morphine titration was significantly more so the need to re-dose bolus of morphine was 1.94 the titration method.

However, contrary to what was observed in our study, Chang and colleagues in 2013 examined elderly patients for pain management in the emergency department, 153 patient received hydromorphone 0/5 mg / kg in titration and a single dose of morphine in 166 patients injected. The results of their study showed that the two groups were not significant in analgesia^[11].

However, in a study Lvovschi et al. 2008^[14], Chang and colleagues in two studies in 2009^[12], 2011^[15] on population did similarly with our study showed that administration of morphine with titration injections is more effective.

In our study, the incidence of complications with bolus injection of morphine was significantly higher when compared to titration So that the risk of complications in the bolus procedure was estimated 1.69 times more than titration method. Chang and colleagues in contrast to our study, the incidence of medical complications between the two groups was identical (titration and bolus)^[15]. At the same time Lvovschi and colleagues conducted a study that indicated the effects was significantly lower in the titration group^[14].

The most common side effects between the two groups in our study were dizziness, vomiting and nausea. However itching in patients with titration and hypotension was found only in patients with bolus. Results of previous studies showed that administration of morphine has variety of side effects such as nausea and vomiting, respiratory depression, urinary retention, pruritus, allergy and dizziness associated^[14, 16].

According to the findings of our study, it seems that the incidence of complications is reduced with the administration of morphine titration method.

7. Conclusions

The study showed that administration of morphine at a dose of 0/1 mg / kg to titration (divided doses) compared to bolus associated with fewer side effects and greater effectiveness.

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