Original Article DOI: 10.22114/ajem.v0i0.273

Analgesic Effects of Ketamine Nebulizer vs. Intravenous Morphine in Limb Trauma Patients in Pre-Hospital Emergency Setting; A Randomized Double-Blinded Clinical Trial

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Published online: 2020-01-09

Abstract

Background: Limb trauma is one the main causes of emergency room (ER) referrals and patients often complain of pain from the very moment of arrival.

Objective: We decided to compare the analgesic effect of ketamine nebulizer with intravenous (IV) morphine in trauma patients referred to ER.

Methods: In this clinical trial study trauma patients referred to ER of Alzahra and Kashani hospitals in Isfahan, Iran were selected. All trauma patients older than 18 years with limb pain who had a pain score ≥ 7 based on visual analogue scale (VAS) criteria were included. During pre-hospital management, patients were divided into two groups of receiving ketamine nebulizer with a dose of 1.6 mg/kg and receiving IV morphine with a dose of 0.1 mg/kg. Pain score, vital signs and complications were recorded 5 and 15 minutes after receiving the first dose of drug and also at the time of arrival to ER.

Results: Finally, the records of 391 patients were analysed. There was no significant difference between the two groups in terms of pain intensity, vital signs before intervention, the first 5 and 15 minutes after and the time of arrival in ER ($P>0.05$). But the changing of VAS scores in different times was significant in both groups ($P<0.001$). There was a significant difference between the two groups in complications including nausea and vomiting ($P<0.001$), and also delirium ($P=0.010$).

Conclusion: Using ketamine nebulizer can produce similar analgesic effects as IV morphine in trauma patients referred to ER.

Key words: Emergency Medical Services; Ketamine; Morphine; Pain Management; Trauma

Cite this article as: Azizkhani R, Boroumand A, Hassan S, Rastin G, Ghasemi A, Shahbazi A. Analgesic Effects of Ketamine Nebulizer vs. Intravenous Morphine in Limb Trauma Patients in Pre-Hospital Emergency Setting; A Randomized Double-Blinded Clinical Trial. Adv J Emerg Med. 2020;4(4):e84.

INTRODUCTION

The importance of pain as the most annoying complaint of trauma patients in ER has led pain control to be one of the top priorities of the health system dealing with trauma patients. Different drugs are used to control pain in trauma patients, opioids and especially morphine are still considered as the first line of treatment of pain in emergency rooms (1). Using opioids as an analgesic treatment can cause many complications and problems the most important of which is respiratory depression and even apnea. Also, due to higher risks of airways obstruction and aspiration pneumonia in trauma patients, nausea and vomiting after opioid administration has a significant higher risk (2). Therefore, it seems that safer methods should be applied to reduce pain in trauma patients. Ketamine is one of the drugs with analgesic characteristics which is soluble in water and fat and has different ways of administration (3, 4). The analgesic effect of ketamine associated with its other characteristics are among the reasons why ketamine has been considered as a safe analgesic drug in recent years. Ketamine helps to calm patients by sedative and pain relieving effects and unlike opioids not only it does not cause respiratory depression, on the contrary it leads to bronchus dilation which can be very useful in trauma and pulmonary patient management. Different studies have been conducted on ketamine efficacy as an analgesic drug in ER and trauma patients which have pointed ketamine out as a safe and effective analgesic drug (5, 6). In previous studies respiratory depression, reduced respiratory capacity, nausea and vomiting were less frequently noted which distinguishes ketamine from opioids especially morphine.

According to the easier and more accessible ways of ketamine absorption in body, using ketamine nebulizer may be an efficient way to reduce pain in patients and prevent over-sedating (7). Therefore, due to the importance of pain control in trauma patients referred to emergency rooms and also use of different drugs with different side effects such as morphine, we decided to compare the analgesic effects of intravenous morphine with ketamine nebulizer in patients referred to emergency departments.

METHODS

Study design

This randomized, double blinded, clinical trial was conducted in ER of Alzahra and Kashani hospitals, Isfahan province, Iran from 2017 to 2019. The protocol of present study was approved in medical ethics committee of Isfahan University of Medical Sciences (code: IR.MUI.REC.1396.3.457). After explaining the methods and purposes of the study, written consent forms were filled out by all the patients included in the study. The authors were fully adhered to declaration of Helsinki Principles throughout the study.

Study population

The sample size was calculated 180 patients in each group using mean differences formula with considering mean differences (pain) of 0.17, α=0.05, β=0.1, and differences of standard divisions of 0.24. Considering 9% loss, at least 200 random samples from each of the two groups (ketamine and morphine) and a total of 400 random samples should be studied to obtain a 90% probability of 24% difference was found in the standard deviation of pain on the visual analogue scale (VAS) scale with the first type error of 5%. The sampling was performed based on consecutive method. All the patients who had a pain score of seven or more based on VAS and were above the age of 18 were included in the study. However, patients with head trauma, coronary ischemic disease, acute cardiac and pulmonary failure, systolic blood pressure more than 180 mmHg or less than 90 mmHg, alcohol abuse, pulmonary failure, asthma, high intracranial pressure (ICP) symptoms, pregnancy, history of allergy to morphine or ketamine, prior administration of analgesics before admission, addiction, need to more than twice doses of analgesic drugs, contraindications for receiving ketamine or morphine, changing the sedative drugs during study, incapability of describing pain severity and incompetency to give informed consent were considered as exclusion criteria. Patients arriving to the hospital in less than thirty minutes were also excluded. Patients were divided randomly with using random allocation software into two groups as ketamine and morphine. Also the patients and resident or emergency medical technician (EMT) were blinded about group names.

Intervention and data gathering

All patients were visited by an emergency medicine resident and a trained EMT. The EMTs were trained by the main operator of the study on how to measure pain intensity using VAS, how to properly administer the drugs and their possible side effects and complications. These trainings took place in a workshop before the study began. Patients' information was primarily collected through an interview performed by the EMTs and recorded in pre-made checklists. The checklist was included demographics, heart rate, blood pressure, respiratory rate, oxygen saturation percentage, consciousness level (based on Glasgow coma scale (GCS)), primary VAS, complications after drug administration (like nausea, vomiting, delirium), onset of analgesic effects and efficacy duration. Ketamine nebulizer was administered with a dose of 1.6 mg/kg and then was diluted with 5cc of sterile water. Morphine was administered intravenously (IV) with a dose of 0.1 mg/kg after being diluted with 5cc of sterile water. Patients received these drugs twice within 10 minutes and those who needed more than twice of drug doses were excluded.

All the patients with an oxygen saturation percentage less than 92% received oxygen bag masks providing 4-6 liters of oxygen per minute. Vital signs and GCS of the patients were also measured and registered within 5 and 15 minutes after drug administration and at the time of arrival to the hospital.

Outcome assessment

VAS was used to measure pain intensity in patients. It has a domain of 0 to 10 scores with 0 corresponding a non-painful condition and 10 corresponding the highest conceivable amount of pain. VAS score was measured in two steps, at first VAS score was calculated before ketamine or morphine administration. In the second step it was calculated within 5 and 15 minutes and at the time of arrival to the hospital after receiving ketamine or morphine. This information was registered in checklists. A 50 percent decrease in VAS score or reaching to score 3 showed the succession of treatment. Patients were also asked if they were experiencing any side effects including nausea, vomiting, increased saliva secretion, hypotension, hallucination and agitation.

Statistical analysis

All data were enrolled into SPSS software version 24, variables were shown based on frequency and percentage or mean and standard division, Independent t test was used to compare quantitative variables between groups and Chi Square and fisher's exact test was used to compare qualitative variables between groups. Also repeated measure ANOVA was used to compare changing variables in times. P-value less than 0.05 was considered significant.

RESULTS

Figure 1 shows the CONSORT flowchart of study patients. In the beginning 400 patients were included in the study and 391 of them were finally analysed. Patients were divided into two groups: morphine (196 patients) and ketamine (195 patients). Three patients (1.5%) in morphine group and 14 patients (7.1%) in ketamine group had need more than two doses of analgesics, so excluded of final analysis. Baseline data of study patients are reported in table 1. Based on the findings, there was no significant difference between the two groups regarding their gender and age (P>0.05). Nineteen patients (9.6%) in morphine group and 72 (36.9%) patients in ketamine group had need more than one dose of drugs There was also no significant difference in VAS before intervention, 5 and 15 first minutes and the moment of admission in ER between the two groups (P>0.05), but according to repeated measure ANOVA test, the changing of VAS scores in different times was significant in both groups (P<0.001). Also, there were no significant differences of systolic and diastolic blood pressures, respiratory rate and heart rate before intervention, first 5 and 15 minutes and at the time of admission in ER between the two groups (P>0.05); however, based on repeated measure ANOVA test, the changings of systolic and diastolic pressures, respiratory rate and heart rate were significant in different times in each group (P<0.001). Pain intensity and hemodynamic variables studied in the two groups at different times are reported in table 2. The incidence of nausea and vomiting was 27% (53

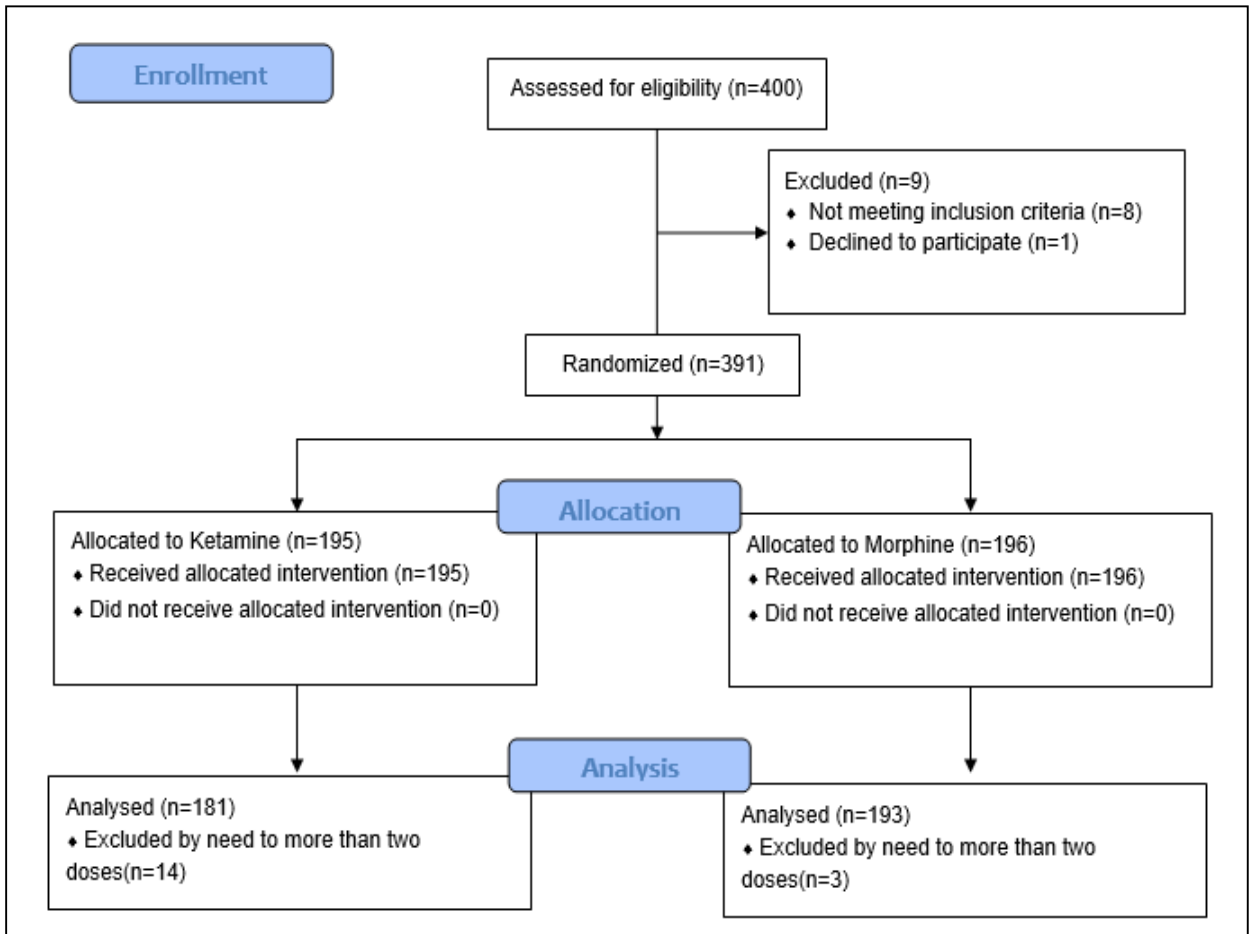

Figure 1: CONSORT flowchart of study patients

Table 1: Variables studied between the two groups

Variable		Morphine group	Ketamine group	P-value
Age, mean±SD (years)		39.28 ± 9.53	39.57 ± 9.65	0.758*
Gender, n(%)	**Male**	126 (64.3%)	112 (57.4%)	0.1**
	Female	70 (35.7%)	83 (42.6%)	
Primary pain intensity, n(%) (VAS)	**7**	151 (77.4%)	143 (73.3%)	0.47*
	8	39 (20%)	42 (21.5%)	
	9	4 (2.1%)	6 (3.1%)	
	10	1 (0.5%)	4 (2.1%)	

*Independent t test, **Chi Square

Table 2: Pain intensity and hemodynamic variables studied in two groups at different times

Variable		Morphine group		Ketamine group		P-value*
		Mean ± SD	n	Mean ± SD	n	
Severity of pain	**Before intervention**	7.25 ± 0.51	196	7.33 ± 0.64	195	0.164
	First 5 minutes	5.67 ± 0.92	196	5.73 ± 1.02	191	0.532
	First 15 minutes	4.68 ± 1.13	195	4.84 ± 1.25	186	0.173
	The moment of emergency	3.38 ± 1.23	193	3.53 ± 1.35	181	0.247
	P-value**	<0.001		<0.001		
Systolic blood pressure	**Before intervention**	125.20 ± 13.23	196	123.80 ± 13.86	195	0.314
	First 5 minutes	124.44 ± 13.09	196	123.59 ± 14.56	191	0.545
	First 15 minutes	124.76 ± 11.80	195	123.01 ± 16.22	186	0.227
	The moment of emergency	126.35 ± 11.24	193	125.20 ± 11.33	181	0.316
	P-value**	<0.001		<0.001		
Diastolic blood pressure	**Before intervention**	76.50 ± 7.35	196	78.26 ± 8.28	195	0.091
	First 5 minutes	80.44 ± 14.16	196	80.78 ± 13.74	191	0.810
	First 15 minutes	76.94 ± 8.27	195	79.85 ± 7.83	186	0.100
	The moment of emergency	81.73 ± 12.49	193	81.35 ± 13.25	181	0.778
	P-value**	<0.001		<0.001		
Respiratory rate	**Before intervention**	21.52 ± 3.85	196	23.10 ± 3.73	195	0.102
	First 5 minutes	19.42 ± 2.28	196	20.13 ± 2.53	191	0.233
	First 15 minutes	18.88 ± 2.36	195	19.40 ± 2.23	186	0.202
	The moment of emergency	19.23 ± 2.64	193	21.90 ± 3.33	181	0.155
	P-value**	<0.001		<0.001		
Heart rate	**Before intervention**	79.52 ± 12.48	196	80.28 ± 13.82	195	0.573
	First 5 minutes	77.39 ± 11.40	196	78.62 ± 12.83	191	0.331
	First 15 minutes	74.90 ± 10.56	195	75.82 ± 11.25	186	0.414
	The moment of emergency	74.44 ± 11.55	193	76.05 ± 13.46	181	0.211
	P-value**	<0.001		<0.001		

*Independent t test, **Repeated measure ANOVA

cases) in the morphine group and 5.1% (10 cases) in the ketamine group, and the rate of delirium was 1% (2 cases) in the morphine group and 5.6% (11 cases) in the ketamine group. There was a significant difference between the two groups in complications including nausea and vomiting (P<0.001), and also delirium (P=0.010).

Discussion

According to the results of this study, there was no difference between using morphine and ketamine in pain management in trauma patients before they were referred to the ER and there was no difference in the hemodynamic variables, but the rate of complications like nausea and vomiting was significantly higher in patients receiving morphine and the rate of delirium was significantly higher in patients receiving ketamine. As mentioned earlier, pain control is very important in patients especially in traumatized patients. In this study, by assessing ketamine nebulizer and IV morphine, we concluded that there is no significant difference between these two drugs in terms of pain control but they are different in terms of complications and side effects. Various studies have been conducted on this subject. In a 2015 study by Miller et al., They compared the effects of low-dose ketamine and morphine in trauma patients. In this study, 45 patients were evaluated and finally it was reported that low doses of intravenous ketamine did not make a difference in patients' pain intensity compared to intravenous morphine. But on the other hand, they showed that the analgesic effects of ketamine started within 5 minutes and lasted for about 2 hours (8). The results of this study are consistent with the results of our study because we also showed that there was no difference between ketamine and morphine in terms of pain control.

However, in this study, we used ketamine nebulizers to reduce pain in patients and showed that they had fewer gastrointestinal complications than morphine. Another study by Tran et al in 2014 assessed the effects of ketamine and morphine on pain relief in trauma patients. This study was conducted on 169 patients showing that ketamine and morphine act similarly in reducing pain and there is no difference between them in terms of pain control. It also showed that the risk of airway complications was lower in patients who received ketamine compared to those who were given morphine. In addition, they reported complications such as hallucination and agitation in patients receiving ketamine (6). These results are consistent with the results of our study as we also showed no difference in pain suppression between the ketamine and morphine groups and we also found that complications such as delirium were more frequent in patients receiving ketamine. In addition, the highlight of our study is the bigger statistical population than other studies as well as the use of ketamine nebulizers instead of intravenous ketamine. In a study by Majidinejad et al., comparing the analgesic effects of morphine and ketamine in 126 traumatic bone fracture patients it was concluded that low-dose ketamine administration was associated with significantly reduced pain in patients and that there was no difference in analgesic effects between patients receiving morphine or ketamine (9). This study, similar to previous studies, presented results consistent with our study, suggesting that there was no difference between morphine and ketamine in analgesic effects. Studies have also investigated the effects of simultaneous use of ketamine and morphine and have shown that ketamine use is associated with a decreased morphine requirement in patients with severe pain (10). Thus, studies are trying to find a way to reduce morphine use and patients' needs (11).

Limitations

The limitations of our study were included short period of the follow up and not evaluating other effective factors. Another important missed point was the subgroup analysis, considering the final diagnosis of trauma patients, for example, based on presence or absence of bone fractures. Such limitations and also numerous exclusion criteria in this trial, make it difficult to generalize the results. So further trials are still required in this regard. In contrast, providing a safe drug in the pre-hospital phase for pain control in trauma patients is a significant advantage of the present study.

CONCLUSIONS

According to the results of the current study, it is likely that using ketamine nebulizer can produce similar analgesic effects as IV morphine in trauma patients referred to ER. However, it is recommended to use ketamine with caution in patients with a history of psychiatric or psychological problems, as we have shown that delirium-like effects were more common in patients receiving ketamine.

ACKNOWLEDGEMENTS

We would like to thank all EMTs who helped in management of the study patients.

AUTHORS' CONTRIBUTION

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

None declare.

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