Original Article

Comparison of Efficacy of Nebulized Ketamine with Morphine and Intravenous Morphine in Pain Reduction in Patients with Traumatic Long-Bone Fractures Admitted to Emergency Department

Reza Azizkhani, Kourosh Akhbari, Babak Masoumi, Abdolrahman Parna[1], Keihan Golshani

Department of Emergency Medicine, Isfahan University of Medical Sciences, [1]Department of Emergency Medicine, Emergency Medicine Research Center, Al-Zahra Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

ORCID:

Reza Azizkhani: https://orcid.org/0000-0002-5823-4374
Kourosh Akhbari: https://orcid.org/0000-0003-3539-4129
Babak Masoumi: https://orcid.org/0000-0002-7330-5986
Abdolrahman Parna: https://orcid.org/0000-0003-4810-9462
Keihan Golshani: https://orcid.org/0000-0001-8567-5119

Abstract

Background: Traumatic long-bone fracture is a common cause of referring to the emergency department (ED). The aim of this study was to compare the efficacy of nebulized ketamine and morphine and intravenous (IV) morphine in reducing pain in these patients. **Materials and Methods:** In this clinical trial study, 88 patients with traumatic long-bone fractures referred to the ED were randomly selected and divided into two groups of nebulized ketamine and morphine and IV morphine using block randomization. Changes in pain intensity according to visual analog scale (VAS), patient satisfaction, and clinical features, including oxygen saturation (O_2 sat), systolic blood pressure (SBP), respiratory rate, and pulse rate (PR) were assessed at baseline and 15 and 30 min after the intervention and finally, data were analyzed using the SPSS software. **Results:** Demographic characteristics including sex, age, and site of fracture were similar in the two groups ($P > 0.05$). In the IV morphine group, O_2 sat ($P < 0.001$), SBP ($P = 0.005$), and PR ($P < 0.001$) significantly decreased, but in the nebulized group, SBP ($P < 0.001$) and PR ($P < 0.001$) significantly increased, but O_2 sat did not significantly decrease ($P > 0.05$). The VAS results in the IV group were better at 15 min ($P < 0.001$), but after 30 min, both methods were equally effective in pain reduction ($P = 0.508$). **Conclusion:** According to the results of this study, the pain reduction was similar in both groups after 30 min, but regarding other parameters such as patients' satisfaction and fewer side effects, it can be concluded that the long-term effect of nebulized morphine and ketamine would be more beneficial.

Keywords: Intravenous morphine, nebulized ketamine and morphine, oxygen saturation, pain management, traumatic patient, visual analogue scale

Introduction

Trauma is one of the most common reasons for hospitalization in the emergency department (ED). The majority of patients in EDs have fractures, especially long bone fractures, in which anxiety and pain are the most frequent symptoms. Both symptoms lead to complications such as activation of the sympathetic system, mutual endocrine cell system, respiratory system (hyperventilation), and central nervous system (fear and anxiety), which threaten the patient's health.[1] In the ED patients, pain is the first complaint and presentation which should be relieved. In the past, clinicians pointed out that pain

Access this article online

Quick Response Code:

Website: www.archtrauma.com

DOI: 10.4103/atr.atr_13_18

Address for correspondence: Prof. Kourosh Akhbari, Department of Emergency Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: akhbarikourosh@gmail.com

How to cite this article: Azizkhani R, Akhbari K, Masoumi B, Parna A, Golshani K. Comparison of efficacy of nebulized ketamine with morphine and intravenous morphine in pain reduction in patients with traumatic long-bone fractures admitted to emergency department. Arch Trauma Res 2018;7:114-20.

relief accounted for more than half of ED visits,[2] although the first step is to perform the analgesic treatment. According to the previous reports, pain needs to be addressed within 20–25 min after arrival at the ED.[3,4] In addition to clinical benefits, pain relief has a variety of psychological benefits such as decreased tachycardia and reduced blood pressure (BP) and heart rate resulting from calmness.[5]

The best pain medication for suitable and quick pain reduction should also be taken into account in analgesia methods. Not all pain medications are suggested for all patients due to their side effects and mechanism of pain relief, and a variety of approaches are considered for different parts of the body.[6,7] Availability of specific therapies can result in the management of analgesic agents. Besides that, route of drug administration also has an important role in pain management. For example, when pain is severe, intravenous (IV) route is preferable because of high accessibility and patients' satisfaction.[8] The newer methods, such as intranasal or oral transmucosal, are less known compared with conventional approaches such as oral or IV.[9] It has also been reported that the use of multiple medications would have adverse effects on the pain care. Furthermore, relatively mild side effects may be exacerbated when more than one drug is administrated. Moreover, co-administration of multiple analgesics leads to pharmacokinetic ambiguities, and the selected doses may not have a beneficial effect on pain relief.[5]

Nevertheless, there are some exceptions to the above statement; for example, the use of ketamine as the opioid-sparing agent is beneficial for reducing the overall dose of certain analgesics such as morphine.[10] Morphine is one of the most routine medications for analgesia in ED, which is prescribed for severe acute pain,[11] but some unwanted adverse effects have been observed for morphine during analgesia, which is related to the titration of morphine during IV injection.[12] In this condition, a combination of nonopioid drugs is the best approach to reduce the amount of injected morphine (morphine-sparing effect), which causes less toxicity and leads to higher patients' satisfaction.[13] The best choice for combination with morphine is ketamine, which can block Mg-dependent channel.[14] This combination can be efficiently used as a nebulized analgesic drug because it prevents the airway reflexes and also few side effects have been reported for it.[15] Many studies haverevealed that IV concomitant use of ketamine and morphine provides better analgesia.[16] The benefits of this combination have also been confirmed in both animal studies[17] and human subjects.[18]

It should be noted that pain cannot be relieved if it cannot be evaluated by assessment methods. The most famous pain assessment instrument is visual analog scale (VAS) that provides appropriate data about patient's pain intensity for clinicians. In this method, the pain intensity is reported by patients using a 10-point simple scale.[19] In this way, clinicians can choose the best analgesia approach for reducing the pain that consequently leads to higher patients' satisfaction.[20]

This study was conducted to evaluate the efficacy of nebulized ketamine with morphine compared to IV morphine alone in patients with traumatic long-bone fractures and also to investigate the clinical features of patients before and after analgesic administration and their satisfaction with the two analgesia methods.

Materials and Methods

In this clinical trial, the study population consisted of patients suffering from traumatic long-bone fractures and complaining of severe pain referred to the EDs of Alzahra Hospital and Kashani Hospital during 2015–2016. The sample size was calculated as 44 patients in each group using a sample size formula for comparing the proportion between the two groups and with considering the assumption of noninferiority and with 95% confidence level, 80% statistical power of test and considering that the proportion success rate of pain reduction for nebulized ketamine and morphine in previous studies was 0.524.[21] Furthermore, the rate of noninferiority limit was considered 0.3.

The patients who were suffering from traumatic long-bone fractures and complaining of severe pain with the VAS pain score >7, in the age group of 18–65 years and those who consent to participate in the study with the injured limb of primarily immobilized by a splint before prescribing analgesics were included. The patients with a history of asthma, chronic obstructive pulmonary disease and seasonal allergy, using inhaler to control respiratory symptoms, sensitivity to ketamine, sensitivity to opioids, those with a history of cardiovascular disease, psychotic disorder and any trauma to the head or who wish to discontinue cooperating in the study were excluded.

Then, the patients were randomly allocated into the two groups through the randomized block design [11 blocks with a size of 4 to compose two groups of 44 Figure 1].

The ethics code (no. 395108) was obtained from the Ethics Committee of the Research and Technology, Deputy of the Isfahan University of Medical Sciences, and also from all patients provided a written informed consent form.

Next, we recorded demographic and clinical characteristics of the patients, such as sex, age, site of fracture, pain (by VAS), BP, oxygen saturation (O_2 sat), heart rate, and respiratory rate (RR) at baseline.

Then, in one of the groups, to control pain, IV morphine (Darou Pakhsh Holding Co., Iran) was injected at the standard dose (0.1 mg/kg).

In the second group, nebulized morphine and ketamine by the oxygen flow of 5 l/min using a partial rebreathing mask. The dose of ketamine (RotexMedica GmbH Co., Trittau, Germany) was 1.5 mg/kg and the dose of morphine (Darou Pakhsh Holding Co., Iran) was 0.1 mg/kg. If the sedation of patients was intensified and progressed from mild-to-moderate toward

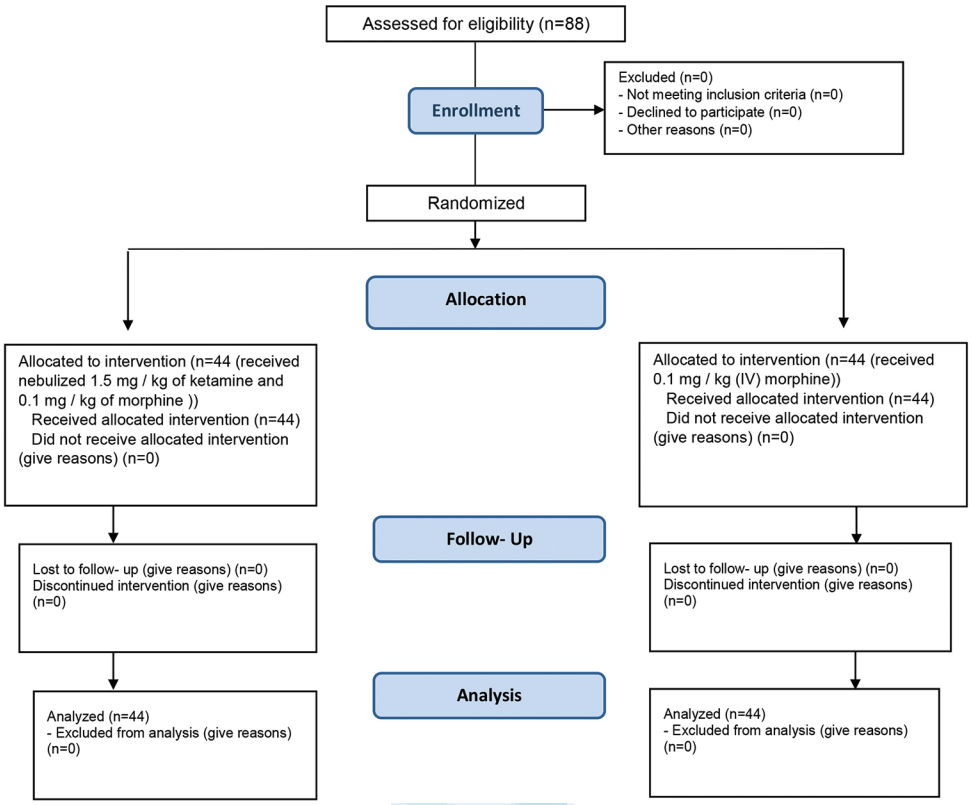

Figure 1: Flowchart consort

the establishment of dissociative sedation (characterized by profound analgesia and amnesia with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability),[22,23] or if any other complications and changes in BP (arbitrary BP ≥ 180/120 or arterial BP <90 mm Hg or mean arterial pressure <65),[24] and life-threatening heart rate (ventricular rate <60 beats/min, or >100 beats/min)[25,26] occurred, the morphine and ketamine flow was discontinued and the patient was excluded from the study.

On the other hand, if no response to pain in the nebulized ketamine and morphine group was observed after 15 min, IV morphine was used to relieve pain and the patient was excluded (in this study, all of the patients reported some relief of pain).

Both groups were evaluated at 15 and 30 min after the intervention. The data on pain scores (by VAS), BP, heart rate and RR, O_2 sat, possible side effects, and the patients' satisfaction were collected by someone who was not blind to the patient's group.

Finally, the collected data were analyzed using the SPSS (version 20; SPSS Inc., Chicago, Ill., USA). Qualitative data in the forms of frequency and frequency percentage and quantitative data in the forms of mean and standard deviation have been demonstrated. As inferential statistics, respectively, Fisher's exact test and Chi-square test were used to compare the frequency distribution of sex and fracture site between the two groups while independent *t*-test was used to compare the age between these two groups. Furthermore, the results of the Kolmogorov–Smirnov normality test indicated nonnormal distribution of the variables; we used the Mann–Whitney test to compare the means of continuous variables between the two groups and repeat measure analysis test was also used for comparing between the two groups in different times. In all analyses, we considered the significance level <0.05.

Results

In this study, the IV morphine group included 38 men (88.4%) and 6 women (13.6%) and the mean age of the patients in this group was 31.60 ± 10.75 years. Furthermore, the nebulized morphine and ketamine group consisted of 37 men (84.1%) and seven women (15.9%) and the mean age of the patients in this group was 36.11 ± 12.63 years ($P > 0.05$). Fractures sites were not statistically significantly different in the two groups ($P = 0.975$). In all patients, the injured limb was immobilized by the splint in all stages, and thus immobilization was performed in both groups [Table 1].

Furthermore, on an average, there was no significant difference between the two groups in terms of the percentage of O_2, systolic BP (SBP), RR and heart rate of patients at baseline. Furthermore, they were not significantly different at 15 and 30 min after treatment (P > 0.05). However, the analysis of the repeated measure showed that the impacts of the follow-up were not the same in the IV morphine group and nebulized morphine and ketamine groups ($P < 0.001$) [Table 2].

The mean pain scores were not significantly different between the two groups at baseline (P = 0.119), but 15 min after the treatment, the mean pain score in the IV morphine group (4.58 ± 1.82) was lower than the mean pain score in the nebulized morphine and ketamine group (6.75 ± 0.92) (P < 0.001), and 30 min after the treatment, pain scores in the two groups were similar. Hence, the mean pain score in the two groups significantly decreased during the treatment (P < 0.001). Furthermore, the effect of the time * group factor in the repeated measure analysis showed a significant difference between the two groups [P = 0.006 and Table 3].

Table 1: Basic and clinical characteristics of patients in both groups

Characteristics	IV morphine group (%)	Nebulized morphine and ketamine group (%)	*P*
Sex			
Male	38 (88.4)	37 (84.1)	0.563
Female	6 (13.6)	7 (15.9)	
Age; year	31.60±10.75	36.11±12.63	0.077
Fracture site			
Humerus	6 (14)	7 (15.9)	0.975
Radius	6 (14)	7 (15.9)	
Femur	11 (25.6)	13 (29.5)	
Tibia	6 (14)	6 (13.6)	
Ulnar and radius	10 (23.3)	7 (15.9)	
Tibia and fibula	4 (9.3)	4 (9.1)	

IV: Intravenous

Furthermore, the pain reduction within 30 min after the treatment was not significantly different between the two groups with respect to the fracture sites [P > 0.05 and Figure 2].

The adverse effects such as nausea and vomiting were reported in three patients (6.8%) in the IV morphine group and in one patient (2.3%) in the nebulized morphine and ketamine group (P = 0.295); however, other complications such as apnea, amnesia, increased salivation, restlessness, nystagmus, laryngospasm, and delirium were not observed .

The mean patients' satisfaction scores in the IV morphine and nebulized morphine and ketamine groups were 1.95 ± 0.58 and 2.07 ± 0.59, respectively, was which showed no significant difference using the Mann–Whitney test (P = 0.360) [Figure 3].

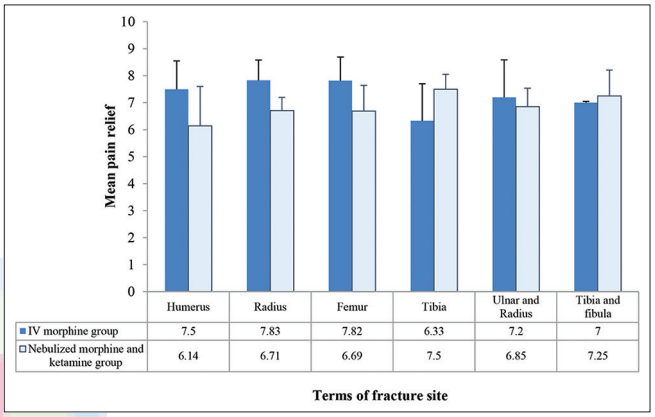

Figure 2: The bar chart illustrating mean pain relief in two groups in terms of fracture site

Table 2: Determination and comparison of clinical factors between the two groups

Variables	IV morphine group	Nebulized morphine and ketamine group	*P****
O_2 sat at baseline	98.00±1.11	97.98±1.07	0.904
O_2 sat after 15 min of treatment	97.72±1.10	97.86±1.17	0.433
O_2 sat after 30 min of treatment	97.58±1.26	97.82±1.23	0.404
P time*	<0.001		
P time × group**	<0.001		
SBP at baseline	125.81±20.64	125.11±20.50	0.716
SBP after 15 min of treatment	123.30±20.18	125.68±20.48	0.521
SBP after 30 min of treatment	122.49±19.10	127.16±19.33	0.214
P time*	0.127		
P time × group**	0.001		
RR at baseline	12.84±1.56	12.93±1.60	0.731
RR after 15 min of treatment	12.77±0.95	12.70±1.62	0.609
RR after 30 min of treatment	12.72±0.93	12.70±1.62	0.881
P time*	0.555		
P time × group**	0.861		
PR at baseline	80.84±5.54	79.93±5.63	0.501
PR after 15 min of treatment	79.49±5.90	79.75±5.60	0.828
PR after 30 min of treatment	79.23±5.99	81.55±5.61	0.091
P time*	<0.001		
P time × group**	0.001		

*Effect of factor of time in repeated measurement analysis, **Effect of factor of time*group in repeated measurement analysis, ***Mann-Whitney U-test for comparison between the two groups. O_2 sat: Oxygen saturation, RR: Respiratory rate, PR: Pulse rate, SBP: Systolic blood pressure

Table 3: Determination and comparison of mean pain scores between two groups

VAS	IV morphine group	Nebulized morphine and ketamine group	*P****
VAS at baseline	9.63±0.62	9.43±0.57	0.119
VAS after 15 min of treatment	4.58±1.82	6.75±0.92	<0.001
VAS after 30 min of treatment	2.28±1.10	2.43±1.04	0.508
P time*		<0.001	
P time × group**		<0.001	
-		0.016	

*The effect time factor in repeated measurement analysis, **The effect of time×group factor in repeated measurement analysis, ***Mann-Whitney U-test for comparison between the two groups. VAS: Visual analog scale, IV: Intravenous

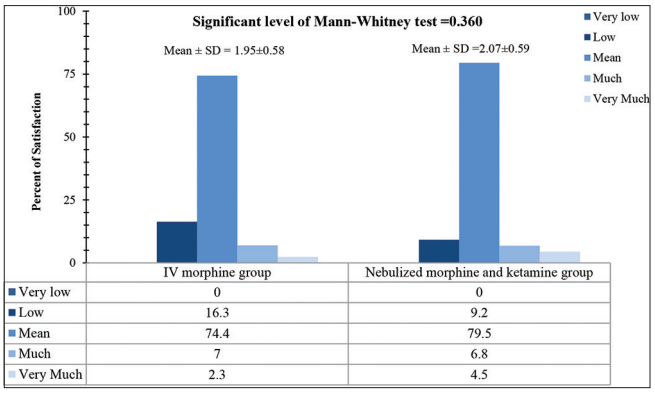

Figure 3: The bar chart illustrating frequency percentage of patient's satisfaction scores in two groups

The results of Table 2 showed that the hemodynamic changes during the study. The effect of time in repeated measures analysis of variance showed that changes in the O_2 sat and pulse rate (PR) were significant. Furthermore, the effect of time × group in O_2 sat, SBP and pulse rate (PR) was significant, which showed that the changes of these outcomes were significant between the two groups during the treatment.

Discussion

The results of this study showed that in patients receiving IV morphine, the amount of saturated oxygen was significantly decreased after 30 min ($P < 0.001$), but the trend of decrease in the nebulized ketamine and morphine group was not statistically significant ($P > 0.05$).

Furthermore, in the IV morphine group, the decrease in the SBP and PR was significant after 30 min; however, both factors in the nebulized group were increased significantly. However, in general, the trend of clinical factors between the two groups was not statistically significant ($P > 0.05$).

Administration of ketamine has been reported to be in the relationship with decreased resistance to the opioid drugs such as morphine in rats.[27-30] Moreover, ketamine could.

In addition, the mean of VAS at the baseline was similar in both groups, but after 15 min of pain treatment, the significant decrease in the IV group was seen in comparison with nebulized patients ($P < 0.001$), and after 30 min, the mean of VAS within both groups was similar again ($P = 0.508$). On the other hand, the mean of VAS from baseline up to 30 min was significantly decreased in each group ($P < 0.001$). Therefore, it could be said that IV morphine is more successful on early pain management than nebulized morphine with ketamine; however, in the long term (30 min), the influence of the two methods in the controlling and reduction of pain is the same. However, if the purpose of treatment is quick treatment with the least complications and no significant decrease in the amount of saturated oxygen, nebulized morphine and ketamine would be a better approach. In addition, the level of the patient's satisfaction was the same in the two groups.

Gurnani *et al*. found that in the ketamine and morphine group, the intensity of analgesia was more than in the IV morphine alone users, and patients in the ketamine group did not require the supplemental analgesia administration after initial analgesic drug administration.[31] Moreover, Weinbroum concluded that administration of small dose of ketamine with morphine was significantly more beneficial than use of IV morphine after 30 min in terms of pain reduction intensity and patient's satisfaction.[32] This issue is due to having more half-life of nebulize ketamine compared with IV ketamine and morphine and therefore, the efficacy of nebulization is more, in terms of the duration.[33] Furthermore, it has been stated that ketamine inhalation can significantly reduce various inflammatory responses, and circulatory parameter, such as BP, the central venous pressure, tidal volume, and fraction of inspired oxygen (FIO_2) were improved better compared to ketamine infusion.[34]

However, at the ED, use of morphine is so popular with relatively few reported risk factors and we did not aim to tell that we should stop using morphine, because according to broad studies about the beneficial effects of IV morphine in abrupt pain relief in emergency situation, such as trauma, and necessity of pain reduction in ED patients as soon as possible, we believe that the limited dose of using morphine in adult patients nowadays has been resulted in providing inadequate analgesia,[35] unwanted side effects for administration of morphine in IV route,[5] and the risk of dependency of patients; we have to change the route of analgesia, and also regarding to patient's preference for nebulized route, because of difficult IV access in some circumstances such as adverse psychological aspects or in shock or among drug users that vascular access are not available, it would be a beneficial possible alternate route which has several advantages, including less sedation compared with IV route,[36] alternate route due to the limited access for IV intervention,[37] and better absorption of drugs in the airway approaches.[38,39] However, it should be noted that we did not observe dissociative sedation by nebulized ketamine with morphine. On the other hand, limitation of morphine dose encourages physicians to use co-administration of safe analgesia drugs for ED patients, in especial ketamine, which leads to maintenance of stable hemodynamics and reduction

of the morphine side effects as an opioid (morphine-sparing effect).[40] We believe that the noninvasive nebulized method could be a promising approach in near future if larger studies with various dosages and longer intervention time perform.

At the end, considering patient's satisfaction levels and according to the fact that drug complication in the IV was more than that in the nebulized method and also according to the advanced trauma life support guideline for trauma patients,[41] it has been stated that all the trauma patients should receive the oxygen. We suggest that at the primary survey, if life-threatening situations are not observed, the nebulized ketamine and morphine could be prescribed with oxygen flow. The subsequent studies can be performed to assess the efficacy of nebulized ketamine (without morphine) in pain relief of traumatic patient.

Conclusion

According to the results of this study, although the use of IV morphine has a faster effect on patient's pain reduction in a maximum of 15 min, the use of nebulized morphine and ketamine does not reduce BP and heart rate of patients, and on the other hand, in the long time of maximum 30 min after administration, it has similar effect in controlling and reducing the pain and patient's satisfaction with this method is more than the IV morphine. Furthermore, it seems that nebulized morphine and ketamine can be more effective in reducing the pain in patients with long bone fracture trauma in the long time.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Marx JA, Hockberger RS, Walls RM. Rosen's Emergency Medicine: Concepts and Clinical Practice. 8th ed. Philadelphia, PA: Elsevier/Saunders; 2014. p. 1-510.
2. Paris PM. No pain, no pain. Am J Emerg Med 1989;7:660-2.
3. Fosnocht DE, Swanson ER, Bossart P. Patient expectations for pain medication delivery. Am J Emerg Med 2001;19:399-402.
4. Grant PS. Analgesia delivery in the ED. Am J Emerg Med 2006;24:806-9.
5. Thomas SH. Management of pain in the emergency department. ISRN Emerg Med 2013;2013:1-19.
6. Todd KH, Ducharme J, Choiniere M, Crandall CS, Fosnocht DE, Homel P, *et al.* Pain in the emergency department: Results of the pain and emergency medicine initiative (PEMI) multicenter study. J Pain 2007;8:460-6.
7. Gaakeer MI, van Lieshout JM, Bierens JJ. Pain management in emergency departments: A review of present protocols in the Netherlands. Eur J Emerg Med 2010;17:286-9.
8. Grass JA. Patient-controlled analgesia. Anesth Analgesia 2005;101:S44-61.
9. Lötsch J, Walter C, Parnham MJ, Oertel BG, Geisslinger G. Pharmacokinetics of non-intravenous formulations of fentanyl. Clin Pharmacokinet 2013;52:23-36.
10. Gharaei B, Jafari A, Aghamohammadi H, Kamranmanesh M, Poorzamani M, Elyassi H, *et al.* Opioid-sparing effect of preemptive bolus low-dose ketamine for moderate sedation in opioid abusers undergoing extracorporeal shock wave lithotripsy: A randomized clinical trial. Anesth Analg 2013;116:75-80.
11. Todd KH. A review of current and emerging approaches to pain management in the emergency department. Pain and therapy. 2017;6:193-202.
12. Paqueron X, Lumbroso A, Mergoni P, Aubrun F, Langeron O, Coriat P, *et al.* Is morphine-induced sedation synonymous with analgesia during intravenous morphine titration? Br J Anaesth 2002;89:697-701.
13. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 1993;77:1048-56.
14. Quibell R, Prommer EE, Mihalyo M, Twycross R, Wilcock A. Ketamine*. J Pain Symptom Manage 2011;41:640-9.
15. Green SM, Krauss B. Should I give ketamine i.v. Or i.m.? Ann Emerg Med 2006;48:613-4.
16. Kapfer B, Alfonsi P, Guignard B, Sessler DI, Chauvin M. Nefopam and ketamine comparably enhance postoperative analgesia. Anesth Analg 2005;100:169-74.
17. Alvarez P, Saavedra G, Hernández A, Paeile C, Pelissier T. Synergistic antinociceptive effects of ketamine and morphine in the orofacial capsaicin test in the rat. Anesthesiology 2003;99:969-75.
18. Bossard AE, Guirimand F, Fletcher D, Gaude-Joindreau V, Chauvin M, Bouhassira D, *et al.* Interaction of a combination of morphine and ketamine on the nociceptive flexion reflex in human volunteers. Pain 2002;98:47-57.
19. McLean SA, Domeier RM, DeVore HK, Hill EM, Maio RF, Frederiksen SM, *et al.* The feasibility of pain assessment in the prehospital setting. Prehosp Emerg Care 2004;8:155-61.
20. Lozner AW, Reisner A, Shear ML, Patel S, Connolly J, Shaltis P, *et al.* Pain severity is the key to emergency department patients' preferred frequency of pain assessment. European Journal of Emergency Medicine 2010;17:30-2.
21. Majidinejad S, Esmailian M, Emadi M. Comparison of intravenous ketamine with morphine in pain relief of long bones fractures: A double blind randomized clinical trial. Emerg (Tehran) 2014;2:77-80.
22. Roberts JR, Hedges JR. Roberts and Hedges' Clinical Procedures in Emergency Medicine. Philadelphia: Elsevier Health Sciences; 2013. p. 587.
23. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med 2011;57:449-61.
24. Hung OL, Nelson L. Tintinalli's Emergency Medicine: A Comprehensive Study Guide. New York: McGraw-Hill; 2004. p. 400.
25. Marx J, Walls R, Hockberger R. Rosen's Emergency Medicine-Concepts and Clinical Practice. Philadelphia: Elsevier Health Sciences; 2013. p. 67-82.
26. Hung OL, Nelson L. Tintinalli's Emergency Medicine: A Comprehensive Study Guide. New York: McGraw-Hill; 2004. p. 112.
27. Kissin I, Bright CA, Bradley EL Jr. The effect of ketamine on opioid-induced acute tolerance: Can it explain reduction of opioid consumption with ketamine-opioid analgesic combinations? Anesth Analg 2000;91:1483-8.
28. Angst MS, Koppert W, Pahl I, Clark DJ, Schmelz M. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. Pain 2003;106:49-57.
29. Dickenson AH. NMDA receptor antagonists: Interactions with opioids. Acta Anaesthesiol Scand 1997;41:112-5.
30. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006;1:CD004603.
31. Gurnani A, Sharma PK, Rautela RS, Bhattacharya A. Analgesia for acute musculoskeletal trauma: Low-dose subcutaneous infusion of ketamine. Anaesth Intensive Care 1996;24:32-6.
32. Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. Anesth Analg 2003;96:789-95.
33. Ahuja V, Mitra S, Sarna R. Nebulized ketamine decreases incidence and severity of post-operative sore throat. Indian J Anaesth 2015;59:37-42.
34. Elhefny R, Elsonbaty M, Nassib S, Mansour M. Is this the time to introduce ketamine in acute respiratory distress syndrome? A pilot study. Egypt J Cardiothorac Anesthe 2015;9:23.
35. Bijur PE, Kenny MK, Gallagher EJ. Intravenous morphine at 0.1 mg/kg is not effective for controlling severe acute pain in the majority of patients.

Ann Emerg Med 2005;46:362-7.
36. Bounes V, Ducassé JL, Bona AM, Battefort F, Houze-Cerfon CH, Lauque D, *et al.* Nebulized morphine for analgesia in an emergency setting. J Opioid Manag 2009;5:23-6.
37. Ballas SK, Viscusi ER, Epstein KR. Management of acute chest wall sickle cell pain with nebulized morphine. Am J Hematol 2004;76:190-1.
38. Wolfe TR, Bernstone T. Intranasal drug delivery: An alternative to intravenous administration in selected emergency cases. J Emerg Nurs 2004;30:141-7.
39. Lipworth BJ. Pharmacokinetics of inhaled drugs. Br J Clin Pharmacol 1996;42:697-705.
40. Kurdi MS, Theerth KA, Deva RS. Ketamine: Current applications in anesthesia, pain, and critical care. Anesth Essays Res 2014;8:283-90.
41. ATLS Subcommittee, American College of Surgeons' Committee on Trauma, International ATLS Working Group, Tchorz KM. Advanced trauma life support (ATLS®): The ninth edition. J Trauma Acute Care Surg 2013;74:1363-6.