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Evaluating the analgesic and sedative effects of intravenous ketamine versus morphine administration on relieving long/short bone-fracture pain in the upper/lower limbs; a phase II clinical trial

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Abstract

Introduction: The importance of pain control in patients with limb trauma admitted to emergency departments as well as its complications is among the main concerns in post-emergency care, which contributes to the accelerated improvement of patients' conditions in a significant manner.
Objectives: The present study was to evaluate the analgesic and sedative effects of intravenous (IV) ketamine versus morphine administration on relieving long/short bone-fracture pain in the upper/lower limbs.
Patients and Methods: The present study is as a double-blind randomized clinical trial. For this purpose, the effect of ketamine and morphine were initially examined using IV ketamine and morphine administration, respectively, at the doses of 0.4 and 0.1 mg/kg/IV/10 min in patients, aged 18-65 years with limb trauma, and admitted to hospital emergency departments. Afterward, the duration of the analgesic effect, the amount of pain relief, according to the visual analog scale (VAS) outcomes, and the complications for each drug, including apnea, bradycardia, tachycardia, altered level of consciousness, nausea, vomiting, hypertension/hypotension, seizures and disturbed sleep were compared, and then the preferred method was introduced.
Results: In this study, 120 patients in total, including 60 cases receiving ketamine and 60 individuals receiving morphine, were recruited. The participants' age range was between 19 -70 years. The patients' mean age was 47.04±12.57 years of whom 89 patients (74.2%) were male. The study results indicated that the potency of the low-dose ketamine infusion in relieving pain in patients was comparable to that of morphine.
Conclusion: It was concluded that ketamine could be administered as an alternative to IV morphine to reduce long/short bone-fracture pain in the upper/lower limbs.
Trial Registration: The trial protocol was authorized by the Iranian Registry of Clinical Trials, (identifier: IRCT20170716035105N3; https://en.irct.ir/trial/26628, ethical code: IR.AJUMS.REC.1396.248).

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Introduction

The importance of pain control in patients with limb trauma admitted to emergency departments as well as its complications is among the main concerns in post-emergency care, which also contributes to the accelerated improvement of their conditions in a significant manner. In addition to inducing physical discomfort in patients, pain can lead to complications, such as hypertension, cardiac arrhythmias, heart attacks, urinary retention, increased length of stay in hospital, and treatment costs (1,2). In this sense, fractures are the common causes of severe pain, and pain relief is assumed as the primary concern among patients with emergency conditions. In this regard, physicians need to find drugs having fewer side effects and no risks, such as morphine sulfate, and even provide more rapid-onset pain relief. Selecting and prescribing appropriate and effective analgesics can thus boost the cooperation between patients and physicians, enhance outcome achievement, and bring about higher levels of satisfaction with the quality of services delivered in emergency departments (3). For this purpose, intravenous (IV), oral, and even rectal ketamine has been administered as an analgesic drug in different studies. Ketamine has a wide range of clinical applications even today. Nevertheless, there is little data about the best routes of administration of this drug (4). Considering its strong analgesic effects and minimal respiratory depression, ketamine also leads to low and predictable adverse events (5,6). There is significant evidence that certain cytokines/chemokines are also involved in not only the initiation, but also the persistence of pathologic pain by directly activating nociceptors. Certain

Key point

The importance of effective pain control in patients with limb trauma admitted to emergency departments as well as its complications is among the main concerns in post-emergency care. The present study aimed to evaluate the analgesic and sedative effects of intravenous (IV) ketamine versus morphine administration on relieving fracture pain. The results indicated that the potency of the low-dose ketamine infusion in reducing pain was comparable to that of morphine.

inflammatory cytokines are further found in central sensitization following nerve injury and inflammation, which is associated with the development of contralateral hyperalgesia and allodynia (7). Ketamine is also known as a drug promoting inflammatory homeostasis. Locally, ketamine may interfere with the earlier mediators of primary immunity. It further prevents the exacerbation and extension of local inflammation without blunting the local process and delaying the inflammatory resolution. As well, ketamine prevents the general anti-pro-inflammatory mechanisms to overcome the pro-inflammatory effects. In other words, it is immunomodulatory rather than immunosuppressive (8). Previous studies have thus far revealed that ketamine causes some side effects, such as restlessness, transient apnea (0.8%), nausea and vomiting (8.4%), nightmares (2%), elevated intraocular pressure, and increased intracranial pressure (9, 10). It also increases blood pressure, heart rates, cardiac outputs, skeletal muscle tones, and salivary secretion (11). A previous study reflected on antinociception of metoclopramide, ketamine, or their combinations in mice. This study reported that the combination of ketamine-metoclopramide had a greater effect on relieving pain than ketamine alone (12).

Objectives

Given that ketamine is the main drug, widely administered in sedation in emergency departments, there is a need for further studies on its effectiveness and creation time. Therefore, the present study aimed to evaluate the analgesic and sedative effects of IV ketamine versus morphine administration on relieving long/short bone-fracture pain in the upper and lower limbs.

Patients and Methods

Study design

The present study, as a double-blind randomized clinical trial, was conducted on a statistical population consisting of all patients with limb trauma, aged 18-65 years, and directly admitted to emergency departments. The individuals with a history of allergies to ketamine and morphine, showing the evidence of brain abnormalities, such as hydrocephalus, microcephaly, tumors, increased intracranial pressure, seizures, as well as a history of apnea, respiratory and airway problems, cardiovascular diseases, severe brain trauma, no sedation with a predetermined dose, need for a higher dose, and low levels of satisfaction were excluded.

Accordingly, normal saline serum, serum set, micro-set, a 5 cc syringe (containing ketamine diluted with a vial of distilled water, each cc with 10 mg of ketamine), and a 10 cc syringe (with two vials of distilled water) were provided in the first box, and normal saline, serum set, micro-set, a 5 cc syringe (containing distilled water), and a 10cc syringe (including diluted morphine with two vials of distilled water, each cc with 1 mg of morphine) were put in the second box, along with the drug injection instructions. The recommended or prescribed daily dose plus the method of dealing with possible side effects were also placed secretly in one part of the box, therefore the sample would be taken out of the research project and referred to the supervising physician to treat the complications immediately. The clinical research physician also examined the patients, and their clinical history was obtained.

As well, a nurse randomly selected a box, and the medication was prescribed according to the protocol recorded there, based on the supervision of the emergency physician at a predetermined dose for sedation and relief. Upon prescribing the drug, the clinical research physician began to measure blood pressure and record sedation and relief using the visual analog scale (VAS) at minutes 0, 5, 15, 30, and 60 without knowing how to prescribe the drug and the prescribed dose, according to the examination form, and then recorded them respectively as quantitative and qualitative variables in the relevant tables. Afterward, the physician recorded the onset of sedation and relief by asking the patients, using the same form, about pain relief at certain intervals.

During sedation and relief, the attending physician also examined and recorded the side effects, including nausea, visual disturbance, vomiting, apnea-based pulse rate, breathing, and seizures.

In case of any complications, the patients were excluded from the research and treated properly.

At the end of the procedure, the executing physician was informed about the way of prescribing the drug. The prescribed dose by the physician or the emergency nurse, as well as the patients' case documentation for recording them in the examination form.

The patients' pain severity and recovery status were further determined, according to the VAS outcomes. Pain severity was evaluated from zero to 10, in which zero was defined as analgesia, 1-3 showed mild pain, 4-6 represented moderate pain, and 7-10 was in severe pain (13).

Statistical analysis

The chi-square test and t-test were employed to compare qualitative and quantitative variables in both routes, respectively. The analysis of variance (ANOVA) was also utilized to compare each group in terms of the quantitative data by modifying the confounding variables. The *P* value less than 0.05 was further considered significant. All the data were analyzed using the SPSS statistics software

package (version 24).

Results

In total, 120 patients – 60 cases receiving ketamine and 60 individuals receiving morphine – with the mean age of 47.04 ± 12.57 years (19-70 years old) including 89 men (74.2%) and 31 women (25.8%) were selected (Figure 1). The individuals' mean weight was also 65.68±11.92 (40-90 kg) and the highest frequency of fractures was related to the forearm bone (31.7%) and then leg (22.5%). The study results also indicated that 60% of the cases in the group receiving ketamine had shown some complications, since only 10% of those in the group taking morphine had demonstrated the aforementioned side effects. Besides, no significant relationship was observed between the VAS values, systolic and diastolic blood pressure values, pulse rate, respiratory rate, and oxygen saturation in both groups receiving IV ketamine versus morphine at different times (Tables 1-7).

Discussion

In managing trauma patients, the priority often goes into evaluating the mechanism of injury, hemodynamic parameters, and mental status, while narcotics are typically involved in assessing their levels of consciousness under these conditions, however some patients require constant monitoring (14). These drugs may also have interaction with other drugs; thus, they should be administered with caution (3). In this regard, a large and growing body of literature has thus far shed light on alternative treatments. Analgesics, such as IV, oral, or rectal ketamine, have been accordingly investigated (15).

The present study aimed to evaluate the efficacy and side effects of IV ketamine and morphine administration on relieving and sedating patients suffering from the upper/lower limb fracture pain.

In this line, Ding et al compared the potency of a combination of morphine and ketamine versus high-dose morphine alone in relieving pain in patients with acute pain. They found that using the combined ketamine-morphine was much better in relieving pain, and had even caused analgesia in patients compared with high-dose morphine administration alone (16). In a similar study by Johansson et al, the effect of a combination of low-dose morphine and ketamine had been also compared with morphine alone in terms of relieving patients' pain, however no significant difference had been observed (17). These studies had used a combination of morphine and ketamine and morphine alone.

Their results were consistent with our findings, in which the ketamine alone was more effective than morphine in relieving fracture pain, although some researchers had examined the potency of ketamine and morphine separately.

Similarly, Barkan et al compared the effects of midazolam placebo and midazolam and oral ketamine, for the sedation of 60 children, aged 1-7 years old, during wound healing. They showed that the combination of midazolam

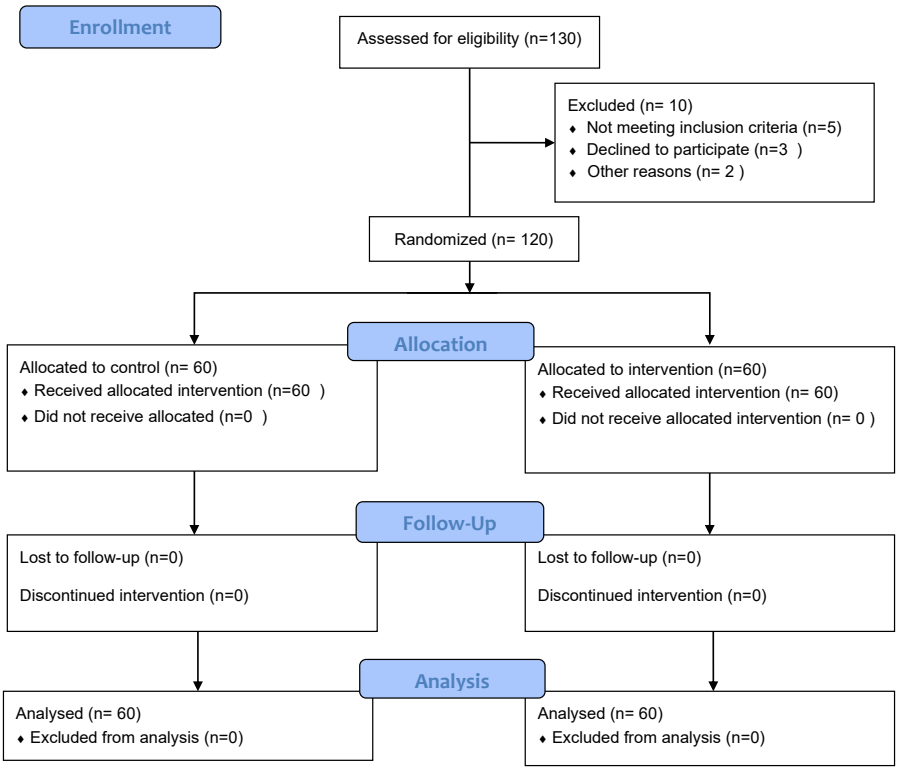

Figure 1. CONSORT Flow Diagram of the Study.

Table 1. Comparison of VAS between ketamine and morphine groups at different times

Time	Group	Number	Mean	Standard deviation	Statistics	*P* value
Before taking the drug	Ketamine	60	8.4833	1.53481	1523.5	0.132
	Morphine	60	7.9333	1.89439		
5 minutes after taking the drug	Ketamine	60	4.6167	2.00078	1562.5	0.207
	Morphine	60	4.2167	2.45703		
15 minutes after taking the drug	Ketamine	60	3.6000	1.79642	1509.5	0.123
	Morphine	60	3.2167	2.53178		
30 minutes after taking the drug	Ketamine	60	2.9833	1.48999	1485.5	0.091
	Morphine	60	2.8500	2.29092		
60 minutes after taking the drug	Ketamine	60	2.8000	1.52716	1520.5	0.130
	Morphine	60	2.7500	2.27458		

Table 2. Comparison of systolic blood pressure between ketamine and morphine groups at different times

Time	Group	Number	Mean	Standard deviation	Statistics	*P* value
Before taking the drug	Ketamine	60	127.6667	15.08357	1719.5	0.663
	Morphine	60	125.9167	13.70054		
5 minutes after taking the drug	Ketamine	60	125.4167	11.72754	1636.5	0.373
	Morphine	60	123.3333	11.74109		
15 minutes after taking the drug	Ketamine	60	124.9167	12.02017	1637.0	0.372
	Morphine	60	122.4000	10.94702		
30 minutes after taking the drug	Ketamine	60	124.5000	11.26341	1595.0	0.263
	Morphine	60	120.1167	17.65401		
60 minutes after taking the drug	Ketamine	60	124.5000	11.26341	1617.0	0.317
	Morphine	60	121.9167	10.49987		

Table 3. Comparison of diastolic blood pressure between ketamine and morphine groups at different times

Time	Group	Number	Mean	Standard deviation	Statistics	*P* value
Before taking the drug	Ketamine	60	74.5833	8.60093	1757.5	0.815
	Morphine	60	74.2500	8.12117		
5 minutes after taking the drug	Ketamine	60	74.5833	8.35097	1644.0	0.395
	Morphine	60	73.3333	9.14417		
15 minutes after taking the drug	Ketamine	60	74.2500	8.17318	1607.5	0.293
	Morphine	60	72.6667	8.70742		
30 minutes after taking the drug	Ketamine	60	74.2500	8.17318	1605.0	0.287
	Morphine	60	72.5833	8.56143		
60 minutes after taking the drug	Ketamine	60	74.2500	8.17318	1605.0	0.287
	Morphine	60	72.5833	8.56143		

and ketamine had caused profound sedative effects (18). The results of a randomized controlled trial had further shown that low-dose ketamine had not produced a greater reduction in numeric rating scale pain scores compared with morphine, for acute pain in emergency departments. However, low-dose ketamine had induced a significant analgesic effect, within five minutes, and had provided a moderate reduction in pain for two hours (19). The results of another randomized controlled trial had also demonstrated that IV low-dose ketamine at 1 mg/kg had provided comparable analgesic effectiveness of IV morphine in the acute treatment of severe painful sickle cell crisis among children in a day care center. However, it was associated with the high incidence of several transient, non-life-threatening, and mild side effects. IV ketamine at 1 mg/kg could be thus a reliable alternative to morphine in the management of severe painful sickle cell crisis, especially in a resource-limited area, where morphine was not readily available (20). These results were in line with the findings of the present study, which had confirmed the improving effects of ketamine at various times. In another investigation, sub-dissociative IV ketamine administered at 0.3 mg/kg had further provided analgesic effectiveness and apparent safety, compared to that of IV morphine for short-term treatment of acute pain in emergency departments (21).

Conclusion

The study results demonstrated that ketamine could be administered as an alternative to morphine administration to reduce the long/short bone-fracture pain in the upper/lower limbs without significant adverse effects.

Limitations of the study

Table 4. Comparison of PR between ketamine and morphine groups at different times

Time	Group	Number	Mean	Standard deviation	Statistics	*P* value
Before taking the drug	Ketamine	60	82.3833	11.33480	1470.0	0.081
	Morphine	60	79.1167	11.79930		
5 minutes after taking the drug	Ketamine	60	77.9333	8.62764	1504.5	0.118
	Morphine	60	75.5167	13.50768		
15 minutes after taking the drug	Ketamine	60	76.9333	7.79149	1531.5	0.156
	Morphine	60	74.4833	11.42921		
30 minutes after taking the drug	Ketamine	60	76.6000	7.13359	1556.0	0.197
	Morphine	60	74.2167	10.83793		
60 minutes after taking the drug	Ketamine	60	76.6167	7.11430	1553.0	0.192
	Morphine	60	74.1833	10.79154		

Table 5. Comparison of RR between ketamine and morphine groups at different times

Time	Group	Number	Mean	Standard deviation	Statistics	*P* value
Before taking the drug	Ketamine	60	19.0000	3.96168	1556.5	0.195
	Morphine	60	17.8833	3.36528		
5 minutes after taking the drug	Ketamine	60	16.8667	2.65832	1795.0	0.979
	Morphine	60	16.8167	2.50756		
15 minutes after taking the drug	Ketamine	60	16.3667	2.09087	1722.5	0.677
	Morphine	60	16.4333	2.06148		
30 minutes after taking the drug	Ketamine	60	16.4333	2.06969	1773.5	0.887
	Morphine	60	16.3667	1.93072		
60 minutes after taking the drug	Ketamine	60	16.4833	2.06251	1785.5	0.938
	Morphine	60	16.3833	1.92302		

Table 6. Comparison of O_2 saturation between ketamine and morphine groups at different times

Time	Group	Number	Mean	Standard deviation	Statistics	*P* value
Before taking the drug	Ketamine	60	98.4667	1.78949	1707.5	0.610
	Morphine	60	98.6333	1.82233		
5 minutes after taking the drug	Ketamine	60	98.6833	1.61026	1736.5	0.725
	Morphine	60	98.6500	1.83030		
15 minutes after taking the drug	Ketamine	60	98.7167	1.61656	1747.5	0.771
	Morphine	60	98.7167	1.68836		
30 minutes after taking the drug	Ketamine	60	98.6833	1.61026	1702.0	0.587
	Morphine	60	98.6833	1.76108		
60 minutes after taking the drug	Ketamine	60	98.6833	1.61026	1708.0	0.611
	Morphine	60	16.3833	1.92302		

Table 7. Comparison of both groups for adverse events

Adverse events	Group	Patients	Number	Ratio	*P* value
Drowsiness	Ketamine	Reported	34	0.566	<0.001
		Not reported	26		
	Morphine	Reported	1	0.016	
		Not reported	59		
Vomiting	Ketamine	Reported	2	0.033	0.156
		Not reported	58		
	Morphine	Reported	0	0.000	
		Not reported	60		
Nausea	Ketamine	Reported	0	0.000	0.156
		Not reported	60		
	Morphine	Reported	5	0.083	
		Not reported	55		

The present study had some limitations; for instance, the patients were not followed up for a long time to determine the adverse effects. The research design also did not allow for repeating the drug administration. Therefore, the effects of repeated drug administration on pain relief were simply examined.

Authors' contribution

MM conceived the manuscript and revised it. HM, MAF, and AKh did the statistical analysis, wrote the manuscript, and prepared the tables and figures. All authors read and approved the manuscript.

Conflicts of interest

The authors declare no competing interests.

Ethical Issues

This study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, also approved this study. As well, the Institutional Ethical Committee at Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, endorsed all the study protocols (IR.AJUMS.REC.1396.248). Accordingly, written informed consent was taken from all participants before any interventions. This study was one part of the thesis for emergency medicine residency fulfilled by Azam Khilghi at this university. The trial protocol was further authorized in the Iranian Registry of Clinical Trials (identifier: IRCT20170716035105N3; https://en.irct.ir/trial/26628). Besides, the ethical issues, including plagiarism, data fabrication, and double publication were completely observed by the authors.

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References

1. Niesters M, Hoitsma E, Sarton E, Aarts L, Dahan A. Offset analgesia in neuropathic pain patients and effect of treatment with morphine and ketamine. Anesthesiology. 2011;115:1063-71. doi: 10.1097/ALN.0b013e31822fd03a.
2. Subramaniam K, Akhouri V, Glazer PA, Rachlin J, Kunze L, Cronin M, et al. Intra- and postoperative very low dose intravenous ketamine infusion does not increase pain relief after major spine surgery in patients with preoperative narcotic analgesic intake. Pain Med. 2011;12:1276-83. doi: 10.1111/j.1526-4637.2011.01144.x.
3. Thomas SH. Management of Pain in the Emergency Department. ISRN Emerg Med. 2013;2013:583132. doi: 10.1155/2013/583132.
4. Grathwohl KW. Does ketamine improve postoperative analgesia? More questions than answers. Pain Med. 2011;12:1135-6. doi: 10.1111/j.1526-4637.2011.01199.x.
5. Gao M, Rejaei D, Liu H. Ketamine use in current clinical practice. Acta Pharmacola Sinica. 2016;37:865-72. doi: 10.1038/aps.2016.5.
6. Jonkman K, van Rijnsoever E, Olofsen E, Aarts L, Sarton E, van Velzen M, et al. Esketamine counters opioid-induced respiratory depression. Br J Anaesth. 2018;120:1117-27. doi: 10.1016/j.bja.2018.02.021.
7. Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin. 2007;45:27-37. doi: 10.1097/AIA.0b013e318034194e.
8. De Kock M, Loix S, Lavand'homme P. Ketamine and peripheral inflammation. CNS Neurosci Ther. 2013;19:403-10. doi: 10.1111/cns.12104.
9. Marland S, Ellerton J, Andolfatto G, Strapazzon G, Thomassen O, Brandner B, et al. Ketamine: use in anesthesia. CNS Neurosci Ther. 2013; 19:381-9. doi: 10.1111/cns.12072.
10. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, et al. Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined with a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). Int J Neuropsychopharmacol. 2019;22:616-30. doi: 10.1093/ijnp/pyz039.
11. Venkatesh AK, Savage D, Sandefur B, Bernard KR, Rothenberg C, Schuur JD. Systematic review of emergency medicine clinical practice guidelines: Implications for research and policy. PLoS One. 2017;12: e0178456. doi: 10.1371/journal.pone.0178456.
12. Mohammad FK, Al-Baggou B, Naser AS. Antinociception by metoclopramide, ketamine and their combinations in mice. Pharmacol Rep. 2012; 64:299-304. doi: 10.1016/s1734-1140(12)70768-5.
13. Wasiak J, Mahar PD, McGuinness SK, Spinks A, Danilla S, Cleland H, et al. Intravenous lidocaine for the treatment of background or procedural burn pain. Cochrane Database Syst Rev. 2014;2014:CD005622. doi: 10.1002/14651858.CD005622.pub4.
14. Vella-Brincat J, Macleod AD. Adverse effects of opioids on the central nervous systems of palliative care patients. J Pain Palliat Care Pharmacother. 2007; 21:15-25.
15. Balzer N, McLeod SL, Walsh C, Grewal K. Low-dose Ketamine For Acute Pain Control in the Emergency Department: A Systematic Review and Meta-analysis. Acad Emerg Med. 2021;28:444-454. doi: 10.1111/acem.14159.
16. Ding X, Jin S, Niu X, Wang T, Zhao X, Ren H, et al. Morphine with adjuvant ketamine versus higher dose of morphine alone for acute pain: a meta-analysis. Int J Clin Exp Med. 2014;7:2504-10.
17. Johansson P, Kongstad P, Johansson A. The effect of combined treatment with morphine sulphate and low-dose ketamine in a prehospital setting. Scand J Trauma Resusc Emerg Med. 2009;17:61. doi: 10.1186/1757-7241-17-61.
18. Barkan S, Breitbart R, Brenner-Zada G, Feldon M, Assa A, Toledano M, et al. A double-blind, randomised, placebo-controlled trial of oral midazolam plus oral ketamine for sedation of children during laceration repair. Emerg Med J. 2014;31:649-53. doi: 10.1136/emermed-2012-202189.
19. Miller JP, Schauer SG, Ganem VJ, Bebarta VS. Low-dose ketamine vs morphine for acute pain in the ED: a randomized controlled trial. Am J Emerg Med. 2015;33:402-8. doi: 10.1016/j.ajem.2014.12.058.
20. Lubega FA, DeSilva MS, Munube D, Nkwine R, Tumukunde J, Agaba PK, et al. Low dose ketamine versus morphine for acute severe vaso occlusive pain in children: a randomized controlled trial. Scand J Pain. 2018;18:19-27. doi: 10.1515/sjpain-2017-0140.
21. Motov S, Rockoff B, Cohen V, Pushkar I, Likourezos A, McKay C, et al. Intravenous Subdissociative-Dose Ketamine Versus Morphine for Analgesia in the Emergency Department: A Randomized Controlled Trial. Ann Emerg Med. 2015;66:222-229.e1. doi: 10.1016/j.annemergmed.2015.03.004.