American Journal of Emergency Medicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Can low-dose of ketamine reduce the need for morphine in renal colic? A double-blind randomized clinical trial☆

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ARTICLE INFO

Article history:
Received 27 July 2017
Received in revised form 8 August 2017
Accepted 12 August 2017
Available online xxxx

Keywords:
Pain
Renal colic
Morphine
Ketamine

ABSTRACT

Background: The combination of morphine with low doses of ketamine (MK) has been utilized in the Emergency Department (ED) compared with morphine and placebo (MP) for the treatment of acute pain in few studies. The purpose of this study was to compare the effect of MP with MK for the treatment of severe pain with renal colic of patients who had been referred to the ED.
Methods: This study is a double blind randomized clinical trial on patients with severe renal colic pain who were referred to the ED. Patients were enrolled with pain severity of at least 6 of the 10 visual analogue scales (VAS). Patients were divided into two groups: Morphine 0.1 mg/kg and placebo (MP group) and morphine 0.1 mg/kg and ketamine 0.15 mg/kg (MK group). Pain of patients was studied in 10, 30, 60, 90, and 120 min after injection.
Results: Totally, 106 patients were enrolled in study groups. Assessment of the average pain during 120 min at 10 and 30 min after the start in the drug, MK group was significantly lower than the MP group ($p = 0.019$ and $p = 0.003$ respectively).
Conclusion: Given that combinations of morphine with low doses of ketamine in patients with renal colic pain causes more pain and morphine consumption reduction then this combination is suggested as an alternative treatment that could be utilized in patients with renal colic.

1. Introduction

Renal stone (urolithiasis) is a very common disease. Renal colic as acute pain may be developed by different causes including obstruction of urinary flow or increased pressure on the walls of urinary tract as a result of the stones, muscle spasms, inflammatory reaction around stones or external pressure ducts, and is known as the worst pain ever experienced by the patient [1-3]. The use of effective analgesics such as non-steroidal drugs (NSAIDS), opioids, or combination of drugs (anti-inflammatory and anti-spasmodic) plays an essential role in the treatment of this disease [4]. Opioids are often used in the management of renal colic pain. Advantages of opioids include low cost, good effects, and the possibility of titration while their disadvantages include sedation, respiratory depression, hypotension, nausea, vomiting, dizziness, and drug dependence [5].

Ketamine is a noncompetitive antagonist of N-Methyl-D-aspartate receptor. NMDA receptors play essential roles in pain perception and have led to studies in this field. In various studies of NMDA receptor inhibitors, it has been demonstrated that these inhibitors stimulate the receptor for opioids and opioid effects have been enhanced [6,7]. A limited number of studies have been carried out on the effects of low-dose ketamine with morphine in the ED. Morphine and ketamine (MK) compared with morphine and placebo (MP) for the treatment of severe pain and different results are obtained [8-10]. According to the present

☆ The authors have no financial or other conflicts of interest related to the submission.Registration number: (IRCT201109297667N1).

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[3] S.A, B.M and N.B: Data collection (visiting the patients, ultrasonography).
[4] M.M, P.H: Quality control.
[5] M.R and D.F: Writing the article (search, data bank, primary manuscript).
[6] M.R, D.F, and M.M: Analysis by SPSS and finalizing the article.
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http://dx.doi.org/10.1016/j.ajem.2017.08.026
0735-6757/© 2017 Published by Elsevier Inc.

search, no study related to the MK combination compared to MP in pain control in patients with renal colic pain in the ED has been carried out.

The purpose of this study was to compare the analgesic of MP with MK, dosage and side effects of morphine consumption in patients with renal colic who has been referred to the ED.

2. Materials and methods

2.1. Study design, setting, and selection of participants

This is a double-blind randomized clinical trial on patients with severe pain and acute renal colic in 2014, who had been referred to the ED of a large academic teaching hospital with >50,000 census annually in Tehran, Iran.

This study was carried out according to the Helsinki Declaration on ethical principles for research involving human subjects, and with the approval of the Ethics in Clinical Research Committee and Institutional Review Board of the Faculty of Medical Sciences, University of Teheran. This study is registered with the International Clinical Trials Registry Platform. (NO: IRCT201109297667N1) Informed consent was also obtained from each patient.

Inclusion criteria included: age between 18 and 65 years, having been previously diagnosed with nephrolithiasis or urinary stone by a urologist, a visual analogue scale of pain intensity of at least 6 out of 10 (VAS), stable vital signs include systolic blood pressure equal to or higher than 90 mmHg, heart rate between 60 and 120 per minute, respiratory rate between 8 and 22 per minute, oxygen saturation greater than or equal to 92%, lack of the narcotic analgesics consumption before admission, no history of liver disease, kidney disease, chronic respiratory, cardiovascular disorders, known blood coagulation, lack of chronic mental illness, and the use of psychiatric drugs. Patients who did not want to participate in the study, had addiction to drugs and psychotropic substances, had known hypersensitivity to morphine or ketamine, and inability to understand the concept of VAS were excluded from this study.

2.2. Intervention

Patients who met the inclusion criteria and had no exclusion criteria were randomly divided into two groups. MP group received standard dose of 0.1 mg/kg morphine plus placebo (normal saline) and MK group received the standard dose of morphine with ketamine. Ketamine (Injection as HCI: 50 mg/ml (10 ml, ROTEXMEDICA, Germany)) was prepared in 5 cm^3 syringe with a concentration of 10 mg/ml and 0.15 mg/kg and was then administered. For all patients, ketamine was intravenously injected while morphine injection continued until a pain score of 3 or less was achieved on the VAS scale or expiration of 120 min or 30 mg morphine consumption. Ketamine and placebo were injected by emergency nurses who did not participate in data collection and evaluation of patients in single syringes with the same appearance. Information of patients was recorded before prescribing medication and within 10, 30, 60, 90, and 120 min after drug administration. Data collection and evaluation of patients was carried out with emergency physicians who were not aware of the prescribed medications. Visual Analogue Scale (VAS) was utilized for measuring pain that has color grading from 0 to 10. No pain had a score of zero and a score of 10 indicate worst pain. Patient vital signs including blood pressure, pulse and respiratory rate and oxygen saturation by pulse oximetry (SpO2) were recorded. Hemodynamic disorder was considered including systolic blood pressure drop below 90 mmHg or reduction of 30 mm initial blood pressure. In this study, apnea is defined as not breathing, and reduction in respiratory rate <8% per minutes or oxygen saturation percent to <90%. Patient and assessor satisfaction were measured in terms of pain on a Likert scale (poor, average, good and excellent).

2.3. The sample size

In order to achieve an error <5% and study power of 90%, the number of samples in each group was estimated to be almost 35 people and the number of patients in each group was considered as 42 by accounting for 20% addition of possible withdrawal patients for any reason. Finally, 106 patients were analyzed.

2.4. Data analysis

SPSS 18 software was utilized for analysis. Descriptive variables have been reported as frequency and frequency percentage while quantitative variables have been reported as the mean with confidence range of 95%. The average pain intensity at different times were compared using independent *t*-test. Fisher Exact test was utilized to compare treatment adverse effects. <5% was considered as significant. Intention to treat analysis was done.

3. Results

Finally, 53 patients were enrolled in each group (Fig. 1).

A total of 106 patients, 71 patients (75–58 95% CI, 67%) were men and 35 of them were women. The average age of 40.92 years (42.1–39.61, CI 95%) was obtained. The mean age of the patients was similar (49.42 versus 51.58 years in morphine group (MP) versus the morphine group with ketamine (MK) ($p = 0.7$)). With respect to age, 26% of patients were between the age of 30–35 years, 15% of them were between 36 and 41 years, while 28% were between the age of 42–47 years, and subsequently 31% were 47 years or older. As a result, most respondents were 47 years old or older than.

Analysis revealed that the average pain score of patients between the two groups which were recorded at 0, 60, 90 and 120 min had no significant difference. At the time of 10 and 30 min after starting the medication, the mean pain was lower in the MK group ($p = 0.019$ and $p = 0.003$ respectively), furthermore in MP group, the morphine injection time at 10 and 30 min after the drug was started was higher ($p = 0.005$ and $p = 0.02$ respectively). In fact, for MK group, the dose of morphine was used for 12 times while for MP group, a second dose of morphine was used for 28 times which was significantly lower in MK group ($p = 0.01$). Results are presented in Table 1.

As can be seen in Table 2, side effects such as nausea, vomiting, respiratory depression and hypotension were significantly more common in patients of MP group, while nystagmus complications were more common in patients in MK group.

Assessor satisfaction and patient satisfaction were evaluated in 30 and 120 min after the relief and the reduction of pain in both groups. According to the data analysis, patient and assessor satisfaction after 30 min was significantly higher in MK group, nevertheless, there was no difference in satisfaction in 120 min.

4. Discussion

In the present study, it was determined that combination of morphine with low doses of ketamine compared with morphine administration in order to control pain and reduce pain in patients with renal colic caused a further decrease in morphine consumption.

The combination of morphine and low-dose ketamine on pain management in emergency patients compared to the treatment with morphine alone in the last few years has been investigated in several studies. In this study, this combination was studied in patients with renal colic pain which is a common cause of reference to the ED and it was discovered that during the first 30 min after treatment, pain reduction was significantly higher in the MK group and the reuse of morphine in order to control pain during this period was also significantly reduced pain in this group. The study also indicated that 30 min after the end of

Please cite this article as: Abbasi S, et al, Can low-dose of ketamine reduce the need for morphine in renal colic? A double-blind randomized clinical trial, American Journal of Emergency Medicine (2017), http://dx.doi.org/10.1016/j.ajem.2017.08.026