Original Contribution

Comparison of intranasal ketamine versus IV morphine in reducing pain in patients with renal colic

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Keywords: Ketamine, Morphine, VAS, Intranasal

1. Introduction

Patients’ pain management in the emergency department (ED) is very important and it is usually provided by intravenous (IV) narcotics [1,2]. Intranasal (IN) access is another option which contrary to IV route, is much less invasive and time consuming. One of the most popular drug used IN, is ketamine. IN ketamine is an effective analgesic with minimal cardiovascular impact [2,3]. Its analgesic dose is less than its sedative dose. It has different routes of administration (IM, IV, IN, SC) [4].

Ketamine, structurally similar to Phencyclidine (PCP), non-competitively blocks N-Methyl-D-Aspartate (NMDA) receptors. It is said that the function on these receptors are responsible for the analgesic and behavioral effects of ketamine [5,6]. Although its main mechanism of action is antagonism of NMDA receptor, it also interacts with opioid receptors, monoamine, cholinergic and adrenoceptor systems as well as having local anesthetic effects. It is believed that ketamine’s immediate analgesic effects are mediated predominantly by a combination of opioid function on these receptors and antinociception [7,8]. Ketamine has a sympathomimetic activity, thus it will result in tachycardia, hypertension, high myocardial and cerebral oxygen consumption, elevated cerebral thomimetic activity, thus it will result in tachycardia, hypertension, high myocardial and cerebral oxygen consumption, elevated cerebral

2. Methods

A randomized double-blind controlled trial was performed in 53 patients with renal colic recruited from the emergency department (ED) in 2015. Finally, 40 patients were enrolled in this study. Patients in the ketamine group received IN ketamine 1 mg/kg and IV placebo while patients in the control group received IV morphine 0.1 mg/kg and IN placebo. Our goal was to assess visual analogue scale (VAS) changes between the 2 groups. Patients’ VAS scores were recorded before and 5, 15, 30 min after drug injection.

Results: Before drug administration, the mean ± SD VAS score was 7.40 ± 1.18 in the morphine group (group A) and 8.35 ± 1.30 in the ketamine group (group B) (P-value = 0.021). After adjustment by the appropriate analysis, the mean ± SD VAS score in group (A) and (B) at 5 min were (6.07 ± 0.47 vs 6.87 ± 0.47; mean difference = 0.79, 95% confidence interval (CI) −1.48 to 0.97) (P-value = 0.025), at 15 and 30 min, the mean ± SD VAS score in group (A) and (B) were (5.24 ± 0.49 vs 5.60 ± 0.49; mean difference = 0.36, 95% CI −1.08 to 0.34) and (4.02 ± 0.59 vs 4.17 ± 0.59; mean difference = 0.15, 95% CI −0.71 to 0.701) (P-value = 0.304 and 0.719) respectively.

Conclusions: IN ketamine may be effective in decreasing pain in renal colic.
There are many studies which demonstrate the efficacy of IN ketamine in the treatment of severe acute pain.

The dose of 1.5 mg/kg IN ketamine was studied as an acute pain reliever and it was showed that it could enhance postoperative analgesia after endoscopic nasal surgery [9]. In another research, it was found that 7.5 mg IN morphine and 30 mg IN ketamine, delivered by nasal spray devices, provided analgesia of about 5 mg IV morphine after molar extraction model with acute moderate-to-severe pain [10].

The analgesic effect of 0.5 mg/kg IN ketamine was evaluated in 44 patients, coming to ED in a trauma center, suffering acute pain (Visual Analogue Scale (VAS) >5). Conclusion was that IN ketamine might provide rapid and clinically significant analgesia in ED patients [2].

Since there has been no similar study in pain management in renal colic, this study compares the analgesic effect of IN ketamine versus IV morphine in patients suffering renal stones.

2. Materials and methods

2.1. Participants

The study was approved by the ethics committee of Tehran University of medical sciences and it was registered in www.irct.ir with the trial number of IRCT201412208872N8. All patients were required to read informed consent letter and signed it if they accepted to participate in our study. We conducted a prospective, randomized, double-blind and placebo-controlled study (block randomization with block sizes of 4) in patients with renal colic recruited from EDs of Shariati and Imam Khomeini Hospitals, two tertiary referral center, from January 2015 to March 2015. Eligible patients were older than 15 years’ old who presented to the ED because of renal colic pain and they did not need any surgical intervention for their urolithiasis. The diagnosis was confirmed by ultrasound evidence of renal stone and hematuria in urine analysis. We excluded patients with opioid addiction and prior use of analgesics, pregnancy, history of ketamine or morphine hypersensitivity, nasal occlusion, systolic blood pressure (SBP) >180 or SBP <90 mm Hg, respiratory distress, altered level of consciousness and anyone with no cooperation. The treating emergency physician confirmed diagnosis and contacted the chief investigator. Subjects were randomly divided into two groups of 20 each: a morphine group (A) and a ketamine group (B). Each patient had a code in block randomization, and only the chief investigator and the triage nurse were aware of the assignment and patient’s group. The specified drug and dose were provided by the triage nurse based on the code and it was injected to the patient by the treating emergency physician who was blinded to the study.

2.2. Drug administration

All patients were interviewed and the method of drug administration and VAS (where 10 represented the worst imaginable pain and 0 was pain-free) were discussed to them. During drug administration and follow-up, patients were monitored with standard monitoring included ECG, pulse oximetry and non-invasive blood pressure cuff. Demographic data including age, sex, past history of renal stone, need for rescue analgesia and any side effects (e.g., nausea, dizziness, and hypotension or emergence reactions) were collected through a questionnaire by the emergency physician. We chose 1 mg/kg IN ketamine based on its wide range of IN administration mentioned in different studies [2,9]. In group A 0.1 mg/kg diluted IV morphine + IN placebo and in group B 1 mg/kg IN ketamine + IV placebo was administered. Morphine was used as IV bolus.

2.3. Primary and secondary endpoints

Patients were requested to express their degree of pain using the VAS score, before, 5, 15 and 30 min after initiation of injection. In case of failure and no decrease in VAS scores in either group after 30 min, fentanyl was administered. The rate of fentanyl infusion was 1–2 μg/kg administered every 5 min and titrated to the effect. Our primary endpoint was changes in VAS score. Adverse reactions and the need for rescue analgesia were our secondary endpoints. The treating emergency physician performed the outcome assessments and monitored the adverse events objectively.

2.4. Statistical analysis and sample size calculation

In order to produce 13 mm difference in the mean VAS score, which is considered a clinically significant change in pain score [2,10], with Power of 80%, CI of 95% and SD of 1.1, a sample size of 20 per treatment group was calculated.

All data were analyzed using SPSS V.22 software. In order to evaluate the normal distribution of quantitative data such as VAS score, we conducted a Kolmogorov–Smirnov (KS) test. Analytical statistical tests included the unpaired, two-tailed t-test for continuous normally distributed data. Because baseline VAS score had significant difference between the two groups before drug administration, we conducted general linear model (multivariate) ANCOVA analysis (analysis of Covariance) on both sample groups in order to adjust the mentioned difference. We used a repeated measures ANCOVA to adjust for both baseline differences and for the repeated measures analysis to adjust for multiple observations within the same individual. All the descriptive data are given as mean ± SD. Variances of the two groups at 5, 15 and 30 min were equal by Levene’s test (P-value = 0.459, 0.860, 0.442 respectively). The chi-square and Fisher’s exact tests were used to compare proportions of the qualitative variables. Repeated measure ANOVA was used to determine the difference within each group. The level of significance was 0.05. All data had normal distribution between the two groups.

Table 1

Demographic feature of study groups.

<table>
<thead>
<tr>
<th></th>
<th>Morphine group (N = 20)</th>
<th>Ketamine group (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>3 (15.0%)</td>
<td>8 (40.0%)</td>
</tr>
<tr>
<td>Men</td>
<td>17 (85.0%)</td>
<td>12 (60.0%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>34.75 ± 11.71</td>
<td>39.25 ± 10.75</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.14 ± 10.32</td>
<td>74.10 ± 9.58</td>
</tr>
<tr>
<td>History of renal stone</td>
<td>16 (80%)</td>
<td>12 (60%)</td>
</tr>
</tbody>
</table>

Fig. 1. Side effects distribution in the 2 groups.
3. Results

During the study period 53 patients were diagnosed with renal colic and 13 patients were excluded: five patients had respiratory distress, four had SBP below 90 mm Hg, three had morphine hypersensitivity and one had no cooperation. The remaining 40 patients were randomly divided into two groups of 20 each (Fig. 1). The mean age ranges of group A and B were similar (34.75 ± 11.71 years and 39.25 ± 10.75 years, respectively). The morphine group included 17 men and 3 women and the ketamine group included 12 men and 8 women. The mean weight ranges of group A and B were similar (76.14 ± 10.32 kg and 74.10 ± 9.98 kg respectively). Eighty percent of patients in group A and 60% of patients in group B had the history of renal stone. There were no significant differences in the baseline participant characteristics. Data are shown in Table 1.

At baseline the mean ± SD VAS scores were 7.40 ± 1.18 in group A and 8.35 ± 1.30 in group B (P-value = 0.021). Comparison of VAS scores before adjustment is shown in Table 2. In order to adjust the significant difference at baseline, we conducted ANCOVA analysis. The results after adjustment are shown in Table 3. These results showed that at 5 min after drug administration there was significant difference in the mean VAS score and morphine was more effective than ketamine. At 15 and 30 min there was no significant difference between the two groups. The VAS score of 7 patients in group A and 5 patients in group B remained the same after 30 min so fentanyl infusion was started (P-value = 0.37). Using repeated measures ANOVA, within subject groups, mean VAS pain score reduction along frequent intervals after both morphine and ketamine administration had significant difference (P-value = 0.000), thus ketamine also caused significant pain reduction along time.

Comparing side effects, hypotension was seen in 8 patients all in group A, and emergence phenomenon in 6 patients all in group B. All patients had at least one side effect (data shown in Fig. 2).

4. Discussion

Renal stone is one of the most common presentations in EDs and affects near 5–15% of the population all around the world [1]. Pain management in these patients is necessary and most drugs used for this purpose are NSAIDs or narcotics with IM, IV or oral administration. Ketamine is most commonly used as analgesic in acute pain control by different routes of administration including IN [11]. A pharmacokinetic study in healthy volunteers calculated the bioavailability of IN ketamine 45%, peak plasma level was seen in <30 min and terminal half-life was around 2 h [11]. Ketamine can induce apnea, laryngospasm, vomiting, elevated intracranial pressure and emergence phenomenon. In contrast morphine starts its analgesic effect in <10 min with peak plasma level of 20 min and its duration of action is near 4 h. Its usual side effects include: hypotension, nausea, vomiting, respiratory depression and altered mental status [5]. The use of opioid analgesia can suppress respiratory system especially when used in non-monitored bed. Respiratory depression and deep sedation have been regarded as the main causes of withholding opioid analgesia [2].

Based on the results of previous studies [9,10], we used the dose of 1 mg/kg IN ketamine in group B via mucosal atomization device. Our study shows that IV morphine provides more considerable analgesic state in patients with renal colic at 5 min after drug administration. Comparing VAS scores at 15 and 30 min, in the two groups, no significant difference was found. Our results concluded that IN ketamine 1 mg/kg could be effective in reducing renal colic pain but with a delay of 10 min.

Huge et al. showed that IN ketamine’s activity in pain reduction would last for about 3 h [12]. Carr et al. shown that IN ketamine would reach a detectable blood level after 2 min, with a maximum concentration at almost 30 min. Both of these studies showed that IN ketamine was effective and its adverse effects were minor and transient.

Successful postoperative pain management trial of IN ketamine was observed in a precedent study. This study tested 10–30 mg of IN ketamine in acute postoperative pain, molar extraction. Patients reported rapid pain relief with no significant side effects. Integrated pain relief over 1 and 3 h after drug administration was significantly better for ketamine than placebo [13].

Elia and Tramer in 2005 reviewed different modalities of studies working on varying routes of ketamine administration and dosing regimens. They found no clinically significant effect on pain scores (VAS) for 48 h after surgery. This study showed that ketamine could decrease opioid dose with no change in opioid-related adverse effects [14].

5. Limitations of the study

One limitation of our study was that we were not able to determine the plasma level of ketamine to control its analgesic effect. Our sample size was not sufficient to detect the exact drugs’ effects and adverse events. Further clinical trials with larger sample sizes and longer follow-up should therefore be performed to identify adverse events. The other limitation was that we did not choose one-time point as our primary outcome, rather we decided to follow VAS score changes along the study over 30 min. Our patient population was homogenous in the 2 centers, thus there may be issues with external validity.

6. Conclusion

This study shows that IN ketamine might be effective in alleviating pain in patients with renal colic. Adverse effects were seen in both

### Table 2

<table>
<thead>
<tr>
<th>VAS 0 min</th>
<th>VAS 5 min</th>
<th>VAS 15 min</th>
<th>VAS 30 min</th>
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<tbody>
<tr>
<td>7.40 ± 1.18</td>
<td>5.60 ± 1.46</td>
<td>4.75 ± 1.90</td>
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<td>8.35 ± 1.30</td>
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<tr>
<td>-0.95</td>
<td>-1.75</td>
<td>-1.35</td>
<td>-1.10</td>
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<tr>
<td>-1.75</td>
<td>-2.77</td>
<td>-2.40</td>
<td>-2.22</td>
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### Table 3

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<tbody>
<tr>
<td>7.40 ± 1.18</td>
<td>6.07 ± 0.47</td>
<td>5.24 ± 0.49</td>
<td>4.02 ± 0.59</td>
</tr>
<tr>
<td>8.35 ± 1.30</td>
<td>6.87 ± 0.47</td>
<td>5.60 ± 0.49</td>
<td>4.17 ± 0.59</td>
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<tr>
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<td>-0.79</td>
<td>-0.36</td>
<td>-0.15</td>
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<tr>
<td>-1.75</td>
<td>-1.08</td>
<td>-1.02</td>
<td>-0.29</td>
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Mean value of pain scores in the two groups done by ANCOVA analysis.
groups. The need for rescue analgesia in ketamine group was less than in morphine group but this observed difference was not statistically significant.

**Funding source**

We have no funding source.

**Author's contributions**

Farnia M; study design, Jalali R; data gathering and study design, Vahidi E; data analysis, Seyedhosseini J; drafting, Momeni M; data gathering and drafting, Saeedi M; critical revision.

**References**