Original Article

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A comparative study of intranasal desmopressin and intranasal ketamine for pain management in renal colic patients: A randomized double-blind clinical trial

Running head: Intranasal ketamine in renal colic

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Abstract

Backgrounds and aims: Urolithiasis is one of the most common urological diseases worldwide, commonly presenting as renal colic, requiring analgesic treatment due to the severe pain it causes the patients. This study aimed to compare the efficacy of Ketamine and Desmopressin in the pain management of renal colic patients.

Methods: This double-blind, randomized clinical trial study was conducted on renal colic patients referred to emergency departments (ED) from June 2021 to July 2022. Patients were randomly assigned to three groups. In the Desmopressin group, patients were treated with intranasal desmopressin and intravenous ketorolac. The ketamine group was treated with intranasal ketamine and ketorolac. The placebo group received ketorolac and an intranasal placebo. Vital signs were evaluated at baseline and 60 minutes and pain scores were assessed at baseline, 10, 30, and 60 minutes after the treatment.

Results: 135 patients enrolled, the mean (standard deviation) of age was 44.1 ± 11.4, and 82 (60.7%) were men. The mean VAS scores were significantly lower at 10, 30, and 60 minutes in ketamine (5.6±1.2, 3.0±1.1, 0.9±0.9) compared to the placebo (8.2±1.1, 5.1±2.0, 2.3±2.6) and desmopressin (6.7±1.8, 4.2±2.2, 1.3±1.4) groups (P<0.05). Although patients in the desmopressin group had lower mean pain scores than the placebo group at 10, 30, and 60 minutes, this difference was only significant at 10 minutes after the intervention (P<0.05). No significant differences were found regarding vital signs 60 minutes after the treatment.

Conclusion: Ketamine showed more favorable analgesic effects in renal colic patients than desmopressin, although desmopressin showed promising efficacy in the first minutes of the treatments.

Keywords: Emergency department, Ketamine, Desmopressin, Intranasal, Pain.
Introduction

Urolithiasis is one of the most common urological diseases worldwide, with a 1-13% prevalence in different regions (1, 2). Urolithiasis commonly presents as renal colic to the emergency department (ED) with unbearable pain. Millions of patients worldwide refer to the ED annually with renal colic. The rate of renal colic presentations at ED has been reported to be 6.7 to 27.9 per 1000 ED visits (3). Renal colic is a severe pain in the flank or abdomen, generally radiating to the groin or genital area, caused by obstructions in the urinary tract. The leading cause of renal colic is urinary flow obstruction and increased pressure proximal to this obstacle (1-3). Although this pain is one of the most intense pains patients can experience, most urinary tract stones are eliminated spontaneously and do not require surgical intervention. Therefore, effective analgesic treatment is a primary goal in managing renal colic (4-6).

Many therapeutic agents are prescribed for pain management in patients with renal colic, including opioid and non-opioid drugs. The commonly used non-opioid drugs are NSAIDs, corticosteroids, and alpha-blockers. NSAIDs and opioids are recommended as the first and second lines of treatment by recent guidelines (4, 7). However, these drugs have many side effects and contraindications that require investigation of alternative and adjuvant drugs (7, 8).

Ketamine is an anesthetic agent whose analgesic effects have recently been studied for renal colic. Studies have indicated intranasal and injectable ketamine to be effective in treating severe acute pain and renal colic, particularly compared with opioids (7, 9). The primary mechanism of action of ketamine is through the antagonistic effect on the n-methyl-d-aspartate (NMDA) receptors. However, the analgesic effects have mainly been attributed to interactions with opioid receptors (10).

Desmopressin is another drug recommended for managing renal colic. Desmopressin is an analog of an antidiuretic hormone that has shown favorable effects with few side effects for treating renal colic in both sublingual and intranasal forms (4, 5). Renal colic results from acute dilatation of urinary tracts along with spasms of smooth muscles at the site of obstruction. This dilation leads to the release of prostaglandin E2, which causes diuresis by dilating the afferent arterioles and leads to further dilation of urinary tracts (11). The marked antidiuretic effect of desmopressin is likely responsible for its efficacy in treating renal colic.
Furthermore, desmopressin suppresses the contraction of the renal pelvis's smooth muscle fibers, which might help pain management in renal colic. Likewise, stimulation of beta-endorphin release can be effective in the analgesic effects of this drug; However, the mechanisms effective in relieving the pain of renal colic by this drug are still unknown (12, 13).

Studies have indicated that patients prefer analgesics with immediate effects and painless administration routes. Common administration routes of analgesics, including oral, intravenous, and intramuscular, have limitations. For instance, oral administration is not common and routine for nil per os (NPO) patients. Intravenous injection requires the insertion of the peripheral venous catheter by emergency personnel. Intramuscular injection, in addition to pain at the injection site, is associated with delayed onset of the drug action and is challenging in obese people. The intranasal administration route is favored due to its painlessness, fewer adverse effects, and sufficient effectiveness (9, 14, 15). According to the necessity of investigating alternative and adjunctive treatments for pain relief in renal colic patients and challenges common administration routes of analgesics, in the present clinical trial study, we investigated the analgesic effect of intranasal ketamine and desmopressin in renal colic patients referred to the emergency department.

Methods

Study design
This double-blind, randomized clinical trial study was conducted in Al-Zahra and Kashani hospitals' ED in Isfahan from June 2021 to July 2022. This study was approved by the Research Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1400.191) and registered in the Iranian Registry of Clinical Trial (IRCT; ID: IRCT20190422043340N12)

Study population
Inclusion criteria included renal colic pain (flank or abdominal pain with or without radiating to the groin and genitalia and a previous history of urolithiasis) diagnosed by the emergency physician, having severe pain (Visual Analogue Scale (VAS)>5), with or without accompanying symptoms and signs (i.e., dysuria,
dribbling, and costovertebral angle tenderness) or laboratory findings in favor of diagnosis such as hematuria, and aged 18 to 65 years. The diagnosis of renal colic was considered based on history, physical examination, and urine analysis. After that, depending on the need, the presence of renal stones was confirmed in all patients using ultrasound or computed tomography. Exclusion criteria included having a history of hypertension, cardiac diseases, peptic ulcer or active gastrointestinal bleeding, chronic hepatic or renal failure, drug reaction, being pregnant or lactating, unstable vital signs (systolic blood pressure less than 90 or less great than 180 mmHg or heart rate less than 50 and greater than 150 beats per minute), receiving analgesics in the last 24 hours of hospitalization, any drug reaction, or loss of consciousness during the survey, and the final diagnosis of other than renal colic.

**Randomization and blinding**

Patients were randomly assigned to desmopressin (A), ketamine (B), or control group (C) using a computer-generated random number table with 4 blocks. Medications were prepared daily by an ED nurse based on patients' codes and labeled A, B, or C (blind to the researcher). The emergency physician who was blinded to the type of agents used a 1-cc syringe in each group to spray the prepared medication (0.5 cc in each nostril of the nose) by intranasal Mucosal Atomization Device (MAD; Teleflex Medical, Morrisville, USA). All the patients were also blinded to their study group.

**Interventions**

Group A patients receive intranasal desmopressin at a dose of 40 micrograms and intravenous ketorolac at 30 mg. In group B patients, intranasal ketamine was administered at a dose of 1 mg/kg and intravenous ketorolac at 30 mg. Group C patients received an intranasal placebo (DB-SALINE 0.9%, DB Pharmacy, Tehran, Iran) and intravenous ketorolac at a dose of 30 mg.

**Study protocol**

After obtaining the ethics code and training of emergency physicians, eligible patients were selected by them to participate in the study. The demographic information including age, sex, and body mass index was recorded. Patients were asked to determine their degree of pain using a VAS on a range of 0 to 10, where 0 represents no pain and 10 represents the most intense (16). Pain severity was recorded at the baseline, 10,
30, and 60 minutes after the beginning of the treatment. Vital signs, including heart rate, respiratory rate, and systolic and diastolic blood pressure, were recorded at the baseline and 60 minutes after the beginning of the study. The emergency physician regularly monitored patients during treatment. If the patient's pain did not reduce effectively (a 50% decrease in VAS score or reaching to score ≤3) after 30 minutes of treatment, 0.1 mg/kg with a maximum dose of 5 mg of morphine was administered as the rescue analgesia and the need for rescue analgesia was recorded. The primary outcome was the comparative reduction of VAS scores between three groups after intervention. Secondary outcomes were the occurrence of hemodynamic changes and the need for rescue treatment.

**Sample size**

Considering an \( \alpha = 0.05, \beta = 0.2 \), the statistical power of 80% for the study, and the final differences between the two groups at least 2 scores on VAS (6), the sample size of 40 in each group was determined. To increase the power of this study, 45 patients were included in each group.

**Statistics analysis**

Collected data were analyzed using SPSS V.28 software. Frequency and percentage were used to describe qualitative data, and mean, and standard deviation (SD) were used to describe quantitative data. Independent t-tests, Chi-square, and repeated measure ANOVA were used for inferential analysis.

**Results**

Finally, 135 patients were enrolled (Figure 1), the mean (SD) of age was 44.1 ± 11.4, and 82 (60.7%) were men. All patients who were included in the study with a diagnosis of renal colic had a final diagnosis of renal colic, completed the study, and were analyzed. Age, gender, weight, and morphine requirements are compared between the three treatment groups in Table 1. As indicated in Table 1, the three groups did not have significant differences in age, gender, and weight (\( P \geq 0.05 \)). Therefore, the demographic variables were not considered confounders. Also, the need for morphine was similar between groups (\( P \geq 0.05 \)).
Table 2 indicates the mean ± SD of the three groups' VAS scores during the treatment. The degree of perceived pain of the three groups at the baseline did not have a significant difference (P≥0.05). Pain scores of the patients in the control group were higher than the other two groups at 10, 30, and 60 minutes after the intervention. Therefore, ketamine and desmopressin, along with ketorolac, caused better improvements in pain scores compared to ketorolac alone. VAS scores difference in the Ketamine and Desmopressin group compared to the control group were significant at 10, 30, and 60 minutes (P<0.05). In comparing the two groups of Ketamine and Desmopressin, it was observed that pain scores in the Ketamine group at 10, 30, and 60 minutes are significantly lower compared to the Desmopressin group (P<0.05).

No significant difference was found in the comparison between the three groups and the two intervention groups in terms of vital signs 60 minutes after the beginning of the treatment (Table 3). The three groups did not have significant differences in the need for morphine (P≥0.05) (Table 1).

Using repeated measurement ANOVA, it was observed that perceived pain scores reduced significantly in three groups (Figure 2 and Table 2).

Discussion

Desmopressin is a synthetic replacement for antidiuretic hormone with more powerful and longer-lasting antidiuretic effects. This drug has advantages such as ease of administration, fewer contraindications, and side effects compared to NSAIDs (17, 18). These anti-inflammatory agents can lead to acute kidney failure (AKI) by reducing the glomerular filtration rate (GFR) and renal blood flow in a kidney that is already at risk of failure due to hydronephrosis. Studies have shown that desmopressin exerts its diuretic effects without affecting renal blood flow or GFR. Significant adverse effects of desmopressin, such as hypotension, tachycardia, hyponatremia, and gastrointestinal symptoms, usually resolve within 24 hours after administration and are more noticeable in old patients or repeated administrations. Our study showed that the patients who received desmopressin did not have a significant difference in vital signs compared to other patients one hour after the treatment.
Some human studies investigating desmopressin's effectiveness on renal colic have shown conflicting results. However, most previous studies have examined the effects of desmopressin in the short term and are limited to hospitalized patients in the ED (17-19). In our study, patients receiving desmopressin and ketorolac treatment reported lower pain scores 10, 30, and 60 minutes after the treatment compared to ketorolac alone. Hence, our study confirms the immediate effects of desmopressin in renal colic patients, which is consistent with previous studies (4, 5, 19). Arhami Dolatabadi.'s study (4) aimed to investigate the effectiveness of intranasal desmopressin on renal colic patients compared to intravenous ketorolac. The pain of the patients who received only desmopressin decreased significantly in the first ten minutes, as well as those who received diclofenac. Until the 20th minute, the desmopressin group patients' pain scores decreased but had a rising trend after that. Also, during the study, there was no significant difference in the pain scores of patients receiving diclofenac alone and patients receiving diclofenac along with desmopressin. However, at the 30th minute, the VAS scores of patients receiving combination therapy were insignificantly lower. Furthermore, fewer patients receiving combination therapy reported that their pain intensity had not changed (20). Consistent with Lopes et al.'s study (20), our patients in the desmopressin group had a non-significantly lower morphine requirement than the controls. It can be concluded that although in some previous studies, treatment with desmopressin alone has not shown favorable results (21), in combination with NSAIDs, primarily in the first minutes of treatment, desmopressin can increase the effectiveness of the treatment and, as a result, reduce the dosage of prescribed NSAIDs. It is important to note that a dose of 40 μg of desmopressin was administered in the present study and most previous studies (17, 19). Pricop et al.'s study showed that doses of 60 and 120 micrograms of sublingual desmopressin have equal or greater efficacy than NSAIDs in renal colic patients (11, 17).

Ketamine is an NMDA receptor antagonist widely used for anesthesia. In recent decades, low-dose ketamine has been used to treat moderate to severe pain (16). The analgesic mechanisms of this drug are not limited to interactions with NMDA receptors. Studies have shown that ketamine has agonistic effects on opioid receptors, gamma-aminobutyric acid (GABA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, cholinergic and dopaminergic receptors; However, the
analgesic mechanism of this drug yet unknown (10). In recent years, the effectiveness of this drug on renal colic patients has been examined (9, 22-24). The study of Hosseininejad et al. (7) investigated and compared the effects of intravenous ketamine and morphine on renal colic. The results of this study indicated the combined treatment of morphine and ketamine to be significantly more effective than morphine alone; However, patients receiving ketamine demonstrated more adverse effects and changes in vital signs. In the present study, the vital signs in patients receiving ketamine were not significantly different from other patients, the leading cause of which can be attributed to the intranasal administration of ketamine in our study.

Although intravenous ketamine has shown promising analgesic effects, the analgesic effects of intranasal ketamine have been studied in recent years, and ketamine has shown favorable effectiveness and few adverse effects in this case (9, 14). The intranasal form of ketamine reaches a detectable concentration in the blood after two minutes and reaches its maximum effects within 30 minutes, which is one of the factors that make this drug suitable for managing renal colic patients (24). Our study showed that patients receiving intranasal ketamine with IV ketorolac had significantly less pain severity than those receiving ketorolac alone or combined with desmopressin throughout the study. Therefore, unlike desmopressin, ketamine has shown favorable results in causing a fast and stable analgesic response. Sotoodehnia et al. (25) investigated and compared the effect of intravenous ketamine compared to ketorolac in relieving pain in patients with renal colic. There was no significant difference in the mean pain scores of the two groups of patients during the study. Similar results were observed in the study of Khavanin et al., (9) the mean pain scores of the patients in the intranasal ketamine group were significantly lower in the 5th minute of examination. Also, in this study, hospitalization duration and the need for additional analgesics were significantly lower in the ketamine group, and patients were significantly more satisfied with their pain relief. In addition, the two groups did not differ significantly in terms of vital signs during the study (9). Pouraghaei et al. (22) found intranasal ketamine to be as effective as intravenous morphine for pain control in renal colic.

**Limitations**
The present study had limitations. This study was conducted single-centered due to the limited budget. In addition to not recording and investigating non-life-threatening adverse effects of treatments, this study examined the patients only for one hour; Therefore, it does not provide information on the long-term outcomes and possible side effects. Also, the changes in VAS cannot be explained by the study drugs alone, because the sample size was very small and the effect of ketorolac cannot be ignored. In the control group, patients receiving ketorolac and a placebo also had a significant improvement in their pain scale. To eliminate the effect of ketorolac in future studies, it is recommended that ketamine and desmopressin be used as the only drugs.

Despite the limitations, the present study had strengths. Among these strengths, we can mention the large sample size and the longer follow-up period compared to previous studies, which helps strengthen our study's results. Considering that the exact analgesic dose of ketamine and desmopressin is not known, it is recommended to conduct multicenter studies with larger sample sizes and longer follow-up duration.

**Conclusion**

Ketamine had favorable analgesic effects in renal colic patients. Intranasal ketamine had better pain control as compared to intranasal desmopressin, although desmopressin showed promising efficacy in the first minutes of the treatments. The need for rescue treatment in the ketamine group was less than in other groups but this was not statistically significant.
References


Table 1: Studied variables in three groups

<table>
<thead>
<tr>
<th>Group Variables</th>
<th>Desmopressin (n=45)</th>
<th>Ketamine (n=45)</th>
<th>Control (n=45)</th>
<th>P-value\textsubscript{1}</th>
<th>P-value\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.2 ± 9.8</td>
<td>43.6 ± 13.7</td>
<td>42.5 ± 10.3</td>
<td>0.294</td>
<td>0.286</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>29 (64.4 %)</td>
<td>28 (62.2 %)</td>
<td>25 (55.6 %)</td>
<td>0.668</td>
<td>0.613</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.8±9.9</td>
<td>76.2 ± 10.1</td>
<td>73.2 ± 9.7</td>
<td>0.889</td>
<td>0.823</td>
</tr>
<tr>
<td>History of renal stone</td>
<td>33 (73.3%)</td>
<td>35 (77.8%)</td>
<td>30 (66.7%)</td>
<td>0.493</td>
<td>0.624</td>
</tr>
<tr>
<td>Morphine required</td>
<td>8 (17.8)</td>
<td>3 (6.7)</td>
<td>11 (24.4)</td>
<td>0.070</td>
<td>0.197</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation or number (%)

P-value\textsubscript{1}: Comparison between three groups

P-value\textsubscript{2}: Comparison between two intervention groups (Ketamine and Desmopressin)
Table 2: Comparing VAS pain score between three groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Difference (95% CI)*</th>
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</thead>
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<tr>
<td></td>
<td>Desmopressin (n=45)</td>
<td>Ketamine (n=45)</td>
</tr>
<tr>
<td>Pain Score 0 min</td>
<td>9.5±0.7</td>
<td>9.4±0.7</td>
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<tr>
<td>Pain Score 10 min</td>
<td>6.7±1.8</td>
<td>5.6±1.2</td>
</tr>
<tr>
<td>Pain Score 30 min</td>
<td>4.2±2.2</td>
<td>3.0±1.1</td>
</tr>
<tr>
<td>Pain Score 60 min</td>
<td>1.3±1.4</td>
<td>0.9±0.9</td>
</tr>
<tr>
<td>P-value**</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The mean difference is significant at the 0.05 level.

**Repeated measure ANOVA

Data are expressed as mean ± standard deviation or number (%)

*Reduced to fit page width*
Table 3: Comparison of Vital Signs Before and After Intervention

<table>
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<th>Groups</th>
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<th></th>
<th>P-value₁</th>
<th>P-value₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Desmopressin (n=45)</td>
<td>Ketamine (n=45)</td>
<td>Control (n=45)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>120.7 ± 6.3</td>
<td>121.8 ± 10.4</td>
<td>119.2 ± 5.1</td>
<td>0.263</td>
<td>0.499</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>121.6 ± 9.9</td>
<td>122.9 ± 11.6</td>
<td>120.4 ± 8.7</td>
<td>0.135</td>
<td>0.374</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>After</td>
<td>77.5 ± 4.7</td>
<td>77.9 ± 5.0</td>
<td>76.4 ± 3.5</td>
<td>0.223</td>
<td>0.653</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>78.5 ± 5.4</td>
<td>79.1 ± 6.8</td>
<td>77.7 ± 4.1</td>
<td>0.335</td>
<td>0.669</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>After</td>
<td>77.3 ± 6.5</td>
<td>78.3 ± 7.6</td>
<td>77.4 ± 6.3</td>
<td>0.759</td>
<td>0.499</td>
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<tr>
<td></td>
<td>Before</td>
<td>79.2 ± 8.5</td>
<td>79.4 ± 8.9</td>
<td>79.4 ± 7.8</td>
<td>0.574</td>
<td>0.355</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>After</td>
<td>18.6 ± 1.1</td>
<td>19.0 ± 1.5</td>
<td>18.6 ± 1.4</td>
<td>0.254</td>
<td>0.152</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>19.1 ± 1.2</td>
<td>19.2 ± 1.7</td>
<td>19.0 ± 1.5</td>
<td>0.345</td>
<td>0.198</td>
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<tr>
<td>Respiratory Rate</td>
<td>After</td>
<td>95.9 ± 1.7</td>
<td>96.6 ± 1.7</td>
<td>96.2 ± 1.6</td>
<td>0.133</td>
<td>0.316</td>
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<tr>
<td></td>
<td>Before</td>
<td>94.3 ± 1.9</td>
<td>95.5 ± 1.0</td>
<td>96.0 ± 1.3</td>
<td>0.165</td>
<td>0.178</td>
</tr>
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</table>

P-value₁: Comparison between three groups

P-value₂: Comparison between two intervention groups (Ketamine and Desmopressin)
Figure 1. Study flowchart (CONSORT format)
Figure 2. The differences in VAS Scores between the three groups at different times