



## Analgesic Effects and Safety of Desmopressin, Tramadol and Indomethacin in Patients with Acute Renal Colic; A Randomized Clinical Trial

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### ► ABSTRACT

**Objective:** To compare the efficacy of desmopressin (DDAVP), tramadol and indomethacin on pain intensity of patients with acute renal colic caused by urolithiasis.

**Methods:** This prospective, randomized clinical trial was conducted between July 2005 and July 2006 including 120 patients (70 men and 50 women, mean age 38.2±5.8 years) referring to emergency room of Shahid Faghihi hospital with renal colic caused by urolithiasis without any previous treatment. The patients were randomly assigned to three groups: group A received tramadol 50mg intramuscularly (n=40), group B received desmopressin 40 µg intranasally (n=40) and group C received indomethacin 100mg rectally (n=40). The pain was assessed both on admission and 30 minutes after the intervention. The pain intensity and the side effects were compared between two study groups.

**Results:** There was no significant difference between two study groups regarding the baseline characteristics. The intensity of pain of presentation was almost similar in all groups. In group A, 30 patients (75%), in group B, 15 patients (37.5%) and in group C, 19 patients (47.5%) had complete pain relief. The pain intensity decreased significantly after the intervention within all three groups ( $p<0.001$ ).

**Conclusion:** According to the results of the current study, rectal indomethacin, intramuscular tramadol and intranasal desmopressin are effective and safe routes of controlling pain in acute renal colic secondary to urolithiasis. Tramadol was the most effective agent in controlling the pain.

**Clinical Trial Registry:** The current study is registered with Iranian Registry for Clinical Trials ([www.irct.ir](http://www.irct.ir); IRCT2015030919470N18)

**Keywords:** Acute renal colic; Urolithiasis; Pain; Tramadol; Desmopressin; Indomethacin.

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## Introduction

Renal colic, defined as acute pain due to passage of a ureteral calculus, is a common urological problem with a lifetime incidence of 2% to 5% of population in industrialized nations [1,2]. Symptomatic ureteric colic represents the most common emergency condition treated by urologists [3]. Renal colic is one of the most intense forms of pain and requires prompt treatment [4]. The pain of renal colic is a consequence of obstruction to urinary flow, leading to an increase in intraluminal pressure [5]. The resulting increase in the intraluminal pressure from ureteric obstruction stretches nerve endings in the mucosa and produces the colicky pain. Moreover, the smooth muscle in the wall of the ureter contracts as it tries to move the stone [6].

Prompt and effective pain control is a critical priority in treating these patients. However, the most effective analgesic regimen has yet to be determined [7]. Several different classes of drug have been recommended in the treatment of renal colic, although nonsteroidal anti-inflammatory drugs and opioids are generally the mainstays of therapy [8]. Opioid analgesic, e.g. morphine and pethidine, are highly effective during the acute episode. Side effects are common, including nausea, vomiting, constipation and drowsiness, and larger doses can cause respiratory depression and hypotension [9]. Tramadol is a synthetic, centrally acting opioid analgesic with fewer opioid side-effects, notably less respiratory depression, constipation and potential for addiction. Another drug used to relieve renal colic, desmopressin, a synthetic analogue of vasopressin, produces an anti-diuretic effect and, in animals, may suppress renal pelvic muscular contractility [10]. Thus the present study was designed to compare the efficacy of aforementioned medications which are out-patiently prescribed in relieving the pain of renal colic caused by urolithiasis.

## Materials and Methods

### Study Population

This prospective, single blind randomized clinical trial was conducted between July 2005 and July 2006 including 120 patients referring to emergency room of Shahid Faghihi hospital with renal colic caused by urolithiasis without any previous treatment. The study protocol was approved by institutional review board (IRB) and medical ethics committee of Shiraz University of Medical Sciences. All the patients provided their informed written consents before inclusion in the study. We included all the patients with acute renal colic secondary to urolithiasis conformed by ultrasonography without previous treatment who presented to our center within the study period. We excluded those patients with hypertension, ischemic heart disease, rhinitis, influenza, those on anticoagulation therapy, peptic

ulcer and those with renal or liver failure. Pregnant women were also excluded from the study. Those who had hypersensitivity to NSAIDs were not included in the study. Use of analgesics within 4 hours and Alpha blockers before admission, history of addiction, surgery on the kidney or ureter, and fluids therapy immediately before admission were among the exclusion criteria. During the study, if a patient could not bear the pain and did not want to continue, he/she was excluded. The study protocol was registered with Iranian registry of clinical trials (IRCT2015030919470N18; www.irct.ir).

### Study Protocol

All the patients were examined and a detailed history was obtained by the emergency room resident and the findings were recorded in the data gathering form. The time of onset and duration of the pain and the associated symptoms were recorded, with the number and dates of former episodes, the elimination of calculus and the previous documentation of stones by imaging (abdominopelvic radiography and ultrasonography). Vital signs were also recorded. After that the patients underwent ultrasonography in order to confirm nephrolithiasis or hydronephrosis. The patients were then randomly assigned to three study groups using a computer based random digit generator based on the admission numbers provided by the registration computer; those who were assigned to group A received tramadol (Mikasa Pharmaceutical, Tokyo, Japan) 50 mg intramuscularly (n=40). Patients assigned to group B received desmopressin (Minirin, Ferring, Kiel, Germany) (DDAVP) 40 µg intranasally (n=40) and those in group C received indomethacin 100mg rectally (Arya Pharmaceutical, Karaj, Iran) (n=40). The primary endpoint of the study was the pain intensity measured on admission and 30 minutes after the intervention. A visual analogue scale (VAS) was used to assess the intensity of pain. This consisted of a 10-cm horizontal scale ranging from no pain to unbearable pain (1 to 10). Patients who had no satisfactory pain relief within 30 minutes, a second treatment were administered. The side effects of each drug was also recorded and compared between groups. As the route of administration was different between three study groups, patients and physicians were not blinded to the study. However those measuring the outcome were blinded to the study groups.

### Statistical Analysis

The data was prospectively entered into the computer database and was further analyzed using statistical package for social sciences (SPSS Inc., Chicago, USA). The result is presented as mean  $\pm$  SD or proportions as appropriate. The parametric data was compared between the study groups using One-Way Analysis of Variance (ANOVA) with Tukey as Post-Hoc test. Paired t-test was used

to compare the changes in pain intensity before and after intervention within groups. Proportions were compared using chi-square test. A two-sided *p*-value of less than 0.05 was considered statistically significant.

## Results

One hundred and twenty patients who the inclusion criteria were randomly assigned to three study groups. There were 40 patients in groups Group A, 40 in group B and 40 in group C. All the patients finished the study and thus the final number of patients undergoing final analysis was 120 (Figure 1). The mean age of the patients was  $38.2 \pm 5.8$  (ranging from 18 to 68) years. Overall there were 70 (58.3%) men and 50 (44.7%) women among the participants. The right and left sided urolithiasis were each reported in 57 (47.5%) patients while 6 (5%)

had bilateral urolithiasis. The baseline characteristics of the patients were comparable between three study groups. Table 1 summarized the baseline characteristics of 120 patients with urolithiasis assigned to three study groups.

The outcome of the patients in three study groups is demonstrated in Table 2. We found that the pain intensity decreased significantly in those who received tramadol ( $p < 0.001$ ), desmopressin ( $p < 0.001$ ) and indomethacin ( $p < 0.001$ ). The pain intensity was significantly lower in those who received tramadol when compared to desmopressin ( $p = 0.01$ ) and indomethacin ( $p = 0.01$ ). There was no significant difference regarding the pain intensity between indomethacin and desmopressin after 30-minute ( $p = 0.28$ ). The number of patients with complete pain relief was significantly higher in tramadol group compared to desmopressin ( $p = 0.01$ ) and indomethacin ( $p = 0.01$ ). In the same way there was no

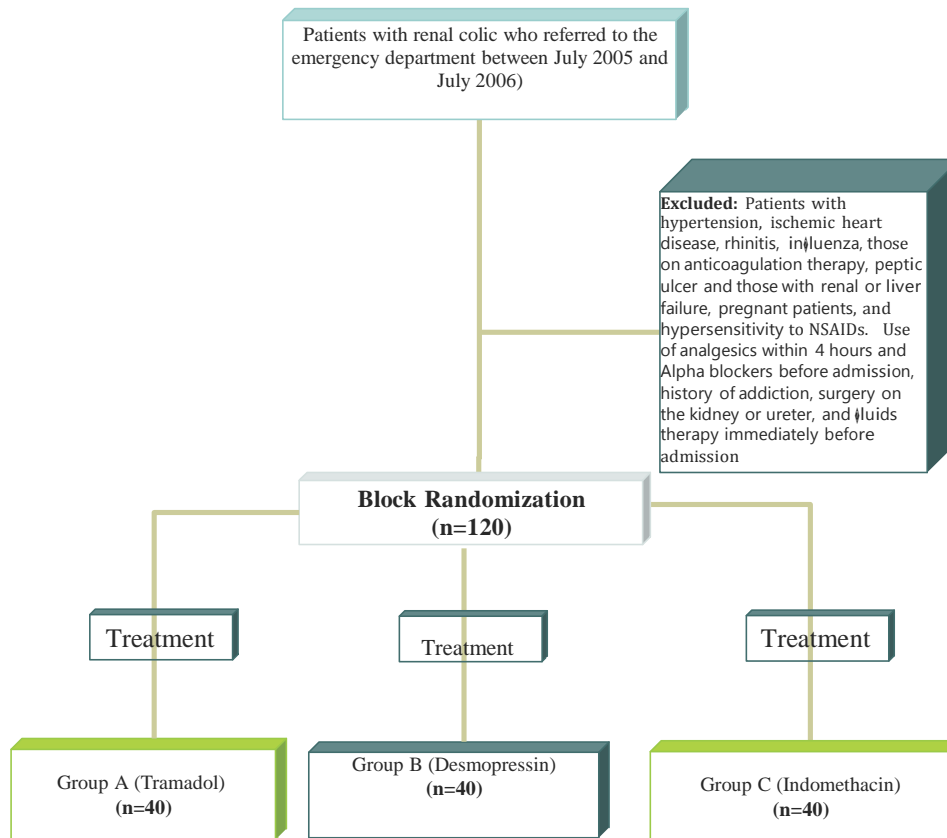


Fig. 1. Consort flow diagram of the study.

Table 1. The baseline characteristics of 120 patients with renal colic secondary to urolithiasis assigned to desmopressin, tramadol and indomethacin groups.

	Tramadol (n=40)	Desmopressin (n=40)	Indomethacin (n=40)	<i>p</i> value
Age (years)	39.1±8.9	38.8±7.6	36.7±9.2	0.412
<b>Gender</b>				
Men (%)	23 (57.5%)	25 (62.5%)	22 (55%)	0.213
Women (%)	17 (42.5%)	15 (37.5%)	18 (45%)	
<b>Urolithiasis</b>				
Right (%)	19 (47.5%)	20 (50%)	18 (45%)	
Left (%)	19 (47.5%)	17 (42.5%)	21 (52.5%)	0.168
Bilateral (%)	2 (5%)	3 (7.5%)	1 (2.5%)	

**Table 2.** The pain intensity and side effects of 120 patients with renal colic secondary to urolithiasis assigned to desmopressin, tramadol and indomethacin groups.

	Tramadol (n=40)	Desmopressin (n=40)	Indomethacin (n=40)	p value
VAS on admission	8.3±1.2	8.4±0.7	8.3±0.9	0.211
VAS at 30-minute	3.6±0.6	5.3±0.5	4.7±0.4	0.032
Complete relief (%)	30 (75%)	15 (37.5%)	19 (47.5%)	0.021
Rescue analgesic (%)	10 (25%)	25 (62.5%)	21 (52.2%)	0.001

difference between desmopressin and indomethacin regarding the number of patients with complete pain relief ( $p=0.32$ ). The frequency of rescue analgesic was significantly higher in desmopressin ( $p=0.02$ ) and indomethacin ( $p=0.01$ ) groups when compared to tramadol.

## Discussion

Opiate analgesics and NSAIDs remain the most effective commonly used analgesic for treating renal colic [11]. As these groups of drugs are associated with several side effects, alternative methods of treatment are sought. Opioid analgesics, e.g. morphine and pethidine, are highly effective during the acute episode. Various preparations are available but the intravenous form has the most rapid onset of action and the advantage that the dose may be titrated to effect. However, prolonged use may cause dependence and tolerance. Side effects are common, including nausea, vomiting, constipation and drowsiness and larger doses can cause respiratory depression and hypotension. The data are conflicting for the effect of opiates a ureteric stone; results generally indicate an increase or no effect [12].

Tramadol is a synthetic, opioid-like, centrally acting analgesic. It is a member of the aminocyclohexonal group and is not chemically related to opiates. The mechanism of action is not completely understood, but is likely to involve a combination of binding to  $\mu$  opioid receptors and inhibition of reuptake of serotonin and noradrenalin in the pain pathways of the central nervous system (CNS) [12,13]. Tramadol has fewer opioid side-effects, notably less respiratory depression, constipation and potential for addiction. Intravenous, intramuscular, subcutaneous and oral preparations are available [14]. When used for treating renal colic, tramadol 100mg had been shown to be as effective as pethidine 50mg [15].

In other study, it was shown that patients with tramadol needed significantly less rescue medication. This study proved that continuous tramadol drip is a safe and valuable analgesic regimen [16]. These studies show similar results to our study in which tramadol was the most effective treatment (75% complete pain relief). Several studies have demonstrated that desmopressin can dramatically reduce the pain of acute renal colic in majority of the patients [17,18]. Animal studies have demonstrated a significant reduction in mean intraureteral pressure following an acute obstruction after receiving desmopressin. It could be postulated

that an ADH-induced decrease in diuresis might contribute to the rapid relief of the pain of renal colic. The marked antidiuretic effect of desmopressin is probably responsible of its efficacy in the treatment of renal colic. Peripherally, it has been shown that desmopressin suppresses the spontaneous contractions of circular smooth muscle fibers in the renal pelvis of rabbits [19]. The same effect could be possible in humans. Some authors reported the role of desmopressin in stimulating the secretion of  $\beta$ -endorphins by hypothalamus, which could explain a possible additional central analgesic effect of the drug [20-23]. Lopes and co-workers performed a randomized clinical trial in which patients with acute renal colic receive intranasal desmopressin, intramuscular diclofenac, or both. All groups showed similar improvement in pain scores at 10 and 20 min, but by 30 min pain scores were higher in desmopressin-only group [24]. Therefore, other double blind, randomized, controlled studies are needed to study the exact role of desmopressin in the relief of renal colic. This finding is compatible to our data which 37.5% had complete pain relief. The ease of administration, low cost, well tolerability, and lack of clinically relevant side effect, make it safe drug in treating renal colic, but optimum dosage method of use need to be explored.

Since 1970, NSAIDs have been widely used outside the USA to treat renal colic and many studies have confirmed their efficacy [1,4,5]. Although NSAIDs reduce pain in patients with renal colic, they potentially interfere with the kidneys autoregulatory response to obstruction with marked reduction in blood flow [25]. In some patients these effects can induce renal failure [26]. NSAIDs can also have severe gastrointestinal side effects. Cyclooxygenase inhibitors had been developed to reduce gastrointestinal side effects, but they also inhibit renal vasoactive substances and are contraindicated in patients with renal insufficiency [27]. In randomized prospective study comparing NSAIDs with morphine in patients with renal colic, both agents provided equally significant pain relief [28]. In our study indomethacin was less effective than tramadol in treating renal colic (47.5% vs. 75% complete pain relief). Desmopressin 40 $\mu$ g intranasal, despite of several advantages was not more effective than tramadol 50mg intramuscularly and indomethacin 100mg rectal. It seems that desmopressin is not effective treatment for pain scores upper than 8; or very severe pain. The anti-diuretic action of NSAIDs may be nephrotoxic, by



decreasing renal blood flow and glomerular filtration rate (GFR) in an already obstructed, dysfunctional kidney. However, in our study, NSAIDs were less effective than tramadol. Among all these drugs tramadol was the most effective one.

In conclusion, desmopressin, tramadol and indomethacin (NSAIDs) are effective and safe agents in management of pain in patients with acute renal

colic. Among these medications, tramadol was the most effective treatment. Considering fewer opioid-type side effects and less potential for dependence, it can be safe drug in treating renal colic, especially in situations where NSAIDs are contraindicated or in patients with a history of substance abuse.

**Conflict of interest:** None declared.

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