



Original Contribution

Desmopressin/indomethacin combination efficacy and safety in renal colic pain management: A randomized placebo controlled trial



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ABSTRACT

Introduction: Renal colic is a prevalent cause of abdominal pain in the emergency department. Although non-steroidal anti-inflammatory drugs and opioids are used for the treatment of renal colic, some adverse effects have been reported. Therefore, desmopressin –a synthetic analogue of vasopressin– has been proposed as another treatment choice. In the present study, indomethacin in combination with nasal desmopressin was compared with indomethacin alone in the management of renal colic.

Methods: Included in the study were 124 patients with initial diagnosis of renal colic and randomized to receive indomethacin suppository (100 mg) with either desmopressin intranasal spray (4 puffs, total dose of 40 micrograms) and or placebo intranasal spray.

Results: All the included patients were finally diagnosed with renal colic. There was no difference between the two groups in pain at the baseline ($p = 0.4$) and both treatments reduced pain successfully ($p < 0.001$). There was no significant difference between the two groups in pain reduction ($p = 0.35$).

Conclusions: While there was significant pain reduction in both patients groups, pain reduction of NSAIDs (e.g. indomethacin) in renal colic, does not significantly improve when given in combination with desmopressin.

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1. Introduction

Renal colic is a prevalent cause of abdominal pain in the emergency department (ED) [1]. It is caused by local stone irritation and increased ureteropelvic pressure via obstruction. Ureteral obstruction increases the release of prostaglandin (PG) which then triggers a vicious cycle, i.e. increased blood flow results in increased urine production which in turn exacerbates the ureteropelvic pressure [2].

Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids have been used for the treatment of renal colic. These agents are generally effective but there are some side effects, such as peptic ulcer, and hypoventilation. Desmopressin (1-desamino-8-D-arginine), a synthetic analogue of vasopressin, has been proposed as another treatment option, assuming that the antidiuretic action of this agent may break the aforementioned vicious cycle and help with pain reduction.

Human studies on the effectiveness of desmopressin, either alone or in combination with other NSAIDs and opioids, have yielded contradictory results. Only one study concluded that diclofenac suppository, when combined with desmopressin, was more effective for pain relief. Indomethacin, a popular NSAID in our country, can easily be

administered per rectum, obviating the need for securing venous access. This is especially an advantage for an overcrowded ED.

In this randomized controlled clinical trial, indomethacin in combination with nasal desmopressin was compared with indomethacin alone in the management of renal colic.

2. Methods

2.1. Study design

This is a prospective, double-blinded, randomized, placebo-controlled clinical trial which compared the effectiveness and adverse effects of desmopressin/indomethacin combination with those of indomethacin alone. The trial has been registered in clinicaltrials.gov with registration number NCT01742689. Our institutional review board has approved the trial protocol provided that written informed consent is obtained from all participants.

2.2. Study setting and population

The study was conducted in the EDs of two academic hospitals with >50,000 patients per year. Our study population included patients with renal colic who presented to the ED between March 2012 and March

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2013. All patients aged 15 years and above were considered for inclusion. Exclusion criteria were pregnancy, presence of acute rhinitis and influenza, hereditary or acquired coagulopathy, history of acute myocardial ischemia, hyponatremia, peptic ulcer disease, asthma, renal failure, and severe liver failure. Patients taking any of the following medications were also excluded: seizure medications, chlorpropamide, clofibrate, epinephrine, fludrocortisone, lithium, alcohol, or analgesics (during the past 4 h).

2.3. Study protocol

A convenience sample of 124 patients was enrolled during the shifts of two of the investigators (HM and MRH). Patients were included based on the initial diagnosis of renal colic by the treating physicians after arrival to the ED and absence of exclusion criteria. Patients' enrollment and flow in the study is further illustrated in Fig. 1. Since rectal administration of indomethacin alone was one of the popular treatment options in renal colic at our institution, patients were randomized to receive indomethacin suppository (100 mg) plus either desmopressin intranasal spray (4 puffs with 10 microgram per puff, total dose of 40 microgram) or placebo intranasal spray. Block randomization was performed using computer generated sequence of 4 numbers. The sprays were covered by manufacturer to appear similarly and named A and B with the patients and physician blinded to the content of them.

An emergency physician (EP) enrolled the patient and documented patient demographic data. Before treatment, the pain was recorded using an 11-point verbal numeric rating scale. Then, 4 spray puffs were applied in patient's nostril, and indomethacin suppository was administered per protocol. Pain was recorded 5, 10, 15, 30, 45, and 60 min afterwards. In addition, during the 1 h period, adverse effects (e.g. dry

mouth, nausea, drowsiness, hypotension, and anaphylaxis) were logged in a data collection sheet. In case of insufficient pain relief or patient's demand for further analgesia 30 min after medication administration, 5 mg of morphine sulfate was administered intravenously. Other medications such as anti-emetics were administered according to the patients' complaints.

In this study, the primary outcome measures were patient pain reduction as measured by 11-point verbal numeric rating scale with 0 representing "no pain" and 10 meaning "worst possible pain". Secondary outcomes were the occurrence of adverse effects and the need for rescue analgesia.

2.4. Data analysis

Data were analyzed using SPSS (SPSS Inc., Chicago, IL) and values were expressed as number (%) or mean \pm standard deviation (SD). Previous studies showed that desmopressin-NSAID co-administration and indomethacin were effective in about 95% and 73% of patients with renal colic, respectively [3,4]. Therefore, a sample size of 49 in each treatment arm was needed for a power of 80% and alpha level of 0.05 for statistical significance. Assuming an estimated 20% drop-out rate, we decided to include 60 patients in each arm. Post-treatment and analysis of covariance and Chi-square were employed for comparison of pain measurements and need for rescue treatment, respectively. Statistical significance was accepted at p values < 0.05.

3. Results

After obtaining informed consent, 124 patients with primary diagnosis of renal colic were randomly assigned to either treatment or

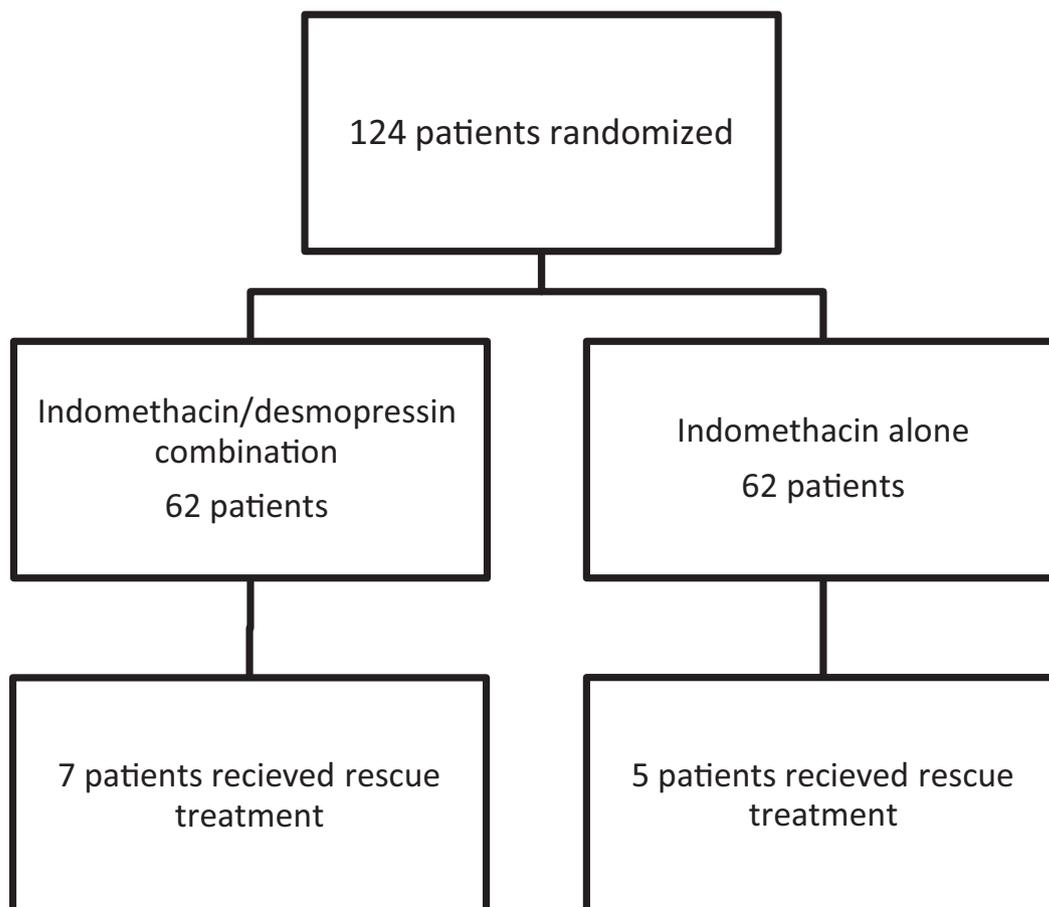


Fig. 1. Patients flow.

Table 1
Participants' baseline characteristics.

	Desmopressin/ indomethacin group (62 patients)	Indomethacin group (62 patients)
Age (year), mean \pm SD	34.67 \pm 10.03	34.31 \pm 10.73
Male (%)	70.15	69.35
Pain at presentation, mean \pm SD	7.7 \pm 1.3	7.9 \pm 1.5

control group in equal proportions (Fig. 1). Patients' characteristics have been provided in Table 1. There was no difference between the two groups in pain severity at presentation. All patients who had received renal colic diagnosis at the time of admission, had final diagnosis of renal colic, completed the study, and were analyzed. Seven patients in desmopressin/indomethacin group and 5 patients in indomethacin group received intravenous morphine as rescue treatment. Table 2 represents the pain scores at different time points. Although pain scores in desmopressin/indomethacin group were lower at the baseline and at each time point afterward, this difference was not statistically significant ($p = 0.4$) (Table 2). Comparing pain scores between the two groups showed that both treatments arms reduced pain significantly ($p < 0.001$) with no difference in pain reduction between two treatment arms ($p = 0.35$). No severe adverse event (e.g. chest pain, anaphylaxis, and dyspnea) occurred for any of the patients; other less serious events are listed in Table 3.

4. Discussion

Excruciating pain is one of the most common complaints in patients with urolithiasis [5]. It is believed that the pain results mainly from increased ureteropelvic pressure due to hyperperistalsis and distension of obstructed ureter. This, in turn, will result in stimulation of PG2 secretion, further renal vasodilatation, subsequent increase in diuresis and exacerbation of pain [6,7].

Rapid pain relief is considered as the main step in management of these patients [8]. NSAIDs and opioids are commonly used for pain management in renal colic patients [9]. Inhibition of PGE2 synthesis by NSAIDs and inhibition of excitatory neurotransmitters release (e.g. substance P) by opioids are the main mechanisms of action [10,11]. Despite their vast usage, NSAIDs can induce gastrointestinal bleeding and renal failure, and opioids are associated with potential for abuse [12].

Considering these drawbacks, desmopressin has been proposed as an alternative medication for renal colic pain relief. The antidiuretic action of the agent may break the vicious cycle of PG release, diuresis, and pain worsening generated in urolithiasis [3,13–15]. In addition, desmopressin is proposed to be associated with less potential for side effects [3,6,16].

Varying results regarding the efficacy of desmopressin in renal colic pain relief have been produced in different studies. Some studies demonstrated that desmopressin can be used for pain relief in patients, alone or in combination with NSAIDs [3,6–8,14,17]. On the other hand, other studies showed no analgesic effect for desmopressin in renal colic [13]. Kumar et al. also suggested that desmopressin does not potentiate the analgesic effect of NSAIDs [13]. In a meta-analysis conducted by Jalili et al., it has been shown that desmopressin has less impact on pain reduction in comparison to NSAIDs [18]. They also demonstrated that desmopressin, combined with NSAIDs, does not provide

Table 2
Pain measurements during trial, mean (SD).

	Time 0	5 min	10 min	15 min	30 min	45 min	60 min
Desmopressin/indomethacin	7.7 (1.3)	7.4 (1.3)	6.4 (3)	4.7 (2.1)	2.6 (2.5)	1.1 (2.1)	0.8 (1.6)
Indomethacin	8 (1.7)	7.8 (1.6)	6.9 (1.9)	5.4 (2.4)	3.2 (2.8)	1.37 (2.2)	0.7 (1.4)

Table 3
Incidence of adverse effects in the two study groups.

Adverse effect	Desmopressin/indomethacin	Placebo/indomethacin
Dry mouth	4 (6.5%)	8 (12.9%)
Nausea	14 (22.6%)	20 (32.3%)
Vomiting	1 (1.6%)	5 (8.1%)
Dizziness	1 (1.6%)	0 (0%)
Chest pain	0 (0%)	0 (0%)
Anaphylaxis	0 (0%)	0 (0%)
Headache	3 (4.8%)	5 (8.1%)
Lightheadedness	1 (1.6%)	0 (0%)
Dyspnea	0 (0%)	0 (0%)

any further benefit in pain management [18]. Kumar et al. believes that these differences in results can stem from several causes such as different time intervals for assessment of pain, individual variations in absorption of drug or the dose of drugs [13]. Of note, while a study showed that desmopressin effectiveness reaches to its peak in 60 min after administration, most studies (including one that used diclofenac suppository) did not follow participants for 1 h. Furthermore, some studies have evaluated the analgesic efficacy of desmopressin through different administration routes. In an interesting study conducted by Pricop et al., it has been shown that sublingual desmopressin can cause an analgesic effect as efficiently as NSAIDs in renal colic [19]. The investigators also demonstrated improved analgesic effect of desmopressin in combination with NSAIDs as compared to NSAIDs alone [19]. These studies suggest that desmopressin efficacy in pain relief and its additive potential as an adjunct, can be related to the route of administration [19,20].

In this study, we observed no significant difference in pain reduction between the two groups. Also, with regard to the need for rescue treatment, we did not detect any remarkable difference between the groups, i.e. the number of patients needing rescue treatment was not significantly different in the two groups. Patients were enrolled in the study based on the clinical symptoms of renal colic and the clinical judgment of the emergency medicine attending physician. Since clinical judgment is not highly accurate in the diagnosis of nephrolithiasis or ureterolithiasis, and considering the fact that no confirmatory study was performed to identify the presence of stone in these patients, this is a limitation for our study and could potentially affect the results. Furthermore, all the cases have been recruited during the clinical shifts of two of the investigators; this can add to the aforementioned limitation. In addition, another limitation of this study was the absence of follow-up data on the patients' condition after 1 h; whether there was any difference between the two groups after 1 h and whether there were any cases of return visit for the same problem is unknown.

In summary, although there was significant improvement in pain score in both groups, desmopressin as an adjunct to NSAIDs in the management of renal colic, does not significantly improve pain relief.

Conflict of interest

None.

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References

- [1] Teichman JM. Clinical practice. Acute renal colic from ureteral calculus. *N Engl J Med* 2004;350:684–93.
- [2] Pedersen KV, Liao D, Osther SS, Drewes AM, Gregersen H, Osther PJ. Distension of the renal pelvis in kidney stone patients: sensory and biomechanical responses. *Urol Res* 2012;40:305–16.
- [3] El-Sherif AE, Salem M, Yahia H, Al-Sharkawy WA, Al-Sayrafi M. Treatment of renal colic by desmopressin intranasal spray and diclofenac sodium. *J Urol* 1995;153:1395–8.
- [4] Nissen I, Birke H, Olsen JB, et al. Treatment of ureteric colic. Intravenous versus rectal administration of indomethacin. *Br J Urol* 1990;65:576–9.
- [5] Soucie JM, Thun MJ, Coates RJ, McClellan W, Austin H. Demographic and geographic variability of kidney stones in the United States. *Kidney Int* 1994;46:893–9.
- [6] Constantinides C, Kapralos V, Manousakas T, Mitropoulos D, Alamanis C, Dimopoulos C. Management of renal colic with intranasal desmopressin spray. *Acta Urol Belg* 1998;66:1–3.
- [7] Majeed IA. Evaluation of using intranasal desmopressin, parenteral diclofenac or their combination in the management of acute renal colic pain in Iraqi patients. *Iraqi J Pharm Sci* 2007;16:1–4.
- [8] Beladi SSM, Darian AA, Forouzan A, Kalantar H, Masoumi K. Renal colic pain relief by intranasal desmopressin. *Life Science Journal-Acta Zhengzhou University Overseas Edition* 2012;9:3354–8.
- [9] Teichman JM. Acute renal colic from ureteral calculus. *N Engl J Med* 2004;350:684–93.
- [10] Labrecque M, Dostaler L-P, Rousselle R, Nguyen T, Poirier S. Efficacy of nonsteroidal anti-inflammatory drugs in the treatment of acute renal colic: a meta-analysis. *Arch Intern Med* 1994;154:1381–7.
- [11] Stein C. Peripheral mechanisms of opioid analgesia. *Anesth Analg* 1993;76:182–91.
- [12] Holdgate A, Pollock T. Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. *BMJ* 2004;328:1401.
- [13] Kumar S, Behera NC, Sarkar D, Prasad S, Mandal AK, Singh S. A comparative assessment of the clinical efficacy of intranasal desmopressin spray and diclofenac in the treatment of renal colic. *Urol Res* 2011;39:397–400.
- [14] Lopes T, Dias J, Marcelino J, Varela J, Ribeiro S, Dias J. An assessment of the clinical efficacy of intranasal desmopressin spray in the treatment of renal colic. *BJU Int* 2001;87:322–5.
- [15] Moro U, De Stefani S, Crisci A, De Antoni P, Scott C, Selli C. Evaluation of the effects of desmopressin in acute ureteral obstruction. *Urol Int* 1999;62:8–11.
- [16] Robinson AG. DDAVP in the treatment of central diabetes insipidus. *N Engl J Med* 1976;294:507–11.
- [17] Roshani A, Falahatkar S, Khosropanah I, et al. Assessment of clinical efficacy of intranasal desmopressin spray and diclofenac sodium suppository in treatment of renal colic versus diclofenac sodium alone. *Urology* 2010;75:540–2.
- [18] Jalili M, Entezari P, Doosti-Irani A, Masoomi R, Mirfazaelian H. Desmopressin effectiveness in renal colic pain management: systematic review and meta-analysis. *Am J Emerg Med* 2016;34:1535–41.
- [19] Pricop C, Branisteanu DD, Orsolya M, Puia D, Matei A, Checherita IA. Sublingual desmopressin is efficient and safe in the therapy of lithiasic renal colic. *Int Urol Nephrol* 2016;48:183–9.
- [20] Entezari P, Mirfazaelian H. Re: Pricop et al.: "Sublingual desmopressin is efficient and safe in the therapy of lithiasic renal colic". *Int Urol Nephrol* 2017;1-1.