

A Comparison of the Effects of Morphine and Sublingual Desmopressin Combination Therapy with Morphine Alone in Treatment of Renal Colic: A Controlled Clinical Trial

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Purpose: To compare the therapeutic efficacy of combined desmopressin and morphine with morphine and placebo on acute renal colic.

Materials and Methods: In a single blind case-control clinical trial 81 consecutive patients, 54 males and 27 females with the mean age of 30.12 ± 9.88 years, presenting with acute renal colic to the urology emergency unit were studied. The patients were randomly assigned into two groups. The 40 cases were treated with 0.1 mg/kg IM morphine and 60 µg of sublingual desmopressin melt; whereas the 41 controls received the same dose of morphine beside a placebo.

Results: There were no significant statistical differences regarding the mean age, gender, stone size, location and affected side between the two groups. Our results showed a significantly higher acuity of pain in the study group in comparison to the controls at 10, 20 and 30 minutes of receiving the medication ($P = .06$, $.017$ and $P = .008$, respectively).

Conclusion: No superiority was found in adding desmopressin to morphine compared to the traditional treatments (opioids only) in relieving the pain of acute renal colic cases.

Keywords: emergency service; kidney calculi; renal colic; drug therapy; morphine; desmopressin.

INTRODUCTION

Renal colic, ureteral colic or any other equivalent terms are indicatives of the third common cause of kidney pain and the most common non-obstructive etiology of acute abdominal pain in pregnant patients in the urology emergency units.⁽¹⁻⁵⁾ Renal colic is a kidney or ureteral originated pain with several reasons, the most common being complete or partial ureteral obstruction by stones. Prevalence of renal colic is about 10-15%. Pain relief is a priority in treating this condition and prescription of opioids, including morphine is the most common method of pain relief. Taken into account that patients often require more than one dose of morphine and high doses of opioids cause respiratory depression and confusion; this study aimed at evaluating the administration of sublingual desmopressin in combination with morphine in order to lessen the toxic side effects of opioids and to reduce the number of doses and its heavy costs on the health system.

MATERIALS AND METHODS

This single-blind randomized controlled clinical trial was performed on patients referring to the urology emergency unit of Imam Reza hospital, Mashhad, Iran from April 2010 to October 2011 with the signs and symptoms of renal colic. The effect of desmopressin in combination with morphine was compared to morphine in combination with placebo.

The study was conducted in accordance to the principles of Declaration of Helsinki 1996 version and Good Clinical Practice standards. The study protocol and informed-consent form were reviewed and approved by the Human Research Ethics Committee of Mashhad University of Medical Sciences. All patients were able to read, understand and were willing to sign the informed consent before entering the study.

Patients with renal colic, hematuria in urine analysis and evidence of urolithiasis in urinary tract ultrasonography plus kidney-ureter-bladder (KUB) X-ray, intravenous urography (IVU) or computed tomography (CT) scan were enrolled in the study. All cases with any of the following criteria were excluded: a history of hypertension, coronary artery disease, azotemia, pregnancy, having received other analgesics within 4 hours prior to admission, treatment with alpha-blockers, participation in another study, pyonephrosis, single kidney and bilateral stones. The inability of the patients to determine the quantitative scores due to illiteracy was also considered as the exclusion criteria.

In total 81 patients entered the study. They were divided into two groups based on the random numbers table.

The study group including 41 patients was treated with 0.1 mg/kg IM morphine plus 60 µg of sublingual desmo-

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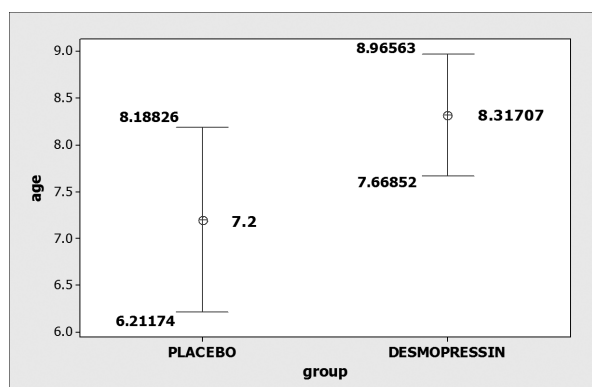


Figure 1. Error bar chart for comparison of pain scores in the first 10 minutes after receiving medication based on the treatment group.

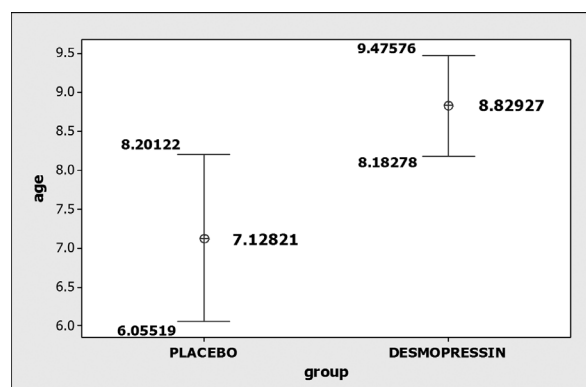


Figure 2. Error bar chart for comparison of pain scores in the first 20 minutes after receiving medication based on the treatment group.

pressin melt, whereas the control group (40 patients) was treated only with the morphine beside a placebo.

The Visual Analog Scale (VAS) was used to assess the severity of pain. The scale ranged from 0 to 10, in which 10 was considered as the highest and zero as the lowest amount of pain experienced. Their pain was evaluated at minutes 10, 20 and 30 after drug administration both subjectively and objectively; vital signs of the patients were also noted. Moreover, possible side effects of the disease, including dry mouth, postural hypotension, dizziness, nausea, vomiting and respiratory depression were recorded.

All of these data along with demographic characteristics such as age, sex, previous medical history and stone properties such as size (mm) and location (middle, upper or lower ureter) were recorded in a designed questionnaire. Data were analyzed using chi-square and student's *t*-tests (Figures 1-3).

The Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 13.0 was used for statistical analysis.

RESULTS

No morbidity was recorded during and after the study in this research. No significant difference was observed in the mean age between men and women ($P = .430$). Also, there were no statistically significant differences between the average age group among two groups ($P = .15$). Of the study subjects 26, 9 and 5 cases in the study group and 27, 8 and 6 patients in the control group had stones in the upper, middle and lower ureter, respectively. Chi-square test showed no significant difference between these two groups ($P = .925$).

Of the patients 57.5% in group 1 and 58.5% in group 2 had stones in their right kidney; Chi-square test showed a similar proportion of right kidney stones in the two studied groups ($P = .925$). The mean stone size was 5.46 mm; which were 5.32 mm in group 1 and 5.60 mm in group 2. The student's *t*-test showed no significant difference

between the two groups ($P = .522$). In total, the mean time from the onset of pain was 4.29 h; which were 3.92 h and 4.66 h in groups 1 and 2 respectively. The student's *t*-test showed no significant difference between the two groups ($P = .676$). The mean VAS score in the first ten minutes after drug administration was 7.77 ± 2.66 ; which were 8.32 ± 2.05 and 7.20 ± 3.09 in groups 1 and 2, respectively. The student's *t*-test showed a significantly higher pain score in the case group than the controls ($P = .042$). Mean pain score in the first twenty and thirty minutes after drug administration was 8.21 ± 2.64 and 8.00 ± 2.85 based on the total VAS score, respectively. The student *t*-test showed that pain intensity in the study group was significantly higher than the control group ($P = .017$ and $P = .008$, respectively)

DISCUSSION

Acute renal colic is a urological emergency which requires immediate attention to relieve pain and has always been described as one of the worst pains a human can experience; hence many treatment modalities (both pharmacologic and non-pharmacologic) have been described and applied only with the aim of lessening the pain.⁽¹⁻⁵⁾ Acupuncture and warming of the flanks are two examples of the non-pharmacologic therapies which have been used to relieve the pain of renal colic. High efficacy in the least amount of time is considered as the most important aspect of any type of therapeutic modality. The effectiveness of administered treatments including the use of opium derivatives as the oldest treatment and non-steroidal anti-inflammatory drugs (NSAIDs) has been proved in several clinical trials. Anti-muscarinic antispasmodics such as hyoscine and newer therapies such as vasopressin/desmopressin derivatives, the topic of research in the current study, have been compared with other medical treatments such as alpha-adrenergic blockers and calcium channel blockers (tamsulosin and nifedipine) to assess their effectiveness.^(3,5)

It is clear that opioids are associated with many side effects, including respiratory depression, sedation (particularly in elderly persons) and gastrointestinal upset which all can endanger the opioid usage.⁽⁵⁾

Also NSAIDs have some known side effects such as gas-

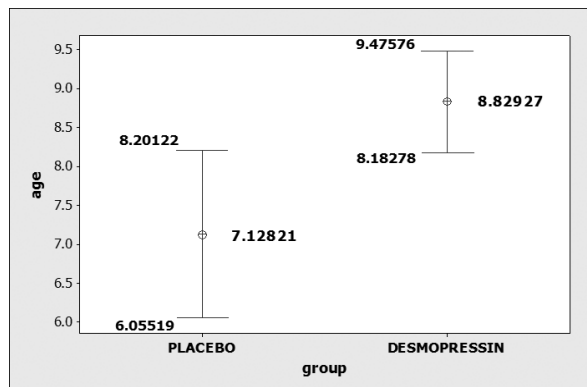


Figure 3. Error bar chart for comparison of pain scores in the first 30 minutes after receiving medication based on the treatment group.

gastrointestinal disorders, particularly peptic ulcers, nausea and vomiting, interference with the clotting process, anti-clotting mechanism and nephrotoxicity,⁽¹⁻⁵⁾ as well as muscarinic antispasmodics. Therefore, the need for a safe drug with high efficiency and low cost seems necessary. Several clinical trials have been conducted aimed at understanding the mechanism of this effect in combination with other medications.^(1,3,6-15) Only in Roshani and colleagues study, most patients aged from 26 to 35 years, although the age range of the subjects in this study was 15-62 years with a mean age of 36.98 years.⁽⁷⁾ The evaluation method of this study, VAS pain evaluation score, was in consistent with many previous studies. It was evaluated at 10, 20, and 30 minutes after drug administration and performed under accepted standard condition. The main difference between this study and other studies on desmopressin was administration of the sublingual form of DDAVP (Melt) which is absorbed faster, whereas in other studies nasal sprays have been used. As mentioned before, in this study it was shown that in patients treated with desmopressin and morphine, pain had a significantly higher score compared to the control group receiving morphine and placebo; in each of the time points (10, 20 and 30 min) the effectiveness of morphine plus placebo in relieving pain was higher than its combination with desmopressin. Hazhir and colleagues⁽⁶⁾ reported that there is no difference in combination therapy. Results of desmopressin and pethidine compared with pethidine alone showed the latter to have higher effectiveness in pain reduction. On the other hand, the same study also suggested that intranasal desmopressin can improve pain in one third of patients but is not as effective as narcotics. Other studies have investigated desmopressin with NSAIDs and antispasmodic drugs like hyoscine which their results are controversial with many contradictions. Ben Rhouma and colleagues⁽⁵⁾, Lopes and colleagues⁽⁸⁾ and Ramirez and colleagues⁽⁹⁾ found no advantage in adding desmopressin to NSAIDs, whereas Bhil and colleagues⁽¹⁰⁾, Roshani and colleagues⁽⁷⁾, Constantinides and

colleagues⁽¹¹⁾ and El-Sherif and colleagues⁽¹²⁾ have all explicitly stated that desmopressin in combination with NSAIDs results in more effective pain relief in renal colic. Kheirollahi and colleagues⁽¹³⁾ also found a higher efficacy in the administration of desmopressin in combination with muscarinic antispasmodic drugs such as hyoscine. Different mechanisms have been proposed in decreasing the renal colic pain including anti-diuretic effects of DDAVP, centrally stimulating effect on release of beta-endorphins, decrease in mean intra-ureteral pressure and inhibition of sudden annular smooth muscle contractions.^(6,16) Considering obstruction of the urinary tract caused by stones in the early hours (especially in the first 4 h), both ureteral and capillary pressures increase, while in the following hours capillary pressure decreases but the ureteral pressure still remains high. If this assumption is correct and there is a rapid effect for desmopressin especially in the early hours, the effect on mean ureteral pressure leads to decrease of ureteral smooth muscle contractions which may ultimately be related to its anti-diuretic effect; on the other hand if a central effect is supposed for its mechanism, it is expected that this phenomenon occurs in the later hours. This is a hypothesis that requires further investigation with a controlled clinical trial to evaluate the effect of desmopressin at different hours after the onset of renal colic. Considering the annoying characteristic of pain for patients, the reasonable path would be recording the duration between the pain onsets till to hospital admission. Studying desmopressin in combination with different drugs in a double blind controlled clinical trial with an appropriate study population divided into several groups is highly recommended in order to identify the most effective and the best combination therapy for renal colic.

CONCLUSION

Although this study showed no benefit in adding desmopressin to the traditional treatment of renal colic (morphine); yet it is an available drug with few and easily manageable side effects compared to other compounds such as opioids, NSAIDs and antispasmodic drugs and has fewer contraindications. Therefore, it is highly recommended to evaluate desmopressin in future clinical trials especially in combination with other compounds.

CONFLICT OF INTEREST

None declared.

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