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Comparison efficacy of oral *Peganum harmala* seed versus tamsulosin on pain relief and expulsion of renal and ureteral stones; a randomized clinical trial

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ABSTRACT

Introduction: Kidney stones are glycoproteins sediments that are formed inside kidney tubules and collecting ducts and are made of acid crystals and minerals.

Objectives: This study aimed to compare the effects of *Peganum harmala* seed and tamsulosin on pain relief and expulsion of renal and ureteral stones in patients candidate for medical therapy.

Patients and Methods: in this randomized clinical trial 80 patients older than 18 years with kidney and ureteral stones sized 4 to 10 mm were randomly allocated to one of two groups by simple sampling method. In group one, after performing ultrasonography and confirming the presence of 4 to 10 mm stone one capsule of tamsulosin 0.4 mg was prescribed per night for two weeks. In group two, harmala seed preparing in form of capsule with dose of 50 mg/kg/d, was prescribed after meal as the same of first group. Two weeks later patients were re-visited and urinary tract ultrasonography was conducted and the change in size of stones and presence of residual stones evaluated and recorded. The severity of pain in the patients was checked using VAS (visual analogue scale). Then the data was collected and analyzed at the end of the study.

Results: Mean size of stones after treatment were 4.07 ± 3.66 and 5.15 ± 3.63 mm respectively ($P=0.21$). Mean numbers of stones before and after treatment were 0.59 ± 1.38 and 1.18 ± 0.94 ($P=0.052$). Pain score decreased significantly in both groups which was more significant in *P. harmala* group ($P=0.002$). Efficacy of treatment (sum of complete and partial response) in the two groups was 77.5 % and 77.8 % respectively and no significant differences between the two groups were seen ($P=0.06$). There was no significant side effect in the two groups.

Conclusion: This study showed that both *P. harmala* seed and tamsulosin decrease urinary stone size and numbers without significant difference, but pain score decreased significantly by *P. harmala*.

Trial Registration: Registration of trial protocol has been approved by the Iranian Registry of Clinical Trials website (identifier: IRCT20081011001323N17, <https://irct.ir/trial/30508>; #IR.YUMS.REC.1396.120).

Implication for health policy/practice/research/medical education:

In a randomized clinical trial on 80 patients with kidney and ureteral stones sized 4 to 10 mm candidate for medical therapy with *Peganum harmala* seed or tamsulosin, we found both *P. harmala* seed and tamsulosin decrease urinary stone size and numbers without significant side effects.

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Introduction

Kidney stones are glycoproteins sediments that are formed inside kidney tubules and collecting ducts and are made of acid crystals and minerals (1). Kidney stones

are formed for various reasons like generic disorders, anatomic malformations metabolic disorders, familial predisposition, urinary infection or unhealthy diet. Treatment of urinary stones depends on quality, size and

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location of the stone and the patient's situation (2,3).

Kidney and ureteral stones less than 4 mm are often excreted with urine by activity and exercise and consuming liquid and also diuretics. Stones sized 4-6 mm are excreted in 50% of the cases with conservative and medical treatment (2, 4). Passage of stones larger than 6 mm is not easy and may cause moderate to severe pain and obstruction. These stones excrete during few days to few weeks with mild to severe pain, since if they are not excreted, they obstruct the urinary tract and cause kidney dysfunction. In this situation; the stones should be crushed and removed by minimal invasive and surgical methods (2,5).

With regard to surgical complications and also recurrence of stones, there is a need to use medical treatment or noninvasive methods with ability of crushing of kidney and urinary tract stones and their painless passage (6-10).

One of these herbs that had various benefits such as analgesic and stone crushing in traditional medicine is *Peganum harmala* (Espand). *Peganum harmala* commonly called wild rue, or hamel is a medicinal plant from the family of Zygophyllaceae, which is a type of wild mirage. It is a herbaceous plant, with a shrub that has a height of up to 15 cm (10,11).

The usable parts of this herb are the seeds using in

treating various diseases such as renal diseases. In Iranian traditional medicine, this herb is used for lung moisture. *Peganum harmala* also improves sexual drives, increases urine and has curative effects on kidney diseases like analgesic effect, disinfecting urinary tracts, treating urinary diseases like gonorrhea and syphilis (9-17).

Objectives

Considering the diuretic, analgesic and antiseptic effects of this herb, the purpose of this study was to evaluate the effects of harmala seeds on improving pain and rate of excretion of 6 to 10 mm stones of kidney and ureter in patients candidate for medical therapy who referred to a urology clinic.

Patients and Methods

Study design

In this randomized clinical trial, 80 patients older than 18 years old with kidney and ureteral stones sized 4 to 10 mm who did not have indications for immediate intervention and severe pain were randomly allocated to this study from June 2018 to May 2019 (Figure 1). History and complete physical exam, basic serum samples including Na, K, CBC, PT, PTT, renal function tests (BUN and creatinine) as well as urine analysis and culture were taken from all patients.

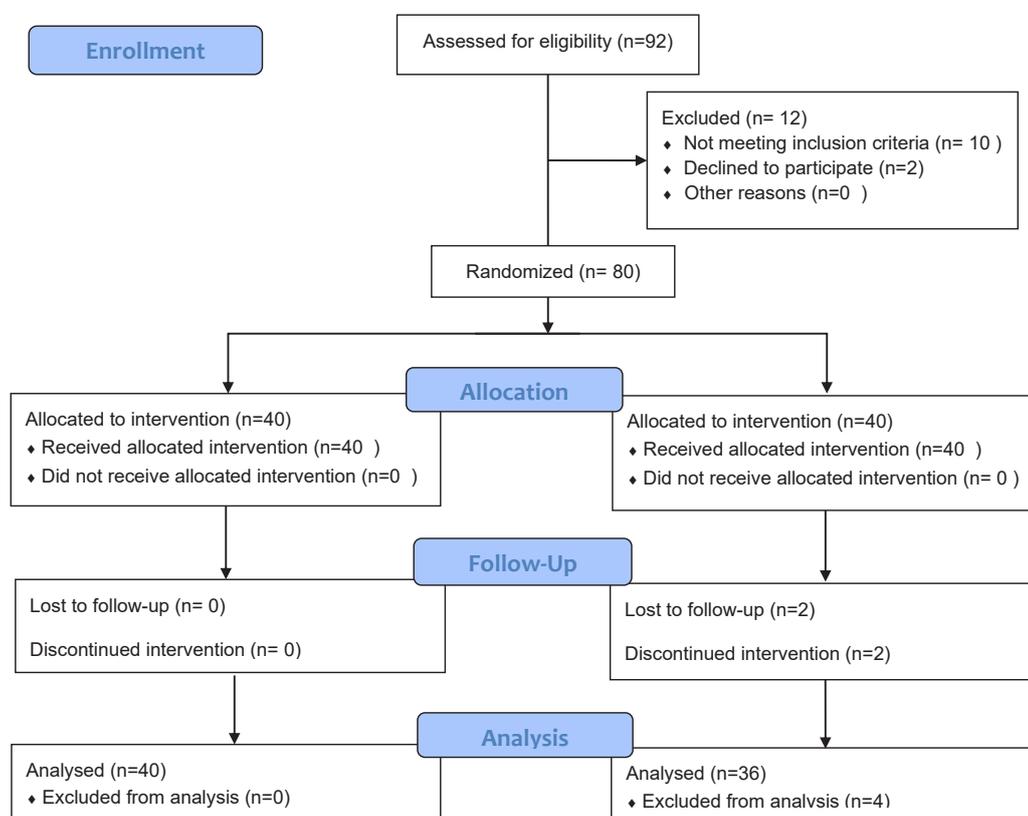


Figure 1. Flow diagram of the study.

Patients with cardiovascular or pulmonary disease, coagulopathy, uncontrolled hypertension, pregnant women as well as those with any contraindication for use of advised sedative and opioid drugs, and with history of drug or herbal allergy were excluded from the study. Then eligible patients were randomly allocated to one of two groups by simple random sampling method. Both groups were advised to drink 10-12 glasses of water daily.

In group 1, after performing ultrasonography and confirming the presence of 4 to 10 mm stone one capsule of tamsulosin 0.4 mg was prescribed per night for two weeks.

In group 2, harmala seed was prepared from Dena region, after determining herbarium number, dried in shadow and the seeds blinded after separating and preparing in form of capsule (both capsules were provided from same company) with dose of 50 mg/kg/d, was prescribed after a meal with one glass of water for two weeks. In both groups, diclofenac sodium was prescribed for pain control if necessary, since in cases of unresponsiveness to medical treatment or any other indication, the lithotripsy was conducted. In addition, patients were advised to do at least 30 minutes of exercise and walking. Two weeks later, patients were visited and urinary tract sonography was conducted and the change in size of stones and presence of residual stones were measured and recorded. The severity of pain was checked using VSA (visual analogue scale). Data were collected and analyzed during treatment and at the end of the study.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Yasuj University of Medical Sciences approved the study (IR.YUMS.REC.1396.120). The study was also registered as a clinical trial at the Iranian Registry of Clinical Trials website (identifier: IRCT20081011001323N17; <https://irct.ir/trial/30508>). Accordingly, written informed consent was taken from all participants before any intervention.

Statistical analysis

All data were collected and analyzed by SPSS software version 21. For analyzing the data, descriptive statistics including frequency, mean, and standard deviation were used. Then chi-square test and *t* test were used for comparing the groups. The significance level was set at 0.05%.

Results

Demographic characteristics of patients such as age, gender, stone location, mean size and number of stones were similar between the two groups. Results of this study showed no significant differences between two

groups regarding stone size ($P=0.314$) and stone numbers ($P=0.052$). Mean size of stones before treatment in both groups were 13.31 ± 7.16 and 10.79 ± 4.82 mm respectively (Table 1). There were no significant differences between the two groups regarding mean stone size after treatment ($P=0.21$), although in both groups stone size decreased significantly after treatment (Table 2). Mean number of stones before and after treatment was 1.38 ± 0.59 and 1.18 ± 0.94 while there were no significant differences between the two groups ($P=0.057$). In addition, no significant differences between the two groups regarding location of stones were seen ($P=0.09$). There were no significant differences between the two groups regarding mean of pain score before treatment ($P=0.055$); however pain score decreased significantly in both groups which was more significant in *Peganum harmala* group ($P=0.002$). Regarding efficacy of treatment, no significant differences between two groups detected, however in both groups the efficacy of treatments was more than 75% after trial (Table 3).

Discussion

The aim of this study was to determine the effects of *Peganum harmala* versus tamsulosin in reducing the

Table 1. Frequency distribution of patients regarding mean stone size before treatment in two groups

Groups	Variable	P value	Confidence Interval
	Mean stone size \pm SD (mm)		
<i>Peganum harmala</i>	13.31 \pm 7.16	0.63	-1.165-6.181
Tamsulosin	10.79 \pm 4.82		

Table 2. Frequency distribution of patients regarding mean stone size after treatment in two groups

Groups	Variable	P value	Confidence Interval
	Mean stone size \pm SD (mm)		
<i>Peganum harmala</i>	4.07 \pm 3.66	0.21	-0.637-2.79
Tamsulosin	5.15 \pm 3.63		

Table 3. Frequency distribution of patients regarding efficacy of treatment after intervention in two groups

Efficacy	Groups		P value
	<i>Peganum harmala</i> No. (%)	Tamsulosin No. (%)	
Complete	10 (25)	14 (38.9)	0.06
Partial	21 (52.5)	14 (38.9)	
Failure	9 (22.5)	8 (22.2)	

pain and in excretion of renal and ureteral stones. After treatment, size and number of stones and pain intensity decreased in two groups but this reduction in *Peganum harmala* group was more than tamsulosin group.

In the study by Li et al, harmala had a good analgesic effect in treatment of renal stones (11). Our results are consistent with this study regarding the good analgesic effect of harmala, although in their study, there was not any control group for comparison.

Additionally in a study by Sharif and colleagues, flavonoids of harmala seeds had suitable analgesic effects in treatment of musculoskeletal and rheumatic pains (12). Our results are consistent with this study regarding positive effect of harmala for pain relief.

Recently, Losek and Mauro in five prospective studies assessed the effects of combined extracorporeal shock wave lithotripsy (ESWL) with tamsulosin in increasing renal and ureteral stone passage. In their study, clearance of renal and ureteral stones in the tamsulosin group was more than the control group and also the reports of pain and taking analgesic medications were consistently lower in the tamsulosin group (18). In our study, pain intensity decreased in both tamsulosin and harmala groups but this response was significantly more in *Peganum harmala* group that is due to suitable analgesic effect of harmala (Espand) in passage of urinary stones.

In a randomized prospective study by Georgiev et al, patients were divided into two groups of case and control, in which 0.4 mg tamsulosin was given as adjuvant therapy. All patients were visited every two weeks after ESWL up to eight weeks until stone clearance; then the clearance time and pain intensity were evaluated. The result of this study showed that tamsulosin had a significant effect on renal stone clearance after ESWL. It also facilitated stone clearance before ESWL and reduced pain intensity (19).

In our study, the size and numbers of stones decreased in two groups, however there was no significant difference regarding efficacy of treatment for passage and decrement of stones that is not consistent with above-mentioned study. This difference may be somehow due to short time of our study.

In addition, Yencilek and colleagues in a study randomly divided 92 patients with upper ureteral radiopaque stones with a size of less than 10 mm in two groups of conservative treatment or tamsulosin. Patients were divided into two groups of stones of less than 5 mm and 5-10 mm stones. They found administration of tamsulosin facilitates the spontaneous excretion of upper ureteral stones in stones less than 5 mm and facilitates the passage of stones to the distal ureter in stones in range of 5 to 10 mm (20).

The result of our study regarding efficacy of tamsulosin in decreasing size and passage of stones in tamsulosin group was consistent with their study, although in the

study by Yencilek et al only ureteral stones were studied and in control group only conservative treatment was conducted.

Regarding complications, Zhu et al investigated the effect of alpha-blockers such as tamsulosin on renal stone clearance after ESWL. Minor complications were reported in eight patients while vertigo was the most common complication (21).

Also Frison et al reported some harmful effects of harmala in β -Carboline alkaloid intoxication and additionally a case report of death after use of harmala seed was reported (22).

In our study only one patient developed rash and itching. This finding is consistent with the studies conducted by Yencilek et al (20) and Zhu et al (21); however the side effect detected in our study was in contrast to the study by Frison et al (22).

Conclusion

This study showed that both *Peganum harmala* seed and tamsulosin without any significant side effects decrease urinary stone size and numbers without significant difference, however pain score decreases significantly by *Peganum harmala*. We suggested that more studies with larger sample size and longer follow up will be done with different doses of harmala seed for making the right decision.

Limitations of the study

The limitations of study are as follows: (1) Some patients had allergy to herbal drugs and were excluded from the study. (2) We used low doses for prevention of any side effects due to some reports regarding toxicity of *Peganum harmala*.

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Authors' contribution

SM; the concept, design, data analysis, and manuscript preparation, manuscript review and final revision. NS; preparing materials, performing study, data collection and proposal writing. AM; data collection and providing first draft and submission. HM; statistical analysis, data collection and first revision. All authors read and signed the final paper.

Conflicts of interest

The authors declared no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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