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Efficacy of tamsulosin versus tamsulosin plus lithorex-B as medical expulsive therapy following extracorporeal shock-wave lithotripsy of renal and upper ureteric stones; a randomized clinical trial

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ABSTRACT

Introduction: Urolithiasis is one of the most common disorders of urinary system.
Objectives: To compare the efficacy and safety of tamsulosin versus tamsulosin plus lithorex-B.
Patients and Methods: This study was an open-label, randomized, controlled trial conducted in Yasuj University of Medical Sciences, Iran in 2014 to 2015. After taking informed consent, a total of 64 patients aged 18 years and over, presenting with renal or upper ureteral stones up to 20 mm in diameter were enrolled in this study. After extracorporeal shock-wave lithotripsy (SWL), patients were randomly assigned to group A (n = 32) received tamsulosin 0.4 mg and group B (n = 32) received tamsulosin 0.4 mg plus lithorex-B 400 mg orally at bed time daily for 2 weeks. Finally, patients were assessed by KUB and sonography. The stone passage rate, drug adverse effects and pain score were evaluated. All data were analyzed using SPSS 21.
Results: There were no significant differences between group A and B regarding stone expulsion rates (40.6% vs 43.7%, $P = 0.83$), adverse effects (34.4% vs 40.6%, $P = 0.79$) and mean score of pain (4.31 ± 2.02 vs 5 ± 2.01, $P = 0.17$) after 2 weeks follow up. Primary stone size was the predicting factor of stone passage (β = -0.42, $P = 0.005$, Exp (β) = 0.65, CI 95%, Exp (β): 0.48-0.88).
Conclusion: Tamsulosin plus lithorex-B is safe and well tolerated with no extra benefit regarding the expulsion rate in 2 weeks follow up. Hence, the necessity of conducting a trial with a longer follow up period providing comparison between tamsulosin and lithorex-B in separate group is felt.

Implication for health policy/practice/research/medical education:
Further studies are necessary to provide comparison between tamsulosin and lithorex-B in separate groups for deciding about treatment with lithorex-B.

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Introduction

Urolithiasis is one of the most common disorders of urinary system and allocates more than one million visits to physician and emergency room annually (1). Urolithiasis affects about 5%-15% of population worldwide (2-4). The incidence of urolithiasis is higher in the Middle East, western India and southern USA (1). In Europe and north America, life time risk of developing urinary tract stones is estimated 5%-10% (5).

The standard and first choice of treatment for renal calculi 6-20 mm is extracorporeal shock-wave lithotripsy (SWL) with a reported stone free rate ranged from 66% to 99% for kidney stones depends on stone size, location and anatomy of renal collecting system (3,5). In the last decades, medical expulsive therapy (MET) has become an accepted modality of treatment (1,3) following SWL that potentially decreases the costs of treatment (5) through facilitating stone passage and decreasing morbidity (6).

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Currently, calcium channel blockers and α1 adrenergic receptor antagonists are the main established treatments of choice for MET (4,6).

Tamsulosin is a selective α1-adrenoceptor antagonist that increases the stone expulsion rate and decreases the expulsion time (3). Moreover, lithorex-B is another commonly used drug for MET in Iran (7).

Its ingredients are dry extract of cucurbita seed, populous nigra and *Solidago canadensis* leaves. *S. canadensis* (Canadian golden rod) has been used in European phytotherapy for seven centuries in treatment of cystitis, chronic nephritis, urolithiasis, rheumatoid arthritis (8,9). It has diuretic, spasmolytic, analgesic, anti–inflammatory, antimicrobial and antiphlogistic effects and has been approved for treatment the infections of urinary tract, expulsion of kidney and bladder stones and prevention of kidney stone formation (10,11).

Populous nigra has antibacterial, antiphlogistic, and spasmolytic effects and is used in treatment of hemorrhoids, wounds, burns and micturition complaints due to prostate hypertrophy (10). *Cucurbita pepo* seeds inhibit 5-α reductase enzyme in vitro.

It has anti-androgenic and anti-inflammatory effect in vivo and has been proved for using in irritable bladder and prostate complaints (10). In one study, *C. pepo* seed has decreased calcium oxalate formation too (7).

Objectives

To our knowledge there is not any study assessing the role of lithorex-B after SWL for renal and upper ureteral calculi. Thus, this study was designed to compare the effect of tamsulosin versus tamsulosin plus lithorex-B on stone expulsion following SWL. On the other hand, we decided to discover whether combining drugs acting through different mechanisms can facilitate and increase stone clearance.

Patients and Methods

This study was an open-label, randomized, controlled trial conducted in an outpatient setting from April 2014-2015 in Yasuj University of Medical Sciences (YUMS), Iran. After obtaining written informed consent, a total of 64 patients aged 18 years and over, presenting with renal or upper ureteral stones up to 20 mm in diameter were enrolled in this study. Presence of stones were diagnosed and confirmed by plain abdominal radiography (Kidney–Ureter–Bladder [KUB] x- ray), sonography or intravenous urography.

Patients with severe scoliosis or kyphosis, pregnancy, uncorrected coagulopathy, urinary tract infection, uncontrolled hypertension, renal insufficiency (defined as estimated glomerular filtration rate < 60 cc/min/1.73 m^2), sever cardiopulmonary disease, hypersensitivity to tamsulosin or lithorex-B, current use of alpha-blockers or calcium channel blockers, and also any contraindication for general or spinal anesthesia were not included to the study' too. Exclusion criteria were patient's tendency to leave the study and developing adverse drug events during consumption of tamsulosin or lithorex–B.

Laboratory tests such as complete blood count, erythrocyte sedimentation rate, blood urea nitrogen, creatinine, coagulation time, prothrombin time, bleeding time, sodium, potassium, urinalyses and urine culture were done for all participant patients. Based on visual analog scale (VAS), pain was assessed and scored from 0-10.

All lithotripsies were performed in supine position after taking intravenous line under general or spinal anesthesia by one urologist using Dornier Delta 2 compact lithotripter, Germany. After single–session SWL, patients without any problem were randomly assigned to one of medical treatment groups according to their inclusion in the study and admission in clinic based on a computer generated random number table.

Patients in group A were given oral tamsulosin 0.4 mg daily at bed time and those in group B were given oral tamsulosin 0.4 mg and lithorex–B 400 mg at bed time daily. The drug administration was started immediately after SWL. In both groups, drugs consumption was continued for 2 weeks.

Diclofenac 50 mg twice daily (every 12 hours) was given to both groups as analgesic. Patients were instructed to drink ≥ 2 L of water daily during treatment. All patients were required to filter their urine to detect stone expulsion. After 2 weeks, all patients underwent follow up examination. KUB and sonography were done and reported for all of them by one radiologist.

The adverse effect of drugs such as gastro-intestinal problem (abdominal pain, nausea, vomiting), headache, vertigo, respiratory and dermatologic reaction were assessed. Also, complete stone clearance rate, size of residual fragments and pain score were assessed at the end of follow up period (Figure 1).

A sample size of 58 patients was calculated using comparing two proportion formulas. It was estimated to yield 80% power (type II or beta error of 0.20%) to detect a difference of 20% or more between two groups (70% expulsion rate in tamsulosin group (1-5) and 90% in tamsulosin plus lithorex –B group), allowing 5% of type I error. Totally, 64 patients were enrolled in the study.

Ethical issues

1) The research followed the tenets of the Declaration of Helsinki; 2) informed consent was obtained; and 3) This study was approved by the Ethics Committee of Yasuj University of Medical Sciences (IR.YUMS.REC. 2015.174) and it was registered in Iranian Registry of Clinical Trials with number: IRCT201606151323N10.

Statistical analysis

All data were analyzed using SPSS 21 (SPSS, Chicago, IL, USA) software. Continuous variables with normal distribution were presented as mean ± standard deviation and were compared by independent samples *t* test and paired *t* test. Nominal variables were taken as counts (or

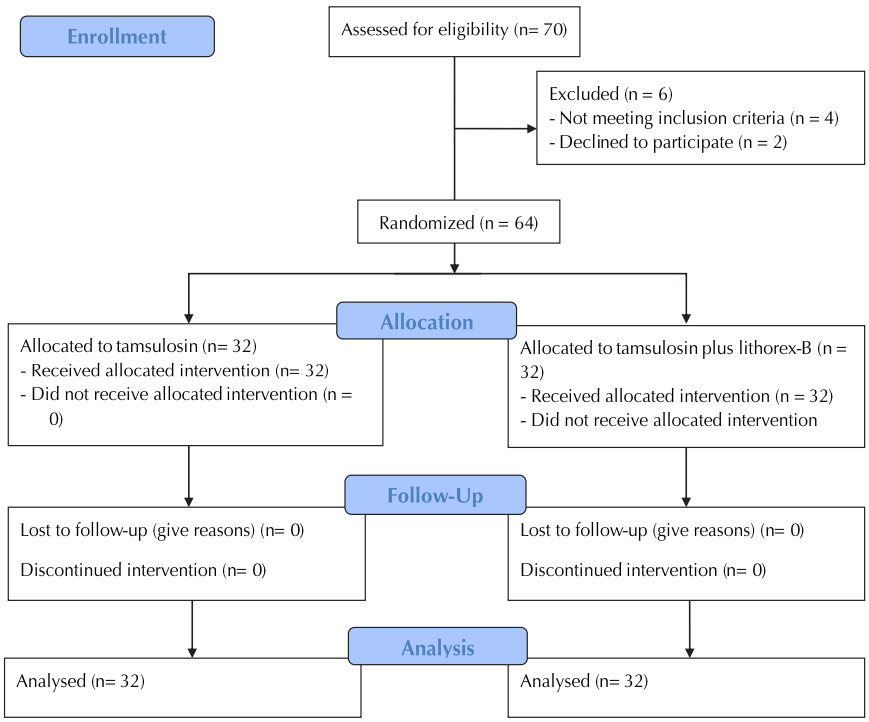

Figure 1. CONSORT statement flow diagram.

frequencies) and were compared by chi-square test. Also, logistic regression was used to assess the predicting factors of stone expulsion. All statistical tests were reported based on two tailed probability. A *P* value < 0.05 was considered statistically significant.

Results

All patients completed their planned out follow up period without drop-outs.

The two groups were comparable regarding their base line demographic and clinical characteristics as shown in Table 1.

Comparison the stone expulsion rate is shown in Table 2. After intervention, size of residual fragments in group A and B was 4.43 ± 0.65 and 4.04 ± 0.22, respectively ($P=0.75$). Also, there was not any significant difference between group A (4.31 ± 2.02) and B (5 ± 2.01) in score of pain at the end of the study ($P=0.17$).

Table 1. Baseline demographic and clinical characteristics of patients

Variable	Group A Tamsulosin (n=32)	Group B Tamsulosin plus lithorex-B (n=32)	*P* value[a]
Age (mean years ± SD)	44.15 ± 12.8	44.56 ± 12.34	0.89
Sex			0.31
Male	21 (65.6%)	16 (50%)	
Female	11 (34.4%)	16 (50%)	
Stone size (mm ± SD)	9.25 ± 3.37	9.53 ± 3.82	0.75
Stone opacity			0.04
Radio-opaque	9 (28.1%)	14 (43.8%)	
Non-radio-opaque	23 (71.9%)	18 (56.3%)	
Side			0.45
Right	15 (46.9%)	13 (40.6%)	
Left	17 (53.1%)	19 (59.4%)	
Stone location			0.42
1 site	30 (93.8%)	27 (84.4%)	
> 1 site	2(6.2%)	5 (15.6%)	
Pain score (mean ± SD)	7.18 ± 1.65	7.81 ± 1.49	0.11

Abbreviation: SD, standard deviation.

[a] Independent samples *t* test and chi-square test were used for analyses.

Table 2. Comparison the stone expulsion rate in two groups

Expulsion[a]	Group A Tamsulosin (n=32)	Group B Tamsulosin plus lithorex-B (n=32)	*P* value[c]
Complete	13 (40.6%)	14 (43.7%)	
Partial[b]	11 (34.4%)	12 (37.5%)	0.83
No expulsion	8 (25%)	6 (18.8%)	

[a] Expulsion rate was compared after controlling for stone opacity as a confounding variable.
[b] Partial expulsion was defined as residual fragments more than 4 mm in sonography and KUB.
[c] Chi-square test was used for analysis.

Table 3. Comparison the adverse effects of drugs in two groups

Drug related adverse effect	Group A Tamsulosin (n=32)	Group B Tamsulosin plus lithorex-B (n=32)	*P* value[c]
Yes	11 (34.4%)	13 (40.6%)	0.79
No	21 (65.6%)	19 (59.4%)	

Comparison the drug related adverse effects are shown in Table 3. None of the adverse effects such as nausea, vomiting, headache and vertigo were significant enough to exclude patients from the study. There was not any report of respiratory and dermatologic problem. Gastrointestinal (GI) problems were reported in five (15.6%) of group A and seven (21.9%) of group B. Frequency of neurologic problems such as vertigo and headache were six (18.8%) and four (12.5%) in group A and B, respectively. Combined GI and neurologic problems were reported in two (6.3%) of group B and none of the patients in group A.

Based on logistic regression only primary stone size was the predicting factor of stone passage ($\beta = -0.42$, $P = 0.005$, Exp (β) = 0.65, CI 95%, Exp (β): 0.48-0.88).

After 2 weeks in patients with partial or none stone expulsion, if stone size was lower than 6 mm and there was not any complication, treatment continued for 2 weeks later. Patients with stone size more than 6 mm, presence of fever and renal function impairment were scheduled for another session SWL or transurethral lithotripsy plus insertion of double J catheter.

Discussion

Urolithiasis is one of the most common problem in referred patients to urologic clinic and emergency room (1,2). The present study investigated the beneficial effects and safety of tamsulosin versus tamsulosin plus lithorex-B in patients with renal and upper ureteral stone after successful SWL.

In brief, there was not any significant difference between group A and B in stone free rate, despite the fact that it was higher in group B. Also, in our study, stone clearance rate was lower in comparison with the most earlier studies in groups received tamsulosin (1-5,12,14,15,17-22).

Unfortunately, we did not find any similar study to compare our results with it. But our study was different from others because of 1) shorter follow up period (2 weeks vs 3-12 weeks in other studies) (1-6,12-23), 2) attendance of patients with more than one stone in different parts of kidney in spite of other studies (1-4,6,14,16,18,19,21,22). Additionally, it is obvious that stone location, size, number and structure, presence of ureteral spasm, mucosal edema or inflammation and ureteral anatomy are the factors influencing stone clearance rate (1).

It should be mentioned that located stones in lower pole of kidney have less benefit from any medical therapy (19) and proximal stones of ureter have a decreased likelihood of passage compared with distal stones (6), 3) Larger size of stones despite some previous studies (1,2,4,6,22).

On the other hand, it has been revealed from some studies that stone expulsion rate was not related to follow up duration (61%, 93% and 78.5%) in 3, 4 and 12 week follow up (18,19,24). Hence, we chosen a 2-week follow up duration. It seems that clinical heterogeneity in participants might have influenced the results. With respect to high possibility of improvement in stone expulsion in European and American, belonging to different geographic regions (13) can be considered as another explanation.

After intervention, there was not any significant difference in the size of residual fragments between two groups.

In other previous studies, stone size after MET was not been measured in partial and no- expulsion groups. So, we could not compare our results.

In our study, pain score did not vary markedly between two groups following intervention. Our finding was in contrast with Jayant et al findings that have used combination therapy (tamsulosin plus tadalafil) versus tamsulosin and led to lower significantly analgesic use, number of colic pain and hospital visits in favor of combination therapy (1). In addition to different combination regimens in our study, another explanation may be the necessity of longer consumption of lithorex-B to obtain more pain relief, because in spite of significant reduction in pain sensation in each group, pain reduction was significantly higher in tamsulosin group.

It should be mentioned that to our knowledge, there are very few comparative studies that investigated combined versus single MET. Also, it should be noted that pain threshold and tolerability is different in patients because it is a complex perceptual experience (3).

The reported side effects in both groups were well tolerated and completely reversible without any drug discontinuation although it was mildly higher in combination therapy with tamsulosin plus lithorex-B without any significant difference.

Similar to some studies (6,18), we found that stone size is an important independent predictive factor of stone passage, so that smaller stone size resulted in higher stone clearance.

Lastly, we could not evaluate the effect of tamsulosin on the expulsion time of stone fragments, because a consistent number of patients did not record the time of residual fragments expulsion.

Conclusion

To our knowledge, this was the first randomized trial that assessed the efficacy of lithorex-B in combination with tamsulosin. Therefore, to evaluate the efficacy and safety of lithorex-B, the necessity of conducting a trial providing comparison between tamsulosin and lithorex-B in separate groups based on tendency to use herbal remedies in general population is felt.

Limitations of the study

There are some limitations to our study that should be addressed; containing its mono centric, small proportion of evaluated cases (due to highly limited similar published available data in the literature), short duration of follow up and absence a separated treated group with lithorex-B because we did not want any patient be deprived from tamsulosin as the proven standard drug of MET.

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Authors' contribution

SM and LM conceived the study and contributed to reagents and tools. SM, A K and FM performed the experiments. LM analyzed the data and drafted the final manuscript. All authors read, revised, and approved the final manuscript.

Conflicts of interest

There were no points of conflicts.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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