



## Research Article

### CLINICAL EVALUATION OF ‘SUSPEND’ TRIAL WITH HERBAL PREPARATION AND TAMSULOSIN: A MEDICAL EXPULSIVE THERAPY FOR UROLITHIASIS

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#### ABSTRACT

Lithiasis occurs in various forms and at various sites in the body and the most common site is urinary tract. Urinary stones are one of the major problems and an important cause of morbidity and end stage renal failure in India. Urolithiasis affects up to 5 % of the population, with a recurrence rate of 50 to 80 %. Males are more frequently affected than the females. The objective of this study is to evaluate and compare the efficacy and safety of Herbal preparation (decoction of *Boerhavia diffusa* roots and *Crataeva nurvala* bark) and Tamsulosin in the treatment of patients with ureteric stones. A total of 110 patients with ureteric stones ranged from 4- 10 mm were selected for the trial according to the inclusion and exclusion criteria of this study and were randomized into two groups where the first group (herbal group) included 55 patients treated with decoction of *Boerhavia diffusa* roots and *Crataeva nurvala* bark in the dose of 50 ml BD daily, and the second group (tamsulosin group) included 55 patients treated with tamsulosin 0.4 mg/day. All patients were randomly assigned to receive the designed SUSPEND trial (Spontaneous Urinary Stone Passage enabled by Drugs) for a maximum of 6 weeks. The Herbal preparation found statistically significant in increasing the expulsion rate, better control of ureteric pain and reduced expulsion time of ureteric stone impacted in any part of the ureter i.e. the upper, middle and lower ureteric tract and thereby decrease in number of URS procedure performed to remove the stone of unaffected patients. Tamsulosin group results in a better control of ureteric pain and reduced expulsion time of stones which are impacted in only lower ureter.

**Keywords:** Ureteric stone, *Boerhavia diffusa*, *Crataeva nurvala*, Tamsulosin, Suspend trail, MET.

#### INTRODUCTION

Mankind has been affected by urinary stones since centuries. Even in the 4<sup>th</sup> century BC, Hippocrates- the Father of modern medicine notes the presence of the renal stone together with the renal abscess and he wrote in his Hippocratic Oath "... I will not cut, even for stone, but leave such procedures to the practitioners of the craft." This denotes the priority of first conservative approach and if it fails, then surgery is to be opted. The urinary stones have peculiar tendency of recurrence even after its surgical removal. Once a stone formed, the person is always a stone former. Therefore, surgery can only be a part of treatment, but not the complete treatment. Minimal invasive techniques such as ESWL<sup>1</sup> and ureteroscopy are frequently applied procedures in ureteral stone disease. The tamsulosin drug is very commonly used after ESWL. Sushruta, the father of surgery has described in his text Sushruta samhita<sup>2</sup> the complete management of the urinary stones by herbal drugs, caustics and also by surgical procedure wherever indicated. The *Boerhavia diffusa* roots with mainly diuretic<sup>3</sup> property and *Crataeva nurvala* bark with anti-lithiatic property has been clearly advocated in the various Ayurvedic texts and is considered as a traditional therapy for urolithiasis.

#### MATERIAL AND METHODS

From May 2009 to January 2011, patients with complaints of solitary ureteral stone located in upper, middle, or lower ureter were selected for the trial in Government hospital Sarwal, Jammu, J and K, India. Written informed consent was obtained from each participant, and the institutional review board approved our study. The assessment of stone

size and location was performed by plain x-ray (KUB), ultrasound imaging (KUB) and/or IVU if found necessary. The inclusion criteria were age between 15- 60 years; unilateral single ureteric stone with size 4-10 mm; and written informed consent from the patient. The exclusion criteria were age younger 15 years; ureteric stone with size >10 mm; kidney stone or bladder stone; multiple stones within a ureter; bilateral ureteric stones; elevated serum creatinine; urinary tract infection; diabetes; peptic ulcers; history of spontaneous stone expulsion; hypotension; coagulopathy; urinary congenital anomalies; previous nephroureteral surgery; patients currently taking an  $\alpha$ -blocker or patients who are unable to understand or complete trial documentation. The patients fulfilling the above criteria were selected and randomly divided into two groups, the Tamsulosin group and the Herbal group, using a random number table. The tamsulosin group received oral administration of tamsulosin 0.4 mg OD in the morning after breakfast. The Herbal group received oral administration of 50 ml decoction of *Crataeva nurvala* and *Boerhavia diffusa* after meals BD. A gastroprotective therapy (40 mg pantoprazol once daily) was given to every patient. The duration of the trial was 6 weeks and patients were advised to drink a minimum of 2 litres of water daily and filter their urine, and those who had passed their stones were asked to stop the medication. During the trial period, diclofenac (75 mg) was given to the patients when needed for pain relief. Patients were evaluated for stone clearance and time to stone clearance. The pain intensity was evaluated with the visual analogue scale (VAS). Follow up of the patients was done up to 3 months. Statistical analysis was performed using SPSS

software, (statistical package for social sciences, version 16.0 standard version. SPSS incorporated 1989-2007). The differences between groups were tested using the *t* test and  $p < 0.05$  was considered statistically significant.

## Drugs Contribute

### Tamsulosin

The drug Tamsulosin is an alpha adrenoceptor antagonists<sup>4</sup> and has been commonly used in Medical Expulsion Therapy (MET) and after endoscopic procedures like ESWL to facilitate movement of small ureteric fragments. The rationale behind the use of  $\alpha 1$ -antagonists in MET has been that they are capable of decreasing the resting tone of the ureter and interfering with ureteric contractions, thereby decreasing the frequency of peristaltic contractions. Several studies have demonstrated that alpha blockers expedite stone passage, decrease pain, and hence, reduce analgesic requirements.

### *Crataeva nurvala*

*Crataeva nurvala* (Capparaceae) is a high-value medicinal tree that grows almost all over India, especially in the semi-arid regions. Medicinal usage has been reported in traditional systems of medicine, such as Ayurveda and Unani, wherein the plant is frequently preferred in the treatment of urinary disorders that reoccur owing to development of antibiotic resistance by the infecting organism. The plant is known to relieve, prevent, and promote the discharge of urinary stones<sup>5</sup>. *Crataeva nurvala* has also been used in the treatment of prostate enlargement and bladder sensitivity. Lupeol, a pentacyclic triterpene isolated from the root bark, has been shown to significantly minimize the deposition of urinary stone-forming constituents. Bark decoction significantly prevented the deposition of calcium-oxalate in the kidneys by inhibiting the glycolic acid oxidase (GAO) and lactate dehydrogenase (LDH) enzyme activity in liver which are the major oxalate synthesizing enzymes<sup>6,7</sup>.

### *Boerhavia diffusa*

*Boerhavia diffusa* (Nyctaginaceae) is one of the renowned medicinal plants used to treat large number of human ailments as mentioned in Ayurveda. Besides a number of properties, *Boerhavia diffusa* roots are found to be with anti-inflammatory<sup>8</sup> and diuretic effects<sup>9</sup>. Maximum diuretic and anti-inflammatory activities have been observed in samples collected during the rainy season. Due to the combination of these two properties, the drug is regarded therapeutically

highly efficacious for the treatment of urinary stones, nephritic syndrome, oedema, and ascites developing at the early onset of the liver cirrhosis and blood pressure.

## Preparation of Decoction

The dried form of the two crude drugs i.e. *Boerhavia diffusa* roots and *Crataeva nurvala* bark were taken and grinded into small fragments. Then 12.5 g of both the grinded material was taken (total = 25 g) and put in a container containing 200 ml of water. The container was left for boiling until the water content evaporated and remained one-fourth i.e. 50 ml. The solution was filtered and allowed to cool at room temperature. The decoction was ready for oral administration.

## RESULTS

Total 110 patients with the complaints of unilateral single ureteric calculus were treated with MET under the trial. Majority of the patients suffering from the disease were males. In herbal group, 34 patients were males and 21 were females and in tamsulosin group, 31 patients were male and 24 were females. The average stone sizes were 7.8 mm in herbal group and 8.1 mm in the tamsulosin group. Statistically significant differences in terms of VAS pain score in upper ureter (mean = 3.074, SD = 0.828 in herbal group and mean = 5.59, SD = 1.140 in tamsulosin group,  $p < 0.001$ ) and middle ureter (mean = 2.909, SD = 0.831 in herbal group and mean = 4.928, SD = 0.828 in tamsulosin group,  $p < 0.001$ ) between the two groups is found where as in lower ureteric patients, the difference is insignificant (mean = 3.235, SD = 1.032 in herbal group and mean = 3.00, SD = 0.942 in tamsulosin group,  $p = 0.163$ ). The stone clearance time of upper (mean = 32.50 days, SD = 8.786 in herbal group and mean = 43.00 days, SD = 5.700 in tamsulosin group,  $p < 0.001$ ) and middle (mean = 27.50 days, SD = 5.976 in herbal group and mean = 36.60 days, SD = 4.219 in tamsulosin group,  $p < 0.001$ ) ureteral stones between the two groups showed statistical significant difference but there is no significant difference in the patients with lower ureteric calculus (mean = 18.00, SD = 8.823 in herbal group and mean = 17.81, SD = 9.123 in tamsulosin group,  $p = 0.861$ ). During the trial course and follow-up, no relevant side effects in connection with the herbal decoction and tamsulosin were observed. At the end of the trial, the patients who did not get rid of their calculus with this MET were advised for URS (12.72 % from the herbal group and 39.09 % from the tamsulosin group).

Table 1: Stone location wise distribution of data

Stone location	Herbal group		Tamsulosin group		Total	
	n	%	n	%	n	%
Upper ureter	27	24.54 %	22	20 %	49	44.54 %
Middle ureter	11	10 %	14	12.72 %	25	22.72 %
Lower ureter	17	15.45 %	19	17.27 %	36	32.72 %
Total	55	50 %	55	50 %	110	100 %

Table 2: Comparison of VAS pain scores according to ureteral stone location

Stone location	Herbal group			Tamsulosin group			<i>p</i>
	Number of patients	Mean pain score	SD	Number of patients	Mean pain score	SD	
Upper ureter (n = 49 )	27	3.074	0.828	22	5.59	1.140	< 0.001
Middle ureter (n = 25)	11	2.909	0.831	14	4.928	0.828	< 0.001
Lower ureter (n = 36 )	17	3.235	1.032	19	3.00	0.942	0.163

Table 3: Comparison of Stone clearance time according to ureteral stone location

Stone location	Herbal group			Tamsulosin group			p
	Number of patients	Mean days to clearance	SD	Number of patients	Mean days to clearance	SD	
Upper ureter (n = 23 )	18	32.50	8.786	5	43.00	5.700	< 0.001
Middle ureter (n = 13)	8	27.50	5.976	5	36.60	4.219	< 0.001
Lower ureter (n = 31 )	15	18.00	8.823	16	17.81	9.123	0.861

Table 4: Incidence of patients with impacted stone at the end of the trial

Incidence of patients with impacted stone at the end of the trial and advised for URS	Herbal group		Tamsulosin group		Total	
	n	%	n	%	n	%
Upper ureter	9	8.18 %	17	15.45 %	26	23.63 %
Middle ureter	3	2.72 %	9	8.18 %	12	10.90 %
Lower ureter	2	1.81 %	3	2.72 %	5	4.54 %
Total	14	12.72 %	29	26.36 %	43	39.09 %

## DISCUSSION

Tamsulosin is a selective  $\alpha$ -1 adrenergic antagonist that has preferential selectivity for the  $\alpha$ -1A receptors in prostate versus the  $\alpha$ -1B receptors in the blood vessels. When  $\alpha$ -1A receptors in the bladder neck and the prostate are blocked, this causes a relaxation in smooth muscle and therefore less resistance to urinary flow. Thus, the pain associated with BPH can be reduced. The rationale for its use in ureteric stones was taken from several studies advocating that Sympathetic nerve fibres seem to be distributed throughout the ureter, and therefore,  $\alpha$ -1 blockers would seem to be effective for elimination of ureteral stones. A pentacyclic triterpane, lupeol isolated from the *Crataeva nurvala* stem bark and its ester derivative lupeol linolate were found to have their anti-inflammatory activity. Lupeol also showed significant anti-oxaluric and anti-calciuric effects in rats against hydroxyproline induced hyperoxaluria. Bark decoction significantly prevented the deposition of calcium-oxalate in the kidneys by inhibiting the glycolic acid oxidase (GAO) and lactate dehydrogenase (LDH) enzyme activity in liver which are the major oxalate synthesizing enzymes. *Boerhavia diffusa* possesses diuretic and anti-inflammatory properties. Due to the combination of these two activities, *Boerhavia diffusa* is regarded therapeutically as highly efficacious for urolithiasis. So the herbal preparation is a combination of anti-oxaluric, anti-calciuric, anti-inflammatory and diuretic properties which probably helped by avoiding further deposition of calcium and oxalates on the stone, loosening and breaking of molecular bonds of the stone, decreasing the local inflammation where the stone is lodged due to anti-inflammatory effect and may flush it out due to diuretic effect.

## Limitations of the Study

- Patient found it difficult to filter the urine especially when he/she was out of his/her place.
- In spite of instructions to the patients, the size of the some expelled stones were not measured and analyzed as some of them were not able to collect them.
- Some of the patients reported that the herbal preparation was having a quite bitter taste.

## CONCLUSION

In conclusion, this study demonstrated that tamsulosin helps in shortening stone expulsion time and reduce the occurrence

of colic episodes only in the lower ureter where as there was no statistically significant difference in terms of stone-free rate between the tamsulosin group and the herbal group in patients with lower ureteric calculus. Patients responded well to herbal preparation and there is statistically significant difference in terms of stone-free rate between the two groups in patients with upper and middle ureteric calculus. No doubt, there is a definite need to do the study on a large scale because the efficacy of this herbal compound needs further exploration, so that new vistas can be opened by further research. The study may also be conducted with varying doses, combinations and duration of treatment.

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