

Safety and efficacy of UNEX capsules in management of ureteric calculi: A prospective, randomised placebo-controlled study

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Renal calculi or urolithiasis is one of the most common problems in the society. In present study, the UNEX, an Ayurvedic herbal capsule, was evaluated for its safety and efficacy regarding Ureteric calculi. This was a phase III, double blind, randomised, placebo-controlled study on 64 patients suffering from upper ureteric calculi. Patients were evaluated by the X-ray KUB kidney, ureter, bladder (KUB) and ultrasonography (USG) renal pelvis for the size of calculi 5 to 10 mm and various clinical symptoms like pain, decrease in frequency of micturition, low backache, etc. The patients were equally divided in study group and control group and advised to take either study drug or placebo in a dose of two capsules b.d. for six months and follow up taken on every second month. Patients were assessed for clinical symptoms and size of stone on every second month. Microscopic evidences and urine analysis were also been evaluated. In the study group, there was a significant relief in the clinical symptoms assessed as compared to placebo group. Microscopic evidence also shows significant improvement and size of stone and its passage was also been significantly improved after six months of treatment as compared to before treatment. Hence, from this study, it was proven that the Ayurvedic herbal capsule UNEX significantly reduces the Ureteric calculi and symptoms associated with it.

Key words: Efficacy, renal calculi, UNEX capsules

INTRODUCTION

Urinary stones have occupied a major place in the urological practices. It is one of the most common and painful urologic disorder of the urinary tract. Generally, the age between 20 to 40 years is more prone to it. As it has a high rate of recurrence, it is affecting economy and general health of the people.^[1]

Age, sex, geographic locations, genetic factors and also the urinary composition are the risk factors for urinary calculi or urolithiasis. Many a times, a specific structure or anatomy is also seen to be responsible for disposing of several urinary infections including calculi.

Environmental and dietary predisposing factors include low urine volumes due to high ambient temperatures and low fluid intake. High protein diet, high sodium excretion, Hypercalcaemia of any cause, ileac diseases,

etc. are some of the acquired factors. However, familial hypercalciuria, medullary sponge kidney, cystinuria, renal tubular acidosis and primary hyperoxaluria are some of the congenital and inherited causes.

Size of the stone is also a very important disposing factor. It was found that the stone ≤ 5 mm in size spontaneously passes through the urine, whereas the size more than it is to be treated properly. Most of the time, the size greater than 10 mm has been treated surgically. Location of the stone is also an important predisposing factor.^[2]

Acute renal colic has symptoms like intermittent colic pain radiating toward lower abdomen, backache, etc. and often associated with symptoms like nausea, vomiting, etc.; lower urinary symptoms like urgency in micturition, dysuria and frequency may also present.

Management of renal calculi is dependent upon size and location of the stone; unbearable pain for the calculi more than 10 mm requires strong analgesics and surgical measures as drugs dissolving such stones have so far been unsuccessful. However, the stones less than this size have been treated successfully using herbal medicines which have diuretic, anti-inflammatory, antimicrobial and antispasmodic activities.

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UNEX [Table 1] is a powerful diuretic and urinary antiseptic. The herbs used in UNEX are time-tested for removing stone from kidney and bladder makes urination normal and helps in restoring the normal kidney function. This formulation has been approved by regulatory authorities in India as an Ayurvedic formulation and is available for clinical practice. This study was aimed to evaluate the efficacy and safety of UNEX capsule in subjects with ureteric calculi.

MATERIALS AND METHODS

This study was a prospective, placebo-controlled, double blind study. The study incorporated a matched pairs design. Each patient has received a single treatment of either the control (Placebo) or investigational product (UNEX). The goal was to enrol approximately 80 patients in order of having 60 patients (30 in each group) to complete the trial and provide data for analysis.

Inclusion and Exclusion Criteria

Patients of either sex aged 15 to 65 years having clinical symptoms with characteristic loin pain, vomiting, fever and confirm diagnosis of ureteric calculi either radiologically or ultrasonographically and measuring between 5 and 10 mm in size and those who are willing to sign the informed consent form and comply with the study procedures were included in the study. Those with larger urinary calculi than 10 mm, any renal or hepatic pathology and systemic disorder, being on other medications or requiring other medication or surgery were excluded from the study. Pregnant and lactating women were not included in the study.

Study Procedure

Patients were enrolled by defined inclusion and exclusion criteria at OPD of Vaishnavi Clinic. Essential documents required for the study, i.e., Study Protocol, Case report form, Informed consent form, etc., have been previously approved by the independent ethics committee. The patients were informed about the study procedure, investigational product, effects and duration of the study. They were included in the study only after signing of written informed consent and they were free to withdrawal from the study at any time.

Detail history of the patient was taken and clinical examination for the symptoms was done by expert physician and noted on the format set at case report form (CRF). Ureteric calculi were determine clinically and confirmed by taking plain X-ray kidney, ureter, bladder (KUB). Actual size and weight was determined by going through ultrasonography (USG). The cumulative size is determined for the subjects with multiple stones.

The patients were advised to take two UNEX capsules twice daily with water for the period of six months. The visits were

Table 1: Principle ingredients of UNEX capsule

Each capsule contains extract from	
Punarnava (<i>Boerhavia diffusa</i>)	2 g
Gokhru (<i>Tribulus terrestris</i>)	1 g

scheduled at every second month. Symptom assessment was done on every visit for severity of pain, low backache and decrease in frequency of micturition, whereas urine analysis and radiological investigations were done on the day of start of treatment, and at every visit. The patients were allowed to take 50 mg of diclofenac tablet in case of severe abdominal or loin pain.

Primary and Secondary Efficacy Parameters

The primary efficacy variable was the time to complete resolution of signs and symptoms of Ureteric calculi and change in size and number of calculi and its passage through. Secondary efficacy variables were adverse events and safety variables compared between the two treatments: Incidence of Adverse events, incidence of drug-related adverse events, exacerbations, changes in vital signs and clinically significant laboratory changes at the end of treatment period.

Adverse Events

All adverse events reported or observed by patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Patients were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to confirm the reason for withdrawing.

Statistical Analysis

Repeated measures of ANOVA followed by Dunnett's Multiple Comparison Post hoc Test were used for analysis of haematological parameters. Calculi size before and after treatment was analysed using Paired Student's 't' test. Values are expressed as mean \pm SD. Statistical analysis was carried out using Fisher's Exact Test for urine analysis and radiological observations. The minimum level of significance was fixed at $P < 0.05$. Statistical analysis was carried out using Instat3 software for Windows.

RESULTS

Total 72 patients were enrolled in the study, out of which 64 patients completed the study. Out of the 64, 42 were male and 22 were female, as shown in Table 2. Out of the 64, 32 received active treatment, i.e., of UNEX capsule, and 32 received placebo. With the treatment with UNEX capsule, significant relief ($P < 0.0001$) was observed in case of

clinical symptoms like pain, low backache and decrease in frequency of micturition after 4th and 6th month of treatment [Figure 1].

There was extremely significant results obtained in case of urine analysis of patients for infection, bacteriuria and haematuria, i.e., $P < 0.0001$ at the end of 6 months, value as compared to before treatment value [Table 3].

Table 2: Demographic data of patients before treatment

Parameters	UNEX	Placebo
Mean age in years	30.00±8.09	32.00±9.65
Male:female	20:12	22:10
Smokers	10	8
Alcoholics	2	2

X-ray KUB shows that renal calculi disappeared in 18 patients at the end of 6 months out of 32 patients, whereas USG of renal pelvis shows disappearance in 16 patients out of 32, which is extremely significant as compared to before treatment value where 32 patients showed presence of renal calculi. However, in placebo, only three patients out of 32 showed absence of renal calculi at the end of 6 months of treatment [Table 4].

Mean reduction in size of renal calculi with the treatment of UNEX capsule was also observed as extremely significant, i.e., from 9.88 ± 3.288 to 3.23 ± 6.541 at the end of 6 months in UNEX group ($P < 0.0001$) as compared to before treatment value [Table 5].

Table 3: Effect of study drug on urine analysis

Parameters	UNEX				Placebo			
	b.t.	2 M	4 M	6 M	b.t.	2 M	4 M	6 M
Urinary infections (microscopic evidence)								
Present	20	16	10	6	18	15	14	14
Absent	12	16	22 ^h	26 ^{a,b}	14	17	18	18
Bacteriuria								
Present	25	17	12	9	25	27	25	24
Absent	7	15	20	23 ^{a,c}	7	5	7	8
Microscopic haematuria								
Present	23	18	12	0	24	22	20	18
Absent	9	14	20 ^g	32 ^{a,c}	8	10	12	14

P value: a: $P < 0.0001$ as compared to 'b.t.' value; b: $P < 0.0169$ is significant as compared to '2 month.' c: $P < 0.0001$ is extremely significant as compared to 2 month value. g: P is 0.0114 which is significant as compared to b.t. value. h: P is 0.0234 which is significant as compared to b.t. value

Table 4: Effect of study drug on radiological parameters

Parameters	UNEX				Placebo			
	b.t.	2 M	4 M	6 M	b.t.	2 M	4 M	6 M
X-ray KUB showing renal calculi								
Present	32	26	22	14	32	32	29	29
Absent	0	6	10 ^a	18 ^{a,b}	0	0	3	3
Renal USG showing calculi								
Present	32	26	23	16	32	32	29	29
Absent	50	6	9	16 ^{a,b}	0	0	3	3

P value a: $P < 0.0001$ is extremely significant as compared to b.t. value. b: P value is very significant as compared to 2 month value KUB - Kidney, ureter, bladder; USG - Ultrasonography

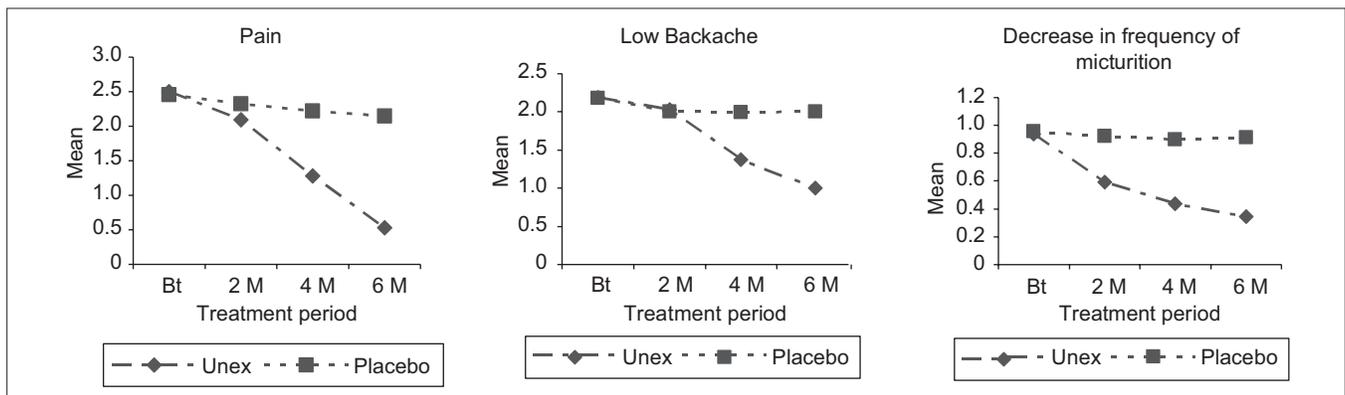


Figure 1: Effect of drug on clinical symptoms. $P < 0.001$ in 4th and 6th months of treatment as compared to before treatment value

Table 5: Effect of study drug on calculi size

Parameters	UNEX		Placebo	
	b.t.	6 M	b.t.	6 M
Mean size of Renal calculi in mm	9.88±3.288	3.23±6.541 ^a	10.12±3.021	10.32±3.112

P value a: P<0.001 is extremely significant as compared to b.t. value

There were no adverse events noted during the study period.

DISCUSSION

Renal calculi are such a severe problem which directly affects lifestyle and economy of the individual. Due to the advancement in medical sciences, there are so many options available for the treatment of renal calculi. In acute cases in modern medicine, generally calcium channel blockers, alpha-adrenergic blockers and steroids are used to suppress symptoms, but the major problem regarding these treatments is about the side effects which restrict their long-term consumption. Recurrence is also a major problem of it.^[3]

Since long several traditional herbal remedies are being used to treat several urinary disorders including renal calculi. They are being used effectively in Ayurvedic treatments by simply knowing pathophysiology of renal stones. They are the cheapest source and can be taken for long duration to exclude the chance of recurrence.^[4] WHO recognised that still 80% of the population is dependent on herbal remedies for primary healthcare.

UNEX is so formulated Ayurvedic remedy that it should counteract exact pathophysiology of renal calculi. Punarnava (*Boerhavia diffusa*)^[5-7] and Gokhru (*Tribulus terrestris*)^[5-7] are the proven herbs for their action on urinary system. Both have proved their diuretic activity, anti-inflammatory and antimicrobial activity also,^[8,9] they also possess antibacterial and astringent activity.^[10] They have a soothing action and help to prevent retention of urine in bladder. Considering all above activities, it helps in preventing and curing renal calculi or urolithiasis.^[11]

Animal study of UNEX capsule against renal calculi shows significant results.^[12]

CONCLUSION

Considering the excellent results of the clinical trial, it can be concluded that UNEX is effective in the treatment of Ureteric calculi, without producing any undesirable side effects. In cases of chronic urinary tract infections, it may be useful if used for long-term prophylaxis. No clinically significant adverse reactions were reported or observed

during the study period. However, a larger clinical trial is proposed to evaluate its efficacy in a wider perspective. The clinical trial of UNEX, an Ayurvedic preparation, has proved its efficacy and safety in upper ureteric calculi.

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