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Original Article

An Open Label Study to Evaluate Safety and Efficacy Of Unex® Capsules In Patients With Urinary Disorders

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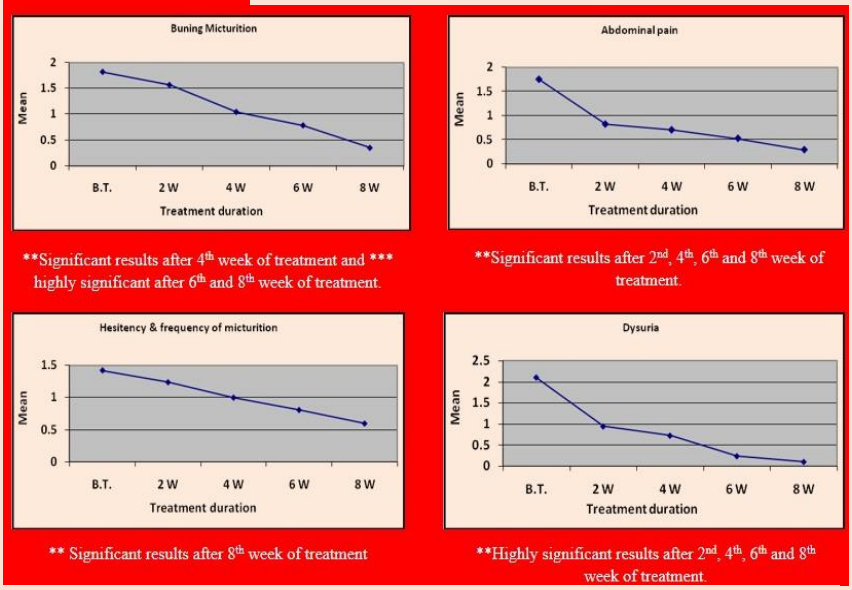
ABSTRACT

Introduction: Urinary disorders are prevalent in middle age group and effective, safe remedies with pathological cure and rejuvenation are really needed to maintain osmosis of the body. Herbal treatments for UTIs have been used for centuries. Herbal remedies may relieve urinary tract infections by combating the bacteria, decreasing irritation and healing urinary tract tissues. Present open labeled study of Unex capsules in a dose of 2 capsules BID of Unijules Life Sciences ltd. was aimed to evaluate its efficacy and safety in UTI one of the most occurring urinary disorder. ***Methods:*** patients aged between 18 to 70 years were enrolled in the study according to inclusion and exclusion criteria as per protocol approved by IEC. A dose of 2 cap BID was given to the patients for 8 weeks and assessment of results was done by analyzing symptom score of clinical response to dysuria, burning micturition, hesitancy and frequency of micturition and abdominal pain. Biochemical parameters like microbiological response etc were analyzed along with other safety parameters. ***Results:*** Total 171 patient data revels that it has highly significant results in various symptoms like burning micturition, dysuria, associated abdominal pain etc. it proves its diuretic and anti-inflammatory activity along with its antibacterial activity as it improves microscopic urinary parameters significantly during the treatment period of 8 weeks.

KEYWORDS Unex capsule, UTI, *Boerrrhavia diffusa, Tribulus terrestris*

PICTORIAL ABSTRACT



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1. INTRODUCTION

A urinary tract infection (UTI) is an infection of urinary tract and most commonly occurred urinary disorder. It is the second most common after respiratory infection[1]. The most common causes of UTIs (about 80%) are *Escherichia coli*, bacterial strain that usually inhabit the colon. However, many other bacteria can also cause an infection for example, *Klebsiella*, *Pseudomonas*, *Enterobacter*, *Proteus*, *Staphylococcus*, *Mycoplasma*, *Chlamydia*, *Serratia* and *Neisseria* spp but are far less frequent causes than *E. coli*. In addition, fungi (*Candida* and *Cryptococcus* spp) and some parasites (*Trichomonas*, *Schistosoma*) also may cause UTIs; *Schistosoma* causes other problems, with bladder infections as only a part of its complicated infectious process[2-4]. Herbal treatments for UTIs have been used for centuries. Herbal remedies may relieve urinary tract infections by combating the bacteria, decreasing irritation and healing urinary tract tissues. Some herbs also help prevent future occurrences. Urinary tract infection is commonly treated with prescription antibiotics. However, it is increasingly recognized that using antibiotics frequently may contribute to recurring UTIs and increased dependency on antibiotic use may further weaken the immune system. Natural remedies can provide an effective alternative to prescription medications and their side effects[5-6].

Unex capsule is a polyherbal remedy of Unijules Life sciences ltd a combination of standardized aqueous extracts of *Punarnava* (*Boerhhavia diffusa* Linn.) and *Gokhshura* (*Tribulus terrestris* Linn.) having effective role in various urinary disorders due to its anti-inflammatory, diuretic, antimicrobial activities[7]. This is single blind, open labeled study on patients with mild to moderate UTI of urinary disorders, to evaluate efficacy w.r.t. dose and time for resolution of symptoms of UTI of this polyherbal remedy.

2. MATERIALS AND METHODS

This study was open labeled to assess safety and efficacy of patients with mild to moderate urinary disorders of UTI before and after eight weeks of treatment period. This study was done in DY Patil College, Hospital and Research Centre, Nerul, Navi Mumbai, Maharashtra, India. Proper protocol, case report form were developed and presented to institutional ethics committee. Necessary amendments as suggested by IEC (IEC no. PDDYPU/1364/2010) were made, and all study was done according to good clinical practices (GCP).

All investigational medicinal products (IMP) were supplied by sponsored company Unijules Life Sciences Ltd with appropriate labeling and packing. Quality assurance audits were also conducted during the study for compliance with protocol, source data verification, patient recruitment etc, by the company. All patients of urinary disorders attending OPD of the hospital were selected and included in the treatment period with following inclusion and exclusion criteria.

2.1 Inclusion criteria

All patients aged between 18 to 70 years of age must have a diagnosis of Dysuria or painful discharge of urine with burning sensation. Urgency or a strong urge to pass urine with recurrent urination. Hesitancy or a feeling of inability to pass urine completely. Pain and discomfort of lower abdomen. Hematuria or bloody urination with foul smell. One positive dipstick urine test positive either for leukocyte esterase or nitrates or have a urinalysis with > 5 wbc/hpf. A pre-treatment clean-catch midstream urine culture with ≥ 104 CFU/mL of a bacterial organism, Voluntary able to understand the nature and purpose of the study, including the risks and adverse effects and with intent to cooperate with the researcher and act in accordance with the requirements of the entire protocol, which was confirmed by signing the consent.

2.2 Exclusion criteria

Patients with significant diseases other than urinary tract disorders were excluded. Patients with a significant disease (defined as a disease which in the opinion of the investigator may either put the patient at risk because of participation in the study or a disease which may influence the results of the study or the patient's ability to participate in the study). Patients with clinically significant abnormal baseline hematology, blood chemistry or urinalysis, if the abnormality defines a disease listed as exclusion criterions were excluded. Female patients who are pregnant or lactating, Patients with known polycystic kidney disease, Patients on permanent renal replacement therapy (hemodialysis or peritoneal dialysis), Patients with history of kidney transplantation, were excluded from the study.

2.3 Assessment of efficacy

The primary efficacy outcome was Clinical response, the resolution of Urinary disorders like burning micturition, dusuria, hesitancy and frequency of urination, Abdominal pain and signs and symptoms at post-therapy compared with those at start of study; Microbiological response, the eradication at post-therapy of infectious organism identified at start of study. Secondary efficacy variables were Overall clinical response, described as cured, improved, or failed; incidence of adverse events throughout the study; Change in clinical laboratory tests and physical examinations from start of study to post-therapy.

Safety was assessed by the changes observed in essential biochemical investigations i.e. LFT, CBC and hazards symptoms observed during the treatment course w.r.t. palatability, convenience and amount of rescue medications utilized by the patient for any untoward sign and symptoms during the therapy.

2.4 Study drug

The study drug Unex capsule was a FDA approved product with a combined aqueous extract of *Tribulus terrestris* and *Boerrhavia diffusa* in a specific technology based dosage form of pellets capsule of 0.470mg pallets. The dose was 2 capsules before meal two times a day was decided for the study which derived from the results of in-house pilot study.

2.5 Study procedure

This study was a prospective, single blind study involving patients with urinary disorders. The study incorporated a matched pairs design. Each patient has received a single treatment of investigational product (UNEX). The goal was to enroll approximately 200 patients in order to have 175 patients to provide data for analysis. Patients selected from the OPD were examined for the adherence to the above mentioned inclusion and exclusion criteria and provided with details about the study, study drug, its effect, dosing schedule etc and asked for signing a written informed consent form. Screening period of 2 days was kept during which patients were checked for all hematological, biochemical and physical tests for analyzing its adherence with the protocol, appropriateness of the patients for further treatment period and also to check safety parameters. Parameters like LFT, KFT etc were done and those who find eligible for further study were enrolled for further treatment period of eight weeks.

It was aimed to enroll at least 175 patients in the study in order to have 150 patients' data for final analysis. Follow-up visits were scheduled after 2, 4, 6 and 8 weeks and during each visit vital signs and severity of symptoms score i.e. from 0 to 3 (Normal, Mild, Moderate, Sevior as defined in protocol) for symptoms like hesitancy, burning micturition, dysuria, abdominal pain etc were noted. Urine examination for routine and microscopic were performed in each visit. Checking of daily diary, use of rescue medications etc were noted and documented during each visit. A window period of +/- 2 days was allowed for the visit. All adverse events were noted and recorded about nature and severity of the symptom, onset action, time to resolution of symptom. Patients were allowed to withdraw from the study at any time and any stage of the study. All data were complied and analyzed by using appropriate analytical test i.e. paired t test for grouped data and unpaired t test for comparing ungrouped data of group I and group II.

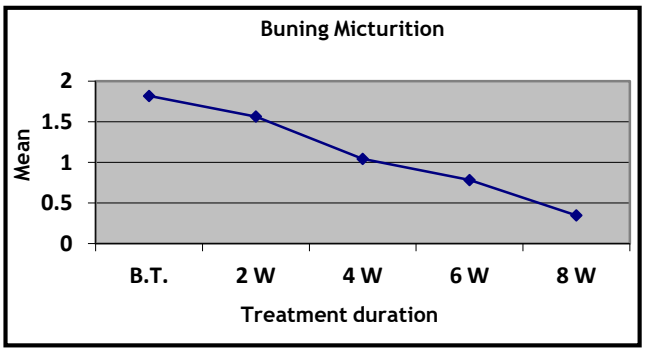
3. RESULTS AND DISCUSSION

In the present clinical study, total 188 patients were screened out of which 179 patients were enrolled (according to adherence with inclusion and exclusion criteria) for the further study and out of them 171 patients have completed their 8 weeks treatment period, (as 8 patients have discontinued the study due to non-follow up after 2 weeks of treatment)

The efficacy of UNEX has been evaluated in 171 cases of Urinary disorders. Patients who presented with various symptoms of Urinary disorders, Hematological Examination: The TLC, DLC and estimation of Hb%, Blood urea and Serum creatinine were done before, during and after the completion of therapy. No significant changes were observed in TLC, DLC and Hb% after treatment with UNEX. Similar observations were also made in blood urea and serum creatinine level. This suggests that the drug has no adverse effect on renal function.

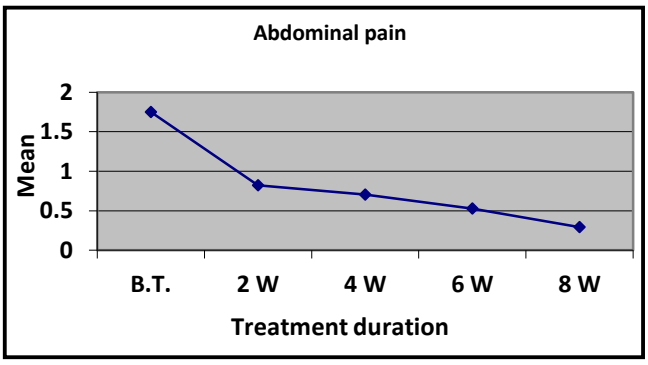
In case of burning micturition (Graph 1) significant results were observed after 4^{th} week of treatment and highly significant results were observed after 6^{th} and 8^{th} week of treatment. In case of hesitancy and frequency of micturition (Graph 2) significant results were observed after 8^{th} week of treatment. And in case of abdominal pain (Graph 3) associated with urinary disorders, significant results were observed after 2^{nd}, 4^{th}, 6^{th} and 8^{th} week of treatment. In case of dysuria (Graph 4) significant results were observed after 2^{nd}, 4^{th}, 6^{th} and 8^{th} week of treatment. In Urine analysis (Table 1) also significant results were noted in case of bacteriuria, microscopic evidences and haematuria after 4^{th} and 8^{th} week of treatment. No any adverse or unwanted observations were noted during and after the completion of 8^{th} week treatment duration.

Graph 1. Burning micturition



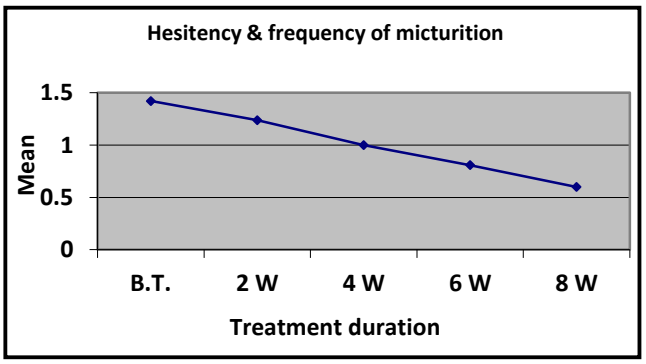
Significant results after 4th week of Tt. And * highly significant after 6th and 8th week of Tt.

Graph 3. Abdominal pain



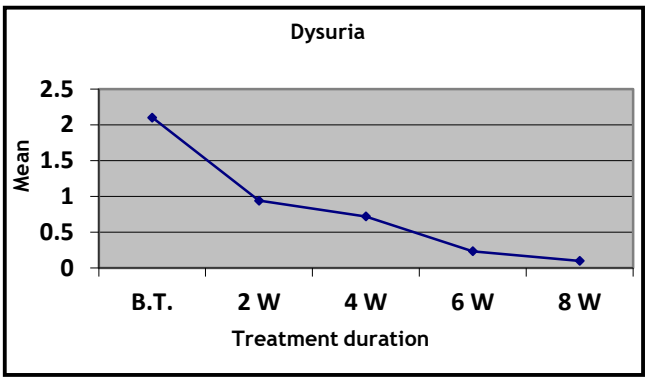
**Significant results after 2nd, 4th, 6th and 8th week of treatment.

Graph 2. Frequency of micturition



** Significant results after 8th week of treatment

Graph 4. Dysuria



**Highly significant results after 2nd, 4th, 6th and 8th week of treatment.

Table 1. Microscopic parameters of urine

		Unex			
Parameters		Initial	2 W	4 W	8 W
Urinary infections (Microscopic evidence)	Present	90	80	50	20
	Absent	81	91	121*	151*
Bacteriuria	Present	70	55	45	10
	Absent	101	116	126	161**
Microscopic hematuria	Present	23	18	12	0
	Absent	148	153	159[g]	171**
Parameters		Initial	2 W	4 W	8 W
Urinary infections (Microscopic evidence)	Present	90	80	50	20

**Highly significant results after 4th and 8th week of treatment

Urinary disorder is more common in females. In women about 50% - 80% of women acquire at least one urinary disorder during their lifetime which is mostly uncomplicated cystitis. The annual incidence of pyelonephritis was approximately 28 per 10,000 women. Urinary disorder is rare in young men. In the elderly age group, benign prostatic hyperplasia has been implicated as a common predisposing factor for urinary disorder. In men, a single episode of urinary disorder has to be investigated particularly if the patient is in the younger age group[8,9]. In this study out of 171 patients treated, 98 were females and 73 were males.

Certain people are more likely to get urinary disorders. Women tend to get them more often because their urethra is shorter and closer to the anus. Elderly people (especially those in nursing homes) and people with diabetes also get more urinary disorders. Cystitis in children can be promoted by abnormalities in the urinary tract. Therefore, children with cystitis, especially those under age 5, deserve special follow-up to prevent later kidney damage. Bacteria that are normally found in the gastrointestinal tract, such as Escherichia coli, cause most urinary tract infections. Other bacteria that can cause urinary tract infections include *Staphylococcus saprophyticus*, *Proteus*, *Klebsiella* and *Enterococcus*[10,11].

In recent years, an increasing number of bladder infections in both men and women have been linked to two sexually transmitted organisms; *Chlamydia trachomatis* and Mycoplasma genitalium. Women are more prone to urinary tract infections because the tube running from the bladder to the outside (the urethra) is much shorter than in men. Because the urethral opening is relatively close to the anus in women, bacteria that are normal present from the colon can easily contaminate the female urethra. A urinary tract infection in young women is often associated with increased sexual activity[12,13].

In men, however, a bladder infection is almost always a symptom of an underlying disorder and a cause for concern. Often the infection has migrated from the prostate or some other part of the body, signaling problems in those locations. Or it may indicate a tumor or other obstruction is interfering with the urinary tract. Chronic kidney infections in children are sometimes caused by a structural problem that allows urine to flow back from the bladder to kidneys (reflux). UNEX capsule 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.

Each capsule contains extract from 2 g *Punarnava* (*B. diffusa*) and 1 g *Gokshura* (*T. terrestris*). *Tribulus terrestris* contain marman as principle constituents. It is diuretic drug useful in urolithiasis, dysuria and kidney dysfunction. It is very useful in disease of genitourinary tract.

It is used as diuretics, cooling, useful in painful micturation, calculus affections, and urinary discharges in gout and kidney diseases, inhibition of tyrosinase, urolithiasis and crystalluria. It helps to maintain efficient kidney and urinary discomfort and reduces renal discomfort[14-15].

The diuretic action of *B. diffusa* has been studied and validated by scientist in several studies, which helps to explain its long history of use in various kidney and urinary conditions. It is used for gall bladder pain and stones, urinary tract and renal disorders and calculi and for cystitis[16,17].

4. CONCLUSION

UNEX Capsules was found to be very effective in symptomatic improvement of UTI within 2 weeks in terms of dysuria, Abdomial pain and burning micturition. Only in case of frequency and hesitancy of micturition it takes 8 weeks for significant improvement. It was also effective in changing urinary pH to alkaline medium which focuses on its affectivity as an alkalizer. It was effective in preventing recurrence of urinary disorder as no recurrence is observed after 4 week of completion of treatment. It also has potentiating antibacterial activity as seen by the decrease in bacterial colony count and absence of pus cells in the urine. No side effects were seen with drug. There was good response in terms of compliance. Considering the excellent results of the clinical trial, it can be concluded that UNEX is effective in the treatment of Urinary disorders like simple burning micturition, UTI, cystitis and chronic prostatitis, without producing any undesirable side effects. In cases of chronic urinary tract infections, it may be useful if used for long term prophylaxis.

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Conflict of interest None declared

Contributors Dr. Sarang contributed for conceptualization, design and intellectual content of the topic, Dr. Shrirang conducted the study, data analysis and editing. Dr. Shivpal and Dr. Shailesh did proof reading, editing and clinical analysis and significance of the results.

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