Evaluating the efficacy and safety of Himplasia (PC-27) in the medical management of benign hyperplasia

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INTRODUCTION
Benign Prostatic Hyperplasia (BPH) also referred to as benign prostatic hypertrophy, is a common disease in aging males. According to WHO, more than 50% males in the 50 plus age groups have BPH and the incidence might be as high as 90% at 85 years.

BPH is characterized by enlargement of prostatic nodules due to a proliferative process involving both the stromal and epithelial elements of the prostate. As the prostate enlarges, the surrounding tissue offers resistance, causing the prostate to press against the urethra. Over a period of time, the urinary bladder wall becomes thicker, sensitive irritation and the bladder begins to contract even with a small quantity of urine, causing more frequent urination. The other clinical manifestations of BPH include obstructive and irritative urinary tract symptoms and infection, urinary retention and hematuria.

The etiology of BPH is not well understood and it is known that BPH doesn't occur in men whose testes were removed before puberty. According to one hypothesis with advancing age, the levels of active testosterone in the blood decrease, leaving higher levels of estrogen; and experimental studies have suggested that BPH may occur because of higher levels of estrogen within the prostate, leading to the cellular hyperplasia. Another hypothesis focuses on dihydrotestosterone (DHT), a potent derivative of testosterone in the prostate, which may promote cellular hyperplasia. Malignant transformation has been found in 9.51% of patients with BPH and often these changes are predicted by the presence of a rise in marker the levels of prostate specific antigen (PSA) and acid phosphatase.

The goal of BPH treatment is to reduce excessive cell growth by inhibiting conversion of testosterone into DHT and preventing attachment of estrogen to its receptors in prostate tissue. Depending on the severity of symptoms, “watchful waiting”, drug therapy and surgery are the treatment options for BPH.

Recent clinical trials have suggested that 5α-reductase enzyme inhibitors and long acting α-adrenoreceptor antagonistic drugs are effective in the treatment of BPH. 5α-reductase inhibitors prevent the conversion of testosterone to DHT; while α-blockers relax smooth muscle tissue in the bladder neck and prostate, which increases urinary flow and reduces
bladder outlet obstruction. But, these drugs have adverse effects like headache, dizziness, hypotension, fatigue, reduced libido, impotence, breast tenderness and breast enlargement, and reduced sperm count\textsuperscript{4,6}. Due to these limitations, phytotherapy has been extensively researched and some phytochemicals have been shown beneficial in the management of BPH\textsuperscript{7-9}.

This study was planned to evaluate Himplasia (PC-27), a polyherbal formulation, in BPH. Each tablet of Himplasia (PC-27) contains powders of Gokshura (\textit{Tribulus terrestris}), Putikaranja (\textit{Caesalpinia bonducella}), Puga (\textit{Areca catechu}), Shatavari (\textit{Asparagus racemosus}), Varuna (\textit{Crataeva nurvala}) and Akika pishti.

**MATERIALS AND METHODS**

**Study design**
The study was an open, non-comparative clinical trial, approved by the Institutional Ethics Committee, conducted between April 2002 and July 2003.

**Inclusion criteria**
Fifty patients suffering from BPH were included in the study, and categorized by the American Urological Association (AUA) symptom score index as mild (0-7 points), moderate (8-19 points) and severe (20-35 points)\textsuperscript{10}.

**Exclusion criteria**
Patients with diabetes mellitus, prostate and bladder carcinoma, prostatitis, neurogenic bladder, stricture urethra, vesical calculus, and those on drugs likely to affect bladder function, were excluded from the study. Patients with severe cardiovascular, kidney or liver disorder an indicated for surgery with refractory retention and recurrent or persistent gross hematuria were also excluded from the study.

**Study procedures**
At the first visit, a detailed medical history, with special emphasis on urinary symptoms (urgency, frequency, nocturia, hesitancy, straining, intermittency, terminal dribbling and sensation of incomplete voiding) was obtained from all patients. In all patients, a thorough systemic examination was done, followed by a digital rectal examination for determining prostate size, presence of nodule, asymmetry and tenderness. Routine biochemical blood and specific tests (LFTs, RFTs, serum PSA) were done for all patients. All patients were investigated by uroflowmetry, and, voided volume, voiding and flow times, time to maximum flow, maximum flow rate (MFR) and average flow rate (AFR) were recorded. The prostate size was determined by abdominal ultrasound and/or transrectal ultrasonography. All patients were advised to consume a capsule of Himplasia (PC-27), once daily, for six months.

**Follow-up and assessment**
The patients were followed up for 6 months and AUA symptom score evaluation was recorded after completion of each month. A complete clinical, biochemical, ultrasonography and uroflowmetry examination was carried out at the end of the sixth month.
Primary and secondary outcome measures
The predefined primary outcome measure for efficacy was a decrease in AUA score at the end of 6 months. Secondary outcome measures were short-term and long-term safety assessed by incidence of adverse events, patient compliance to therapy and improvement in hematological and biochemical parameters.

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. Relation of adverse events to study medication was predefined as “Unrelated” (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), “Possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and “Probable” (follows a known response pattern to the suspected drug that could not reasonably be explained by the known characteristics of the patient’s clinical state).

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 ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

Statistical analysis
Statistical analysis was done according to intention-to-treat principles. Changes in various parameters from baseline values and values after the 6th month were evaluated by a paired ‘t’ test. The minimum level of significance was fixed at 95% confidence limit and a 2-sided p value of <0.05 was considered significant.

RESULTS
In the 50 patients, 3 opted for surgery and 2 developed acute retention of urine and were excluded from the study. The mean age of the remaining patients was 63.77 years (range 50 - 89) (Figure 1).

Almost all patients began to show symptomatic relief by the second month of treatment with Himplasia (PC-27) and further improvement in all parameters was evident by the end of 6 months along with a noticeable alleviation in
symptoms. The average AUA symptom score reduced significantly from baseline 22.15 (range: 10-32) to 12.69 (range: 0-35) ($p<0.0001$) at the end of 6 months, and the difference between the means was statistically significant ($t=7.619$, $p<0.05$, the mean of differences=10.92, and 95% confidence interval: 8.006-13.83) (Figure 2a).

The MFR showed an improvement from the baseline of 9.67 (range: 2-20) to 12.69 (range: 0-35) at the end of study. There was significant reduction in the prostate size from 38.24 (range: 16-80) to 35.304 (range: 16-80) ($t=2.893$, $p=0.0067$) and the difference in the means statistically significant (mean of differences=1.958, 95% confidence interval: 0.5801-3.336) (Figure 2b).

There was significant reduction in postvoid residual urine volume from 83.77 ml (range: 0-300) to 58.67 ml (range: 0-350) ($p=0.0031$, $t=3.262$) and the difference in means was statistically significant (mean of differences=24.30, 95% confidence interval=8.980-39.61) (Figure 2c).

The peak flow values (mean, standard deviation, standard error of means, lower, and upper 95% confidence interval) for both groups at baseline and at the end of study were 10.41 and 14.12, 4.349 and 6.414, 0.7459 and 1.100, 8.894 and 11.88 and 11.93 and 16.36) respectively and the difference in the means was statistically significant ($p=0.0036$, $t=3.138$) (Figure 2d).

The average flow rate (mean, standard deviation, standard error of means, lower, and upper 95% confidence interval), for both groups, at baseline and at the end of study were 5.485 & 7.121, 2.502 & 3.189, 0.4355 & 0.5552, 4.598 & 5.990 and 6.372 & 8.252) respectively and the difference in the means was statistically significant ($p=0.0024$, $t=3.300$) (Figure 2e).
There was no statistically significant difference in the values of the voided volume (p=0.3027, t=1.070), for both groups at baseline and at the end of study. The change in the serum PSA values for both groups at baseline and at the end of study was also nonsignificant (p=0.2875, NS, t=1.081).

There were no clinically significant drug related adverse events reported or observed during the entire study period.
DISCUSSION

BPH is a common condition in older men, leading to morbidity primarily through lower urinary tract symptoms and obstructive urinary symptoms are common, occurring in the majority of males in the 50+ age groups, 20-30% of who undergo prostatectomy. The treatment of BPH has changed substantially in recent years, with an increased emphasis on non-surgical approaches. Improvement in urinary symptoms and the quality of life are important issues for decision making in treating BPH patients.

Uroflowmetry measures the pressure generated in the bladder during voiding. Patients with stress or urge incontinence usually have a normal or increased urinary flow rate and a reduced flow rate may indicate BPH. The post-void residual urine (PVR) test measures the amount of urine that remains in the bladder after urination and a PVR less than 50ml generally indicates adequate bladder emptying; while measurements of 100 - 200ml or more often indicate blockage.

Advances in medical therapy for the management of BPH have lead to development of a formulation that overcomes the symptoms of BPH. Currently used drugs such as 5α-reductase enzyme inhibitors cause a decrease in libido and sexual potency, while α-adrenoreceptor antagonistic drugs can lead to various untoward ailments such as vertigo, fatigue, palpitation, headache, tachycardia, asthenia, nausea, diarrhea, nasal congestion and impotence on prolonged use. Throughout the world, research seeks a remedy for BPH safe and free from side effects on prolonged use. Amino acids (a combination of glycine, alanine and glutamic acid), beta sitosterol, flaxseed oil, and some herbs (Serenoa repens, Pygeum africanum and Urtica dioica) have been found beneficial in management of BPH.

In this study, the significant reduction in the average AUA symptom score at the end of 6 months indicates that Himplasia (PC-27) provides significant symptomatic relief in BPH, which may be due to a significant reduction in the prostate size as confirmed by ultrasound examination. The favourable significant changes in the uroflowmetry parameters (improvement in MFR, reduction in post void residual urine volume and improvement in peak flow values) also suggest that Himplasia (PC-27) had improved the clinical picture of the study patients.

In this study, there were no significant changes in PSA levels from the baseline to the end of the study period. PSA is a specific antigen produced by the cells of the prostate capsule and periurethral glands. Patients with BPH or prostatitis produce large amounts of PSA, and PSA level is also determined in part by size and weight of the prostate. Most men with slightly elevated PSA levels do not have prostate cancer, and many men with prostate cancer have normal PSA levels, but highly elevated levels may indicate the presence of cancer. Age-specific PSA evidence suggests that the PSA level increases with age.
The beneficial effects of Himplasia (PC-27) might be due to the synergistic action of its ingredients. The main constituents of Himplasia (PC-27) are *Tribulus terrestris, Caesalpinia bonducella, Asparagus racemosus, Areca catechu, Crataeva nurvala* and Akika pishti.

*Tribulus terrestris* has analgesic, antibacterial, diuretic and smooth muscle relaxant properties and found beneficial in treating symptoms of BPH. *Caesalpinia bonducella* has anti-inflammatory, urinary antiseptic and diuretic properties. *Asparagus racemosus* is a potent diuretic and antispasmodic, has immunomodulatory effects on the prostate, and anti-inflammatory, lithotriptic, demulcent and tonic properties useful in disorders of urinary tract. *Areca catechu* has antimicrobial properties useful in the treatment of urinary disorders and *Crataeva nurvala* is useful in the treatment of urinary disorders caused by BPH.

In this study, it was observed that on account of its antispasmodic, diuretic and antibacterial property, Himplasia (PC-27) displayed a multi-dimensional favourable effect in patients with BPH. It was also observed that Himplasia (PC-27) alleviated the other symptoms of BPH and displayed a significant improvement in uroflow dynamics. This study also indicated a dependable safety profile for Himplasia (PC-27), for long-term use in the management of BPH.

**CONCLUSION**

With increasing life expectancy, BPH is emerging as an important disease responsible for major chunk of morbidity amongst the geriatric population. The available drug therapy options in the management of BPH are linked with various adverse effects, which limit their long-term usage. In this study, Himplasia (PC-27) was found to be beneficial for symptomatic control and also in reducing prostate size, with significant improvement in uroflow dynamics. From the above results, it can be stated that Himplasia (PC-27) is effective and safe for long-term clinical usage in the management of BPH.

**REFERENCES**


