Role of herbal drugs in the management of benign prostatic hyperplasia: Clinical trial to evaluate the efficacy and safety of Himplasia

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ABSTRACT
This was a double-blinded placebo-controlled clinical trial, which including 98 patients clinically diagnosed as various degrees of benign prostatic hyperplasia and confirmed by pelvic ultrasonography along with uroflowmetry investigations. Himplasia was administered as 1 tablet, twice daily for 6 months. All the patients were clinically examined every month for 6 months and we repeat ultrasonography and uroflowmetry after 6 months treatment with Himplasia. There was excellent compliance with Himplasia. All 98 patients completed the treatment and patient reported any side effects.

Himplasia significantly relieved the symptoms of BPH along with reduction in prostate size revealed by pelvic ultrasonography. Himplasia acts by dual mode of action which is by inhibition of 5-alpha reductase enzyme inhibition with alpha receptor blocking action. By this Himplasia controls the conversion of testosterone to dihydrotestosterone along with relaxation of prostatic smooth muscles. Himplasia may be considered as a therapy for patients with benign prostatic hyperplasia.

Keywords: Benign Prostatic Hyperplasia, Himplasia, 5-α-reductase, adrenoceptor blocker, Uroflowmetry

INTRODUCTION
The prostate gland is located between the bladder and the rectum, and wraps around the urethra. The prostate is composed of smooth muscle cells and glandular epithelial tissue and is surrounded by a dense fibrous capsule. Epithelial cells are those that form the lining of an organ.

The prostate gland undergoes many changes during the course of a man's life. At birth, the prostate is about the size of a pea. It grows only slightly until puberty, when it begins to enlarge rapidly, attaining normal adult size and shape. The gland generally remains stable until about the mid-forties, when, in most men, the prostate begins to enlarge again through a process of cell multiplication called benign prostatic hyperplasia (BPH). The overgrowth, which occurs in both smooth muscle tissue and glandular epithelial tissue, is attributed to a number of different causes, including the aging process, hormones and growth factors.
Cell proliferation in the prostates of older men can cause distressing urination symptoms. In many cases, such symptoms occur when the dense capsule surrounding the enlarging prostate prevents it from further expansion outward, forcing the prostate to press against the urethra partially blocking urine flow. This obstruction, in turn, causes bladder irritation and contraction, even for small amounts of urine. Eventually, the bladder weakens and does not completely empty through urination.

Benign prostatic hyperplasia can affect urination in a number of ways. Symptoms are often classified as either obstructive or irritative. Obstructive symptoms include straining to urinate, a weak or intermittent stream, and a sense that the bladder has emptied incompletely. Irritative symptoms include an increased frequency of urination, an urgent need to urinate, and pain or irritation when urinating. Although urge incontinence is an irritative symptom, it may indicate the presence of obstruction. The causes of benign prostatic hyperplasia are not fully known. Male hormones (androgens) and possibly the female hormone estrogen play a role. The most important androgen is testosterone, which is produced throughout a man's lifetime. The prostate converts testosterone to a more powerful androgen, dihydrotestosterone (DHT), which stimulates cell growth in the glandular epithelial tissue and is the major cause of the rapid prostate enlargement that occurs between puberty and young adulthood. Many experts believe that DHT is also the primary stimulant and cause for prostate enlargement later on. Some authorities believe that the female hormone estrogen may play a role. As men age, testosterone levels drop and the proportion of estrogen increases, possibly triggering prostate growth. Another theory focuses on cells in a certain section of the gland that may become active late in life, signaling other prostate cells to replicate or causing them to be on a sensitive to growth-stimulating hormones.

The causes of urinary symptoms when the prostate is small or normal in size are not yet well understood, and some experts consider this condition something other than the so-called "true" benign prostatic hyperplasia, which is often used to describe typical urinary symptoms only when they accompany an enlarged prostate.

There are multiple approaches for the treatment of Benign Prostatic Hyperplasia, which includes medical therapy with or without surgical intervention. This study was planned to evaluate the role of Himplasia, a polyherbal formulation, in relieving the symptoms of BPH and preventing its complications.

MATERIAL AND METHODS:
This was a double-blind randomized placebo-controlled clinical trial. Ninety-eight male patients showing signs and symptoms of benign prostatic hyperplasia confirmed by clinical and digital rectal examinations were enrolled in the trial. Informed written consent was obtained from all the patients. The institutional ethics committee also approved the conduction of the Phase III clinical trial. All the patients underwent a thorough medical examination including detailed medical history, which included previous history of urinary tract infections or prostatitis and any worsening of urinary symptoms while taking medications for common cold or sinusitis. Complete physical examination was undertaken to detect any urinary irregularities, presence of any abnormal mass in the abdominal or pelvic cavity. Digital rectal examination was carried out to assess the size, shape and consistency of the prostate.
A complete urine analysis was conducted in all the patients, which included a urine culture, to rule out the possibility of urinary infections. In addition to this, complete hematological and other biochemical investigations were carried out to determine the safety of Himplasia.

Special diagnostic tests including uroflowmetry and ultrasonography were conducted to evaluate the effect on post-void urine volume, peak flow rate, and size and weight of the prostate.

Himplasia and placebo were administered at a dose of 1 tablet twice daily for 6 months as per randomization. All the patients were followed up every month for 6 months for complete physical examination. Uroflowmetry and ultrasonography were repeated after 6 months. Clinical evaluation was carried out using International Prostate Symptom Score Questionnaire. The score of 1-7 was classified as mild, 8-19 as moderate and 20 to 35 as severe.

**Statistical Analysis:** All data are expressed as Mean ± SD. For all statistical comparisons, a $p$ value less than 0.05 was considered significant. Difference between pre- and post-treatment values were evaluated using Wilcoxon Signed Rank Test. Analysis was performed using Prism software, version 3.02.

**RESULTS**

There were 57 patients in the Himplasia group and 41 patients in the placebo group. The average age of the patients in Himplasia group is 66.46 years and that of placebo is 64.48 years. AUA symptom score in both the groups of patients was comparable, i.e. 14.91 in the Himplasia group and 14.58 in the placebo group before treatment. Following 6 months of Himplasia treatment, the AUA symptom score was reduced significantly in the Himplasia-treated group as compared to the placebo group. This indicates Himplasia relieves urinary symptoms of BPH. The average symptomatic improvement was 66.34% in the Himplasia group, and 21.13% in the placebo group (Table).

Ultrasonography revealed reduction of prostate size from 36.88 mm to 35.70 mm in the Himplasia group. However, prostate size increased from 31.59 mm to 34.15 mm in the placebo group. Although, decrease in prostate size is marginal in the Himplasia group, Himplasia checks the further progress of BPH (Table).

Post-void residual urine volume was also comparable in both groups before starting the treatment. Himplasia treatment reduced post-void residual urine from 90.74 ml to 57.14 ml. Whereas there was an increase in the post-void residual volume from 91.55 ml to 95.80 ml in the placebo group indicating an increase of prostate size associated with increase in the post-void residual urine volume (Table).

Peak flow rates were also comparable in both groups of patients before treatment, 10.74 ml/sec and 11.68 ml/sec in the Himplasia and placebo group respectively. Peak flow rate was increased from 10.74 ml/sec to 13.77 ml/sec with Himplasia treatment, whereas there was no significant change in the placebo group. Patients treated with Himplasia also showed significant improvement in flow time as compared the placebo group (Table).
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<thead>
<tr>
<th>Parameters</th>
<th>Drug</th>
<th>Placebo</th>
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<tr>
<td></td>
<td>Pre-treatment</td>
<td>Post-treatment</td>
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<tr>
<td>Average age (years)</td>
<td>66.46 ± 7.51</td>
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<tr>
<td>AUA symptom score</td>
<td>14.91 ± 3.87 (p&lt;0.0001)</td>
<td>7.24 ±3.52 (p&lt;0.0001)</td>
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<td>Prostate size (mm)</td>
<td>36.88 ± 14.83</td>
<td>35.70 ± 14.06 (p&lt;0.0004)</td>
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<tr>
<td>Post-void residual volume (ml)</td>
<td>90.74 ± 27.34</td>
<td>57.14 ± 28.03 (p&lt;0.0003)</td>
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<tr>
<td>Peak flow (ml/sec)</td>
<td>10.74 ± 2.19</td>
<td>13.77 ± 3.15 (p&lt;0.0005)</td>
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<tr>
<td>Flow time (sec.)</td>
<td>62.36 ± 30.76</td>
<td>53.88 ± 25.77 (p&lt;0.025)</td>
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<td>Improvement in urinary symptom score (%)</td>
<td>66.34 ± 27.23 (p&lt;0.0001)</td>
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**DISCUSSION**

The main herbs of Himplasia include Tribulus terrestris, Caesalpinia bonducella, Areca catechu, Asparagus racemosus and Crataeva nurvala. Himplasia is also enriched with Akika pishiti. Experimental studies have shown Himplasia reduces the prostate size and inhibits prostatic stromal proliferations\(^1\). Earlier clinical trials also have proved that Himplasia improves urinary flow rate, while reducing post-void residual urine. Himplasia possess both 5-α-reductase enzyme inhibitory activity along with α-adrenoceptor antagonist activity.

*Tribulus terrestris* possesses anti-inflammatory, smooth muscle relaxation and diuretic actions, which are useful in genitourinary infections, painful micturition, hematuria, dysuria and benign prostatic hyperplasia\(^2,3\). The diuretic activity of *Tribulus terrestris* helps relieve associated subclinical urinary insufficiency and also helps to reduce post-void urine. Clinical studies have proved *Crataeva nurvala* effective in the prostatic hypertrophy, neurogenic bladder and chronic urinary infections. Cystometric studies have shown that *Crataeva nurvala* improves bladder tone and relieves post-prostatectomy atony of the bladder. *Crataeva nurvala* has cytoprotective action and prevents urinary tract infections. *Crataeva nurvala* has anti-inflammatory and tonic effect on the smooth muscles of the bladder and the other urinary organs. This helps in the evacuation of the bladder and the control of infections. The anti-inflammatory and diuretic activities are potentiated by *Caesalpinia bonducella*. Herbs like *Crataeva nurvala* and *Areca catechu* possess 5-α-reductase inhibition with α-adrenergic blocking activity. 5α-reductase inhibition blocks the conversion of testosterone to dihydrotestosterone, the major sex hormone in the prostatic cells responsible for BPH. By blocking the α-receptors, Himplasia relaxes the smooth muscles in the prostatic tissue and increase urinary flow while relieving the symptoms of urinary frequency, urinary urgency and nocturia. *Asparagus racemosus* has potent antioxidant properties and prevents chronic prostatitis. Moreover, *Tribulus terrestris, Caesalpinia bonducella, Areca catechu* possess antibacterial activity against susceptible micro-organisms and helps prevent symptoms of urethritis and prostatitis. The various herbs in Himplasia act in a synergistic manner to relieve the obstructive symptoms along with control of prostatic tissue growth.
The results obtained in this trial confirm that Himplasia reduces prostate size along with relieving the obstructive symptoms of BPH by both mechanisms mentioned above. Through its combined action, Himplasia checks the progress of prostatic hyperplasia and results in greater improvement in urinary symptoms.

CONCLUSION
This double-blind placebo-controlled clinical trial confirms the efficacy of Himplasia in relieving the symptoms of BPH along with control of progressive hyperplasia. No side effects were observed in any patients during the trial period, which suggests that Himplasia is safe for long-term administration.

REFERENCES