Efficacy and Safety of ‘Prostane’ in the Management of Symptomatic Benign Prostatic Hyperplasia: A Clinical Evaluation

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ABSTRACT
The objective of this study was to evaluate the efficacy and safety of Prostane, a herbal formulation, in alleviating the symptoms of Benign Prostatic Hyperplasia. Patients with benign prostatic hyperplasia were randomly given Prostane at a dose of 2 tablets, twice daily for 4 months. Subjective efficacy parameters were improvement in the symptoms and total American Urological Association symptom score. Objective efficacy parameters included uroflowmetric studies and an abdominal ultrasound, showing the approximate weight of the prostate and prostate specific antigen. The results showed that there was a statistically significant improvement in all efficacy parameters after treatment with Prostane. The symptoms showed that after 4 months of Prostane therapy, 84% of the patients showed improvement in hesitancy, 66% in intermittent flow, 74% in straining during urination, 70% had improvement in poor flow and 72% had a sense of complete micturition. The frequency of urination at night was less than 2 times in 68% of the patients. There was a reduction of 2 gm of prostatic weight and the maximum flow rate increased by 16.3% after treatment. The post-void residual urine was less by 10.5 ml after 4 months of therapy. There was also improvement in the quality of life of all the patients. Thus, it can be concluded that Prostane was effective, safe, and well tolerated in the target benign prostatic hyperplasia population.

Keywords: Benign prostatic hyperplasia (BPH); American Urological Association (AUA) symptom score; Prostate specific antigen (PSA); Uroflowmetry; Prostane

INTRODUCTION
The expense and complications associated with surgical treatment for benign prostatic hyperplasia (BPH) have led to a search for safe and effective medical therapies. Benign prostatic hyperplasia is a non-malignant condition of nodular but symmetrical enlargement of the prostate in the peri-urethral region, likely due to androgen imbalances associated with aging. It is common in men over the age of 40, regardless of ethnic background. The incidence of BPH can be as high as 50% by the age of 60, and 90% by the age of 85. This makes BPH a condition of increasing importance as the population ages. Due to its proximity to the urogenital tract, prostatic enlargement most commonly presents as obstructive lower urinary tract symptoms, although some are asymptomatic. Bladder outlet obstruction, causing incomplete emptying and subsequent rapid filling, results in urgency, frequency, and nocturia as the primary presenting complaints. The weak and reduced urinary stream in BPH produces
hesitancy, intermittency and post-void dribbling. Urinary retention and stasis predispose BPH patients to infection, which can cause bladder and upper urinary tract inflammation, as well as calculus formation. In severe, prolonged obstruction, there is a risk of hydroureter and progressive renal failure and azotemia. There has been great interest in the effect of alpha1-adrenoceptor antagonists in the treatment of BPH. More selective and long-acting alpha1-adrenoceptor antagonists (terazosin and doxazosin) have also produced statistically and clinically significant improvements in signs and symptoms of BPH. These are also associated with side effects, such as dizziness, asthenia, peripheral oedema, postural hypotension, somnolence, and syncope\textsuperscript{3-8}. Some studies have shown that 5\(\alpha\) reductase inhibitors are effective in reducing the size of prostate, however these patients have to bear with long term side effects such as ejaculation disorders, loss of libido and impotence\textsuperscript{9}. Thus, an alternative herbal therapy was evaluated to treat BPH. Certain herbs reduce the symptoms of benign prostatic hyperplasia. A recent study has shown that \textit{Pygeum africanum} reduces the enlargement of the prostate gland\textsuperscript{10}. A clinical paper was published in Phytotherapy Research, claiming that Prostane was effective in relieving the symptoms of BPH\textsuperscript{11}. Prostane contains many herbs such as \textit{Tribulus terrestris}, \textit{Caesalpina bonducella}, \textit{Areca catechu}, \textit{Asparagus racemosus} and others, which are useful in treating various disorders of the prostate. This clinical study was planned after careful research into the ingredients of Prostane in BPH.

**MATERIALS AND METHODS**

The study was conducted as an open randomised clinical study. During the 1\textsuperscript{st} visit, patients were screened for study eligibility on the basis of a complete medical and medication history and a detailed history of urinary symptoms using the AUA symptom scoring. The investigations included uroflowmetry analysis, abdominal ultrasound or trans-rectal ultrasonography, KUB, PVR, renal function test and cystoscopy if indicated. The previous treatments and/or surgeries done were also recorded. The patients were evaluated at the end of 1 month and 4 months. Baseline characteristics, compliance with study and drug dosing were established during this period.

Patients with diabetes mellitus, prostatic carcinoma, prostatitis, carcinoma bladder, neurogenic bladder, stricture urethra, vesical calculus and patients on medical therapy that is likely to affect bladder function were excluded from the study as these conditions were likely to affect bladder functions. Patients indicated for surgery with refractory retention, recurrent or persistent gross haematuria, bladder stone or renal insufficiency were excluded from the study. Patients with severe disorders of the cardiovascular system, kidney or liver were also excluded. Only those patients who satisfied all inclusion and exclusion criteria were included in the study.

One hundred patients attending the Urology OPD at King George’s Medical College, Lucknow, having symptoms suggestive of bladder outlet obstruction due to benign prostatic hyperplasia were screened, of which sixty four patients were selected for the study. A written, informed consent was obtained from all patients. The evaluation of efficacy was based on symptomatic and urodynamic improvements. The subjective parameters included hesitancy,
intermittent flow, straining during micturition and a sense of incomplete evacuation and frequency of urination at night. The AUA symptom score was also evaluated separately. The objective parameters included uroflowmetry studies and the weight of prostate gland in grams was assessed through ultrasonography. The patients’ complications were also recorded during each visit. Safety was assessed primarily on the basis of adverse event profiles and changes in hemostatic or laboratory parameters. Evaluations included measurement of sitting vital signs (blood pressure and pulse rate), laboratory determinations (including acid phosphatase), ECG findings and physical examination.

RESULTS
Initially, in the clinical study, 64 patients were included. At the end of the study, 9 patients were lost for follow-up, 4 patients were withdrawn from the study as they could not take the medicine regularly; 1 patient who had acute retention of urine was also withdrawn from the study. Therefore, statistical analysis was carried out on 50 patients only.

Statistically significant improvements in all four primary efficacy parameters were observed in the patients treated with Prostane. Tables 1 and 2 show the percentage response to various symptoms before and after treatment. The effect of Prostane on different symptoms score is as follows:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Before treatment (%)</th>
<th>After treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>Intermittent flow</td>
<td>24</td>
<td>41</td>
</tr>
<tr>
<td>Straining during urination</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>Poor flow</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Sense of incomplete micturition</td>
<td>22</td>
<td>20</td>
</tr>
</tbody>
</table>

| Table 2: Showing the frequency of urination at night in patients with BPH (in percentage) |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Treatment                                  | None | 1 time | 2 times | 3 times | 4 times | >5 times |
| Before                                    | 6    | 12     | 38      | 20      | 14      | 10      | 10      | 5   |
| After                                     | 8    | 20     | 40      | 17      | 10      | 5       | 5       | 5   |

**Hesitancy:** Initially 28%, 40%, 27% and 5% had none, slight, moderate and severe hesitancy, which after treatment became, 41%, 43%, 14% and 2% respectively. So a significant improvement in urinary hesitancy was found. More number of patients were relieved in each grade.

**Intermittency:** Initially 10%, 25%, 41% and 24% patients had none, slight, moderate and severe intermittency respectively and after treatment it was 20%, 46%, 22% and 12% respectively. On the whole 31% patients showed significant improvement.
Straining during micturition: Initially 23%, 38%, 36% and 3% patients had none, slight, moderate and severe straining during urination respectively, which was 28%, 46%, 24% and 2% respectively after four months of treatment.

Poor flow: Initially 8%, 52%, 32% and 8% patients had none, slight, moderate or severe poor flow respectively, but after treatment it was 12%, 58%, 25% and 5% respectively. A significant change was recorded in 10% of the patients.

Sense of incomplete micturition: Initially 30%, 28%, 20% and 22% patients had none, slight, moderate and severe sense of incomplete micturition respectively, which was 34%, 38%, 15% and 13% respectively after treatment of 4 months.

Frequency of urination at night (mean): Initially 10% of the patients had frequency of >5 times at night and 14% had frequency of 4 times at night which reduced to 5% and 10% respectively after treatment for 4 months.

Baseline mean symptoms score: It was 14.6 and later on it was 12.4 after 1 month and 9.2 after 4 months’ treatment. There was improvement of 5.4 (36%), which was statistically significant (Figure 1).

Maximum flow rate (mean): Baseline value was 12.2 ml/sec - after 1 month it was 13.4ml/sec and 14.2ml after 4 months. Change of 2.0 ml/sec (16.3%) was observed after 4 months (Figure 2).

Initial mean prostate weight: Initially, it was 34.6 gm and after treatment for 4 months it was 32.6 gm. There was no significant change in the weight of prostate gland (Figure 3).

Post-void residual urine (ml) mean: Mean post-void residual urine changed from 60.5 ml to 50.0 ml, effecting a change of 10.5 ml (Figure 4).

In other observations that were made during the
course of treatment, a positive change was found in the individual quality of life parameters in the treated group.

Analysis of mean sitting vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate and ECG) showed that there were no statistically significant differences before initiating treatment and on completion of therapy. There were no differences among treatment groups in haematological test results, coagulation and biochemical parameters. There was also no statistically significant difference among the treatment groups for alkaline phosphatase value from baseline to end point.

**DISCUSSION**

Potential risk factors for BPH include age, race, ethnicity, family history, smoking, and chronic disease (hypertension, coronary artery disease, and diabetes mellitus), although literature on risk factors is sparse. The incidence of BPH increases with age, especially after the fifty\textsuperscript{12,13}.

The differential diagnosis of lower urinary tract obstruction includes BPH, primary bladder diseases, urethral and bladder neck strictures, genitourinary infections, chronic prostatitis, and prostatic carcinoma. Many men with enlarged prostates may worry about prostate cancer, but it is important to note that BPH and prostatic carcinoma are not associated conditions. While glandular proliferation in BPH tends to occur in the peri-urethral area, prostatic carcinomas tend to arise in the posterior periphery of the prostate in a crescentic pattern. This does not exclude, however, the possibility of co-existence in 10 to 15\% of prostatectomies and BPH, with co-existing prostatic carcinoma.

The diagnostic approach to BPH begins with symptom assessment through history taking. Standardized symptom scoring tools such as the American Urological Association Symptom Index is useful for quantifying and measuring the severity of lower urinary tract symptoms in the diagnosis of BPH, as well as tracking disease progression and response to therapy. Digital rectal examination is also helpful in the diagnosis of BPH and in differentiating between the benign condition and a prostatic carcinoma. In BPH, the prostate is usually enlarged symmetrically with a diffused rubbery consistency. In prostate cancer, hard, irregular nodules are more often found, with occasionally present calculi. It is important to note that even prostates considered to be small on digital rectal examination may be hyperplastic and large enough to result in urinary obstruction.

Urinalysis and serum creatinine should be performed to assess renal function, while serum prostate-specific antigen (PSA) levels should also be measured, as they are moderately
elevated in 30 to 50% of BPH patients, depending on the degree of enlargement and obstruction. Prostate specific antigen levels must be considered with caution, however, as elevated PSA can also occur in prostate cancer, prostatitis, prostatic infarction or ischemia, acute urinary retention, during prostate biopsy or surgery, and with vigorous massage of the prostate. In prostatic carcinoma, serum PSA is elevated in upto 90% of patients, depending on the size of the tumour.

Cystoscopy is an optional investigation, which can provide a more direct evaluation of glandular enlargement, as well as distinguish and confirm BPH from other differential diagnoses, such as bladder-neck contracture, chronic prostatitis or other obstructive conditions. Urinary flow rate measurement and urodynamics testing are procedures that may be used in determining the severity of the disease. A low urinary flow rate with adequate voided volume indicates that an outflow obstruction is likely. In urodynamics testing, both the bladder pressure and urinary flow are measured simultaneously. This process can aid in determining whether a urinary flow problem is primarily obstructive or whether it is actually a result of bladder flaccidity. While urodynamics is completely optional, it can aid in grading the disease and tracking its progression through time. It is also very useful when deciding whether to offer surgical treatment of BPH.

Notably, the effects of Prostane treatment were observed soon after the initiation of therapy. Significant differences as compared to the basal values in the total AUA symptom score were apparent after 1 week of treatment. Prostane was well tolerated. After 12 weeks of therapy, there was statistically significant improvement in primary outcome measures and secondary analyses.

Fourteen patients who were on different alpha-adrenergic blockers had previously responded poorly to the symptoms of BPH and responded well to the treatment of Prostane after 1 month of therapy. Out of these 14 patients, 10 patients responded favourably and their symptoms were totally controlled and 5 patients could reduce the dose of alpha-adrenergic blockers and were later only on Prostane. The drug was well tolerated by patients. Only one patient complained of itching on the body. Cetrizine tablet was added and the patient could continue the medicine. Prostane can be a very safe and promising option for the medical management of benign prostatic hypertrophy.

As shown in this study, Prostane therapy results in almost immediate improvement in urinary flow rates as well as symptomatic improvement, with convenient, twice daily dosing, in patients who do not respond to conventional therapies.

Prostate cancer is the second most common cause of cancer-related deaths in men. Men with an elevated serum PSA level are at increased risk for harbouring prostate cancer. The AUA and the American Cancer Society have advocated annual measurement of serum PSA level for men between 50 and 70 years of age. The present study showed 18% reduction in PSA
values. The present study represents the most rigorous effort to evaluate the efficacy of Prostane in treating Benign Prostatic Hyperplasia.

CONCLUSION
As the population ages, benign prostatic hyperplasia will become an increasingly common condition, making it important for physicians to recognize and diagnose it, and be knowledgeable about the treatment options available. The development of new and cost-effective medical therapy for BPH is also an area of active research, as the incidence of BPH continues to increase. Therefore, Prostane under these circumstances can be considered as an effective and safe therapy in the treatment of BPH.

REFERENCES