Efficacy and Safety of a Herbal Preparation PR-2000 in the Treatment of Symptomatic Benign Prostatic Hyperplasia

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ABSTRACT
As the life expectancy for men increases, more cases of benign prostatic hyperplasia (BPH) will be expected. Symptomatic BPH causes morbidity and can lower the quality of life. We investigated whether short-term administration of a herbal preparation known as PR-2000 could improve BPH symptom in men. Thirty patients with moderate to severe symptomatic BPH were treated with PR-2000, 2 tablets twice daily for 3 months. Patients were evaluated at baseline, during treatment every month and at the end of 2 months after therapy. We determined the effects of PR-2000 on the American Urological Association (AUA) symptom score and pelvic ultrasonography of the prostate to determine prostate size and weight and to measure post void residual volume. Treatment with PR-2000 produced a decline of 52.9% (p<0.0001) in AUA score, a rapid reduction of 27% (p<0.006) in prostatic volume, and an decrease in the urine residual volume by 2.86 mL/s. Our study demonstrates that in patients with symptomatic BPH, treatment with PR-2000 is safe since there was no adverse effects.

INTRODUCTION
Benign prostatic hyperplasia (BPH) is a condition that will affect most men should they live long enough\(^1\)\(^-\)\(^3\). Symptomatic BPH is a frequent cause of morbidity among elderly men and can produce a great decline in general well-being\(^4\)\(^-\)\(^6\). The annual medical costs of BPH are enormous and present an economic burden on the public health systems. The pathogenesis of BPH is incompletely understood\(^7\). Aging and chronic exposure to dihydrotestosterone (DHT) are required for the development of BPH\(^8\). However, the actions of androgen alone do not explain the hyperplastic process or the progression of the disease from pathological to clinical BPH\(^9\). Several peptide growth factors have also been implicated in the development of BPH\(^10\)\(^-\)\(^13\). Thus, the overall disease process that leads to the production of symptomatic BPH is very complex. Improvement in urinary symptoms and the quality of life are important issues for decision-making in the treatment of patients with BPH\(^14\). Medical therapy is usually recommended first because of the probability of clinical improvement and the patients’ concern about surgery or other invasive treatments. Inhibitors of 5α-reductase or α\(_1\) -adrenergic receptor antagonists do not offer long-term remission of urinary symptoms after discontinuation and should be used only in a selected population of patients\(^15\). Experimental
studies have shown that PR-2000 has 5α-reductase activity and also reduces the prostatic weight in experimentally induced prostatic hyperplasia\textsuperscript{16}. Clinical pilot studies have been evaluated in patients with prostate hyperplasia and the results have shown that after PR-2000 therapy there was a reduction in the American Urological Association symptom score, prostatic weight and PSA values\textsuperscript{17}. In view of these favorable clinical results, we decided to evaluate the response to 3-month administration of PR-2000 in 30 men with moderate to severe symptomatic BPH.

**MATERIAL AND METHODS**
Fifty male patients with BPH were initially enrolled in this open phase II study. The criteria for eligibility were: age 50–80 year with no evidence of prostate cancer, previously untreated BPH and a total AUA score of 20 or more; an enlarged prostate estimated by digital rectal exam, serum prostate-specific antigen (PSA) below 10 ng/mL, post-voided residual volume (PVR) of 50 cc or more measured by pelvic bladder ultrasonography. Patients who had taken antiandrogenic drugs during the previous 3 months were not enrolled in the study. The patients included in the study had refused surgery earlier. Thirty three patients, aged between 43-75 years (mean age 58.5 years), with moderate to severe BPH according to the AUA symptom score (21.85) were finally selected for the study. Each patient gave written, informed consent to the study, which was approved by the ethical committee of Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. Each subject acted as his own control. Clinical, laboratory, and radiological evaluations were carried out before initiation of, and after 3 months of PR-2000 therapy to establish the efficacy and safety of the drug. Laboratory evaluations were however carried out on all the subjects during therapy every month up to 3 months. Clinical evaluations consisted of complete history, and complete physical examination including digital rectal examination. (DRE) The severity of the urinary symptoms was estimated according to the AUA symptom index: scores of 1–7 - mild; 8–19 – moderate, and 20–35 - severe. Clinical evaluations were again performed periodically thereafter every month and at the end of 3 months. Baseline laboratory investigations consisted of hematology, such as total count, differential count, hemoglobin %, urinalysis and serum levels of PSA. Abdominal pelvic ultrasonography was done before and after completing the study to estimate the approximate prostate weight and size and to measure the post-void residual volume. PR-2000 tablet consisted the powders of *Tribulus terrestris*, *Caesalpinia bonducella*, *Areca catechu*, *Asparagus racemosus* and *Acacia nilotica*. The dose of PR-2000 was 2 tablets, twice daily, for 3 months. At the end of the therapy the evaluations included progress notes and questions about adverse events. The data are expressed as the mean ± SEM unless indicated otherwise. Statistical analyses of the data were performed with use of two-way ANOVA analysis. Differences were considered statistically significant by the \( p \) value.

**RESULTS**
Thirty men with moderate to severe BPH completed 3 months of treatment with PR-2000. Three patients were withdrawn from the study during week 4 because they were unable to
comply with the schedule of follow-up. Table 1 shows the patients’ ages and the individual percentages of improvements in the AUA during the study. There was an improvement in total AUA, and prostatic size by abdominal ultrasonography (AUS) before and after therapy. The mean basal value for total AUA was 29.50 ± 3.802 (± SD range, 23-35). The decline in total AUA in patients at the end of the 1st, 2nd and 3rd months was 24.08, 18.25 and 12.33 respectively. When compared to the baseline value, after PR-2000 administration the AUA score was significantly reduced to 12.33 ± 7.233 (± SD range, 0-24; p<0.001 by Two-way ANOVA) (Table 1). Calculations by abdominal ultrasonography showed that the prostatic mean weight (in gms) was 34.87 ± 21.01 (± SD range 24-58) after treatment was 21.22 ± 22.60 (± SD range 0-56.76; p<0.0553 by Two-way ANOVA) (Figure 1). The prostatic size (in cc) was 69.81 ± 33.16 (± SD range 42.62-114.75) and after three months of treatment it was 63.66 ± 32.03 (± SD range 30.36-103.2; p<0.001 by Two-way ANOVA) (Figure 2). The ultrasonography of the bladder revealed that at the time of initiation of the study, the post void residual volume was 136.9 ± 179.8 (± SD range 106-603.5) and after treatment, it was 73.33 ± 84.47 (± SD range 78-284; p<0.0480 by Two-way ANOVA) (Figure 3).

<table>
<thead>
<tr>
<th>Before treatment</th>
<th>After treatment</th>
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<tr>
<td>29.50 ± 3.802</td>
<td>24.08 ± 5.017</td>
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<tr>
<td>1 month</td>
<td>2 months</td>
</tr>
<tr>
<td>29.50 ± 3.802</td>
<td>18.25 ± 6.092</td>
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<tr>
<td>3 months</td>
<td>12.33 ± 7.228</td>
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<td>p&lt;0.001 by Two-way ANOVA</td>
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No serious side-effects occurred during therapy with PR-2000, and there were no significant changes in any of the standard blood tests during this study (Table 2). There were no compliance problems with PR-2000 treatment. No patient presented with acute urinary
retention during the treatment period. Five men reported slight to notable hot flashes during PR-2000 therapy, which subsided when the treatment was ended.

DISCUSSION

The natural history of BPH is variable, but the disease is usually slowly progressive\textsuperscript{17,18}. Improvement in the quality of life of patients suffering from BPH is an important issue in the medical management of this condition. In this study, we demonstrated that administration of PR-2000 for 2 months was of great clinical benefit to patients with moderate to severe BPH. During treatment with PR-2000, the high scores of urinary symptoms and quality of life due to urinary symptoms decreased significantly by week 8. Before entering this study, the patients had many symptoms. The reduction in high scores of the AUA due to urinary symptoms was not limited to the few days’ duration of the treatment period, but continued to decline significantly in most patients during the 3 months of follow-up. The prostatic size had increased by 187.5% before treatment and after treatment it was 166%, by showing a reduction of 21.5%. The prostatic weight had increased by 75% before therapy, but post-therapy, the weight was increased by only 5%. This shows that there was a reduction of 70% after 3 months of PR-2000 therapy. The post-void residual volume of urine was reduced by 63.57 ml. These results are very encouraging and PR-2000 can be a useful drug in those patients who are contraindicated for surgery or in those patients who do not went to undergo the strenuous procedure of surgery.

Many studies have shown herbs to be useful in patients with BPH. Saw palmetto has been useful in the treatment of BPH and the results were equivalent to finasteride\textsuperscript{20}. Another placebo-controlled clinical study showed that there was improvement of symptoms of BPH in patients who were administered β-sitosterol plant extract\textsuperscript{21}. The outcome of clinical trials with nafarelin and leuprolide are disappointing, as prolonged administration of these analogues caused shrinkage of the prostate and improved urinary symptoms, but after discontinuing the therapy these effects were reversed\textsuperscript{22,23}. This may explain the slow onset of action of finasteride. The improvement in symptoms after finasteride takes place over 6 months, and prostatic volume is reduced by only 17–21%\textsuperscript{24}. Finasteride significantly reduces acute urinary retention and need for surgery in men with symptomatic BPH\textsuperscript{25}, but causes significant sexual dysfunction. A long acting α-adrenergic antagonistic drug such as terazosin can produce responses within weeks, but needs to be given chronically and may cause orthostatic hypotension and syncope, with a potential risk for falls.

CONCLUSION

In this study, the long-term benefits of PR-2000 were documented by subjective and objective parameters. A short-term administration of PR-2000 to men with symptomatic BPH appears to be safe, provides a rapid onset of action, and tends to have a beneficial effect on the disease process and overall health-related quality of life. Randomized-double-blind, placebo-control

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<th>Parameters</th>
<th>Before treatment</th>
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<tr>
<td>Hemoglobin (%)</td>
<td>12.33 ± 1.893</td>
<td>13.18 ± 1.264</td>
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<tr>
<td>Total count (/cumm)</td>
<td>9225 ± 3206</td>
<td>8525 ± 4077</td>
</tr>
<tr>
<td>Blood urea (mg/dl)</td>
<td>37.31 ± 22.42</td>
<td>21.18 ± 3.43</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.287 ± 0.6717</td>
<td>0.8500 ± 0.2195</td>
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Table 2: Blood analysis - before and after treatment with PR-2000 (Mean ± SD; n=30)
studies are required to confirm these preliminary findings. Long acting depot preparations of PR-2000 that are being presently perfected should greatly facilitate the treatment of BPH.

REFERENCES


