

Urtica dioica for Treatment of Benign Prostatic Hyperplasia: A Prospective, Randomized, Double-Blind, Placebo-Controlled, Crossover Study

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ABSTRACT. *Purpose:* To determine the effects of therapy with *Urtica dioica* for symptomatic relief of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH).

Material and Methods: A 6-month, double-blind, placebo-controlled, randomized, partial crossover, comparative trial of *Urtica dioica* with placebo in 620 patients was conducted. Patients were evaluated using the International Prostate Symptom Score (IPSS), the maximum urinary flow rate (Qmax), postvoid residual urine volume (PVR), Serum Prostatic-Specific Antigen (PSA), testosterone levels, and prostate size. At the end of the 6-month trial, unblinding revealed that patients who initially received the placebo were switched to *Urtica dioica*. Both groups continued the medication up to 18 months.

Results: Five hundred fifty-eight patients (90%) completed the study (287/305, 91% in the *Urtica dioica* group, and 271/315, 86% in the placebo group). By intention-to-treat analysis, at the end of the 6-month trial, 232 (81%) of 287 patients in the *Urtica dioica* group reported improved LUTS compared with 43 (16%) of 271 patients in the placebo group ($P < 0.001$). Both IPSS and Qmax showed greater improvement with drugs than with placebo. The IPSS went from 19.8 down to 11.8 with *Urtica*

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dioica and from 19.2 to 17.7 with placebo ($P = 0.002$). Peak flow rates improved by 3.4 mL/s for placebo recipients and by 8.2 mL/s for treated patients ($P < 0.05$). In *Urtica dioica* group, PVR decreased from an initial value of 73 to 36 mL ($P < 0.05$). No appreciable change was seen in the placebo group. Serum PSA and testosterone levels were unchanged in both groups. A modest decrease in prostate size as measured by transrectal ultrasonography (TRUS) was seen in *Urtica dioica* group (from 40.1 cc initially, to 36.3 cc; $P < 0.001$). There was no change in the prostate volume at the end of study with placebo. At 18-month follow-up, only patients who continued therapy, had a favorable treatment variables value. No side effects were identified in either group.

Conclusion: In the present study, *Urtica dioica* has beneficial effects in the treatment of symptomatic BPH. Further clinical trials should be conducted to confirm these results before concluding that *Urtica dioica* is effective. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2005 by The Haworth Press, Inc. All rights reserved.]

KEYWORDS. Benign prostatic hyperplasia, phytotherapy, stinging nettle, *Urtica dioica*, symptom score, and long-term outcome

INTRODUCTION

There is a general perception that herbal products are, at worst, harmless placebos, but this is not always true. As early as the 15th century BC, the use of plant extracts for the symptomatic treatment of BPH was described on Egyptian papyrus.¹ Unfortunately, many questions remain unanswered; therefore the scientific case for their use remains unproven. With the recent proliferation of nutrition and vitamin stores, use of these agents has greatly increased.² In some European countries, plant extracts are the most commonly recommended initial treatment for men with BPH, and patients are reimbursed for the cost of these agents by health insurance companies.³ Numerous plant extracts have been used in the treatment of LUTS secondary to BPH. Some of these extracts are *Aletris farinose* (Unicorn root), *Serenoa repens* (Saw palmetto), *Pygeum africanum* (African pulm), *Populus tremula* (Aspen), *Echinacea purpurea* (Purple cone flower), *Cucurbita pepo* (Pumpkin seeds), *Secale cereale* (Rye), and *Hipoxis roperi* (South African star grass). The most popular agent is Saw palmetto (*Serenoa repens*, Dwarf

palm), which is derived from the berry of the American dwarf palm tree.⁴ In a variety of clinical trials, the use of Saw palmetto in men with lower urinary tract symptoms secondary to BPH has led to significant subjective and objective improvements.⁵⁻¹⁰ Despite increased awareness and use, basic and clinical research with regard to the role and efficacy of natural remedies in men with BPH continue to lag.

Urtica dioica is extract from the root of a stinging nettle and it is widely used in Germany.¹¹ The extracts of the roots of the stinging nettle contain a complex mixture of water- and alcohol-soluble compounds such as fatty acids, sterols (β -sitosterol, campesterol, and stigmasterol), and flavonoids. There have been three studies that suggest different mechanisms of action for stinging nettle. These include inhibition of prostatic growth factor interaction,¹² inhibition of membrane sodium and potassium-adenosine triphosphate in the prostate, which results in the suppression of prostate cell metabolism and growth,¹³ and modulation of binding of sex hormone-binding globulin to its receptor on prostate cell membranes.¹⁴ These laboratory studies only suggest possible mechanisms of action.

Urtica dioica is widely used in Europe.¹¹ Stinging nettle is found in many areas of Iran. The raw plant is obtained from wastelands, woodlands, and gardens. Compared to other phytotherapeutic agents, *Urtica dioica* has not been extensively studied. Currently, there are no efficacy data on the effects of *Urtica dioica* for the treatment of LUTS secondary to BPH. Thus, we performed a randomized, double-blind, placebo-controlled study to assess the clinical effects and safety of *Urtica dioica* in patients with symptomatic BPH.

MATERIALS AND METHODS

A total of 620 patients, 55 to 72 years old (mean age 63 years), with lower urinary tract symptoms due to BPH 1 to 3 years in duration presenting to the outpatient urology clinic participated in this study. A detailed medical history was obtained from each patient and all patients completed an IPSS questionnaire. A physical examination and laboratory evaluation, including a complete blood count, urine analysis, serum chemistry study, testosterone and Prostatic Specific Antigen (PSA) determination, transrectal ultrasonography (TRUS), ultrasonography from urinary tract, postvoid residual volume (PVR) and maximum urinary flow (Qmax) measurement were performed.

To assess the volume of prostate accurately with TRUS, precise measurements were made in 3 dimensions: the anterior-posterior, the coronal, and the sagittal. The volume was determined using the formula of $\frac{4}{3} \pi r_1 \times r_2 \times r_3$, where r is the radius (each of the 3 radii represent a different dimension).

Serum PSA levels were measured using the Yang assay. Residual urine measurements were made by catheterization and Qmax were recorded electronically.

The following inclusion criteria were used: the patient had no cancer, the laboratory findings were normal; and the patient had no lower urinary tract problem other than BPH. Patients were excluded from analysis if there was: loss to follow-up, surgical intervention for BPH, discontinuation of study medication during the double-blind trial, α_1 -blocker, 5- α -reductase inhibitor or other drug therapy during trial and follow-up, any combination of *Urtica dioica* with other phytotherapeutic agent, and insufficient follow-up. Patients meeting inclusion criteria had their medical histories and demographic information recorded and underwent a full physical examination by the author.

A table of random numbers was used to assign subjects at a 1:1 ratio to receive a sealed opaque bottle of *Urtica dioica* or inert placebo. The placebo was indistinguishable from the *Urtica dioica*. The fluid extract of *Urtica dioica* was synthesized from the roots via a fractional percolation process and standardization. The herbal blend contained a standard preparation of 100 mg of *Urtica dioica* root extract in 1 ml. Each preparation was ingested three times daily with meals. Each patient was given *Urtica dioica* ($n = 305$) 120 mg three times daily or placebo ($n = 315$) in a double-blind, randomized order for six months. At the end of the trial, patients were evaluated according to the original protocol. After completion of the 6-month trial, unblinding occurred, a compliance evaluation was carried out, and patients were asked what they thought they had received. Patients were free to choose further treatment with *Urtica dioica* or discontinue therapy of any kind. Patients who initially received placebo were crossed over to receive *Urtica dioica* for 18 months, and patients who had used the *Urtica dioica* continued their medication in the 18-month follow-up period. A complete crossover design was not used because we believed that patients who had responded to the *Urtica dioica* were deprived of an effective treatment. The patients came for monthly check-ups, and in each visit, they were re-evaluated using the IPSS, Qmax, and PVR.

All patients with a follow-up of > 16 months after recruitment for the double-blind trial were included. Only patients that had been continuously treated for at least 90% of the follow-ups and had no changes in the treatment were included in the analysis. Exclusion and inclusion criteria were also applied in these patients. In all, 340 patients who chose further treatment and 131 patients who discontinued therapy of any kind were eligible for analysis at the end of follow-up. At the 18-month follow-up, patients were re-evaluated using the initial protocol.

The unpaired *t*-test was used to assess differences between all the variables in the original double-blind trial protocol. *P* values reported (compared with placebo) were considered descriptive only, as are all *P* values reported in the follow-up program analysis. The level of significance was defined as $\alpha = 0.05$ (two-sided). Intention-to-treat analyses were performed on all efficacy variables and included the subjects who had a baseline measurement and at least one measurement after the start of treatment.

RESULTS

Six hundred twenty-one patients were recruited, only 558 (90%) completed the whole randomized trial study. The remaining 10% were excluded from the study for several reasons (Table 1). Overall patients' demographics are shown in Table 2. Comparison between the *Urtica dioica* group and the placebo group for IPSS, Qmax, PVR, prostate size, PSA, and testosterone serum levels at various times during the study are shown in Table 3.

Initial 6-month, double-blind, randomized trial: After six months of treatment, patients receiving *Urtica dioica* demonstrated significantly improved LUTS compared to those receiving placebo. The least square mean scores to the IPSS questions assessing the severity of bladder outlet obstruction demonstrated significant improvement among patients receiving *Urtica dioica* compared with placebo ($P < 0.001$, Table 3). In this study, greater improvements in the IPSS, Qmax, and PVR were seen in the treatment group than with the placebo group. The IPSS went from 19.8 to 11.8 with *Urtica dioica* and 19.2 to 17.7 with placebo ($P = 0.002$), which represent decreases from baseline of 40% and 9%, respectively. In terms of peak flow rate, the *Urtica dioica* treated patients improved by 8.2 mL/s and only by 3.4 mL/s for placebo recipients ($P < 0.05$). This is a 77% increase from baseline for the *Urtica dioica* group compared with a 31% increase from baseline for the placebo group.

TABLE 1. Reasons for exclusion from study

Reason for exclusion	<i>Urtica dioica</i>	Placebo
Lost to follow-up	25	36
Surgical intervention	5	14
Medication discontinued during randomized trial	2	10
α-blocker or finasteride therapy	4	9
Combination therapy	0	0
Follow up < 16 months	16	9
Total	65	84

TABLE 2. Baseline characteristics of participants in the 2 groups

Characteristic	<i>Urtica dioica</i>	Placebo
Patients number	305	315
Mean age, y (range)	64 (57-71)	62 (53-73)
Mean duration of LUTS due to BPH, y (range)	2.2 (1-3)	2.3 (1-3)
Education		
Did not complete high school	115	118
High school	155	159
Graduate/Professional	35	38
Mean IPSS ± SD	19.8 ± 4.9	19.2 ± 4.6
Mean Qmax ± SD, mL/s	10.7 ± 2.4	10.8 ± 2.8
Mean PVR ± SD, mL	73 ± 32.6	74 ± 29.6
Mean prostate volume ± SD, cc	40.1 ± 6.8	40.8 ± 6.2
Mean serum PSA ± SD, ng/mL	2.4 ± 1.4	2.7 ± 1.1
Mean serum testosterone ± SD, ng/dL	645 ± 31	651 ± 27

LUTS = Lower urinary tract symptoms, IPSS = International prostrate symptom score, Qmax = Maximum urinary flow rate, PVR = Postvoid residual urine volume, PSA = Prostatic specific antigen, SD = Standard deviation, y = year

Postvoid residual urine (PVR) was decreased in the treatment group (before treatment, 73 cc; after treatment, 36 cc; $P < 0.05$). The placebo group showed no significant change in residual urine volume (before treatment, 74; after treatment 71) ($P > 0.05$). Prostate size (as measured by TRUS) decreased from 40.1 cc to 36.3 cc in *Urtica dioica* group ($P <$

TABLE 3. Effect of *Urtica dioica* in men with symptomatic BPH

Mean ± SD	Baseline	Randomization	At 18-month follow-up	
			<i>Urtica dioica</i> continued at the end of 6-month trial	<i>Urtica dioica</i> discontinued at the end of 6-month trial
IPSS				
<i>Urtica dioica</i>	19.8 ± 4.9	11.8 ± 4 *	11.1 ± 4.8	19.1 ± 4.2
Placebo	19.2 ± 4.6	17.7 ± 3.1	12.1 ± 3.8	19.4 ± 3.9
Qmax (mL/s)				
<i>Urtica dioica</i>	10.7 ± 2.4	18.9 ± 4.7 **	16.2 ± 3.2	11 ± 3
Placebo	10.8 ± 2.8	14.2 ± 3.7	18.2 ± 3.4	10.2 ± 3.3
PVR (mL)				
<i>Urtica dioica</i>	73 ± 32.6	36 ± 25.5 ***	37 ± 28.2	70 ± 28
Placebo	74 ± 29.6	71 ± 24.4	38 ± 25.5	77 ± 22
Prostate volume (cc)				
<i>Urtica dioica</i>	40.1 ± 6.8	36.3 ± 4.2	36.1 ± 7.2	39.5 ± 6
Placebo	40.8 ± 6.2	40.6 ± 5.1	40.6 ± 4.1	42.4 ± 5.2
Serum PSA (ng/mL)				
<i>Urtica dioica</i>	2.4 ± 1.4	2.2 ± 1.2	2.3 ± 1.1	2.5 ± 1.1
Placebo	2.7 ± 1.1	2.6 ± 0.8	2.6 ± 1.2	2.7 ± 1.2
Serum testosterone (ng/dL)				
<i>Urtica dioica</i>	645 ± 31	649 ± 29	650 ± 34	650 ± 32
Placebo	651 ± 27	645 ± 30	649 ± 33	649 ± 29

LUTS = Lower urinary tract symptoms, IPSS = International prostrate symptom score, Qmax = Maximum urinary flow rate, PVR = Postvoid residual urine volume, PSA = Prostatic Specific antigen, SD = Standard deviation
P* = < 0.002 v placebo, *P* = < 0.05 v placebo, ****P* = < 0.001 v placebo

0.001), while no significant change was observed in the placebo group. Testosterone and PSA levels were unaffected in both groups.

Long term results: Those in the primary *Urtica dioica* group continued to have a favorable outcome, with all values remaining stable from the end of the double-blind study to the 18-month follow-up. There was no additional effect from the longer treatment period. All improvements at 18 months were significantly better than participants who never received active treatment (*P* < 0.001).

Of the former placebo group, those who received *Urtica dioica* improved to the same extent as the treated group in the double-blind trial for all variables.

Of the initial 620 patients, 27 (4.3%) reported undergoing surgery for BPH during the whole study schedule: 22 (3.5%) belonged to the placebo group and 5 (0.8%) to the patients who received *Urtica dioica*. The mean time to surgery was 210 days in the patients without active treatment and 448 in those taking *Urtica dioica*.

DISCUSSION

The widespread use of phytotherapeutic products necessitates our need to explore the true magnitude and level of efficacy of these products. Other than alpha-blockers or hormonal agents, medical treatments for BPH have included phytotherapeutic agents, cholesterol lowering agents, amino acid complexes, and organ extracts.¹⁵ In the past decade, the use of phytotherapeutic agents has become particularly popular in men with lower urinary tract symptoms secondary to BPH.

There has only been one recent study on *Urtica dioica* that utilized a liquid dosage form.¹⁶ The liquid preparation has subsequently been removed from the market because of its unacceptable taste.¹¹ In that study, 41 patients were randomized to receive either placebo or the stinging nettle preparation. They were treated for a period of three months. Treated patients had superior improvement compared with placebo recipients in terms of IPSS results.¹⁶ The placebo was the same taste of the stinging nettle extract and was indistinguishable from active treatment.

The data that is available to date does not confirm its efficacy in the treatment of lower urinary tract symptoms secondary to BPH. From the 305 eligible patients taking *Urtica dioica* during randomized trial, only 52 (17%) chose to discontinue after unblinding while most remained on the *Urtica dioica* treatment. The reasons for discontinuation included lack of efficacy (n = 22), bothered by participation in study (n = 16), and achieved enough improvement (n = 14). In these patients, the results were stable over the 18-month follow-up. Of the 315 placebo patients, 236 (75%) subjects chose phytotherapy over the 18-month follow-up period. Interestingly, when starting *Urtica dioica* therapy, they had the same extent of symptom relief as had those taking *Urtica dioica* during the randomized study. Of all eligible patients, most [n = 340 (61%)] chose drug therapy post-unblinding in both *Urtica dioica* and placebo groups. Overall, patients had a substantial and lasting favorable effect compared with the symptom severity at randomization. Active treatment was generally better than watchful waiting.

To interpret the present results correctly, the substantial group of 149 patients who were excluded from the follow-up evaluation (24% of the original recruited 620 patients) were analyzed for possible effects on the results. Three major indicators of treatment failure were surgical intervention, choice of α_1 -blocker or finasteride therapy, and discontinuation of medication during the randomized trial, which were more prevalent in those receiving placebo. In addition, more patients were lost to follow-up in the placebo than in the *Urtica dioica* group. Results from the randomized study phase for the excluded patients showed no substantial differences in outcome compared with those not excluded. Therefore, no relevant factors appeared to affect the results of the 18-month follow-up caused by the exclusion of these patients.

The proportion of patients who underwent BPH-related surgical intervention (4.3%) was about one-fourth to those that reported surgery in the study with finasteride.¹⁷ Of these 27 interventions, 22 were patients who received placebo and also chose no further therapy post unblinding, with only five in the *Urtica dioica* group. These findings further support the beneficial effect of *Urtica dioica* therapy. Since the study was not designed to assess this criterion, it remains unclear whether *Urtica dioica* was solely responsible for this effect. Furthermore, as with many medical therapies for BPH, it is unclear if surgery is postponed rather than prevented in the long-term.

In the open-extension protocol, each patient was free to choose further treatment. When the outcome values for patients after unblinding were compared with their choice of further treatment, no significant factors, such as treatment outcome or treatment arm, were predicted in any of the follow-up groups. Therefore, it appears that additional factors such as personal or doctor preferences influenced the decision.

An unexplained finding in our study is the lack of a change in serum PSA despite decreased prostatic size. This apparent paradox may involve some novel mechanism of action. The results of these studies suggest a wide spectrum of activity. However, precise mechanism(s) of action remain obscure.

CONCLUSION

As there are no known major side-effects with *Urtica dioica* therapy in addition to the fact that the effects are maintained over at least 18 months, *Urtica dioica* may be considered along with other medical ther-

apies for patients with symptomatic BPH. However, it remains unclear which type of patient with symptomatic BPH will benefit the most from this therapy. Although several studies suggest some clinical efficacies with many phytotherapeutic agents, further randomized, placebo-controlled trials are needed to evaluate their efficacy in preventing progressions, such as urinary retention and need for surgery. Further study is also needed to ascertain the mechanism and reproducibility of these effects. More laboratory analyses are also required to determine the active ingredient or ingredients and their mechanism of action. Alpha-adrenergic blockers and 5-alpha-reductase inhibitors are among the most extensively evaluated drugs in urologic practice. It is imperative that phytotherapeutic agents be evaluated to an equal extent.

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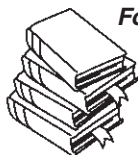
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