ELSEVIER

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF SAW PALMETTO IN MEN WITH LOWER URINARY TRACT SYMPTOMS

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ABSTRACT

Objectives. To assess the effects of saw palmetto on urinary symptoms, sexual function, and urinary flow rate in men with lower urinary tract symptoms using a double-blind, randomized, placebo-controlled trial.

Methods. The eligible patients were 45 years of age or older and had an International Prostate Symptom Score of 8 or greater. After a 1-month placebo run-in period, 85 men were randomized to receive saw palmetto or placebo for 6 months. Patients were evaluated using the International Prostate Symptom Score, a sexual function questionnaire, and by measurement of the urinary flow rate.

Results. The mean symptom score decreased from 16.7 to 12.3 in the saw palmetto group compared with 15.8 to 13.6 in the placebo group ($P = 0.038$). The quality-of-life score improved to a greater degree in the saw palmetto group, but this difference was not statistically significant. No change occurred in the sexual function questionnaire results in either group. The peak flow rate increased by 1.0 mL/s and 1.4 mL/s in the saw palmetto and placebo groups, respectively ($P = 0.73$).

Conclusions. Saw palmetto led to a statistically significant improvement in urinary symptoms in men with lower urinary tract symptoms compared with placebo. Saw palmetto had no measurable effect on the urinary flow rates. The mechanism by which saw palmetto improves urinary symptoms remains unknown.

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The use of nontraditional therapies in men with lower urinary tract symptoms (LUTS) has increased greatly in recent years owing to a variety of factors.[1] These include patient dissatisfaction with standard pharmacologic and surgical treatments, increased marketing of nonprescription products through the media and Internet, and a philosophical congruence between alternative therapies and patient values and beliefs.[2,3] The most popular phytotherapeutic agent in men with benign prostatic hyperplasia and voiding dysfunction is saw palmetto *(Serenoa repens)*.[4] This agent is derived from the berry of the American dwarf palm tree found in many areas of the southeastern United States. A number of placebo-controlled trials have been published concerning the use of saw palmetto in men with LUTS.[5–9] Many of these studies have suggested significant subjective and objective improvement in patients with benign prostatic hyperplasia.[5,6] However, most of these trials were limited by several factors, including small patient numbers, brief study intervals of 1 to 3 months, and/or the absence of standardized testing instruments, such as symptom scores.[5–9] In addition, several investigators have used meta-analyses of saw palmetto and have concluded that this alternative agent is beneficial in men with LUTS.[10,11] Despite the results of these studies, many physicians remain skeptical about the benefits of saw palmetto, and it has been suggested that any improvement in symptoms was largely induced by a placebo effect.[12] For these reasons, there is a continued call for randomized, placebo-controlled trials of saw palmetto to determine the magnitude and level of efficacy of this agent.[4,10]

MATERIAL AND METHODS

Men were eligible to participate in this randomized, double-blind, placebo-controlled trial of saw palmetto if they were 45

The study drug and placebo were provided by Nutraceutical Corp., Ogden, Utah.

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TABLE I. *Changes in International Prostate Symptom Score and quality-of-life score in men treated with saw palmetto and placebo for 6 months*

	Initial	2 Months	4 Months	Final	Change
Symptom score					
Saw palmetto	16.7 ± 4.9	13.1 ± 4.6	12.0 ± 5.1	12.3 ± 5.5	−4.4 ± 5.9
Placebo	15.8 ± 4.8	12.4 ± 5.2	13.3 ± 5.4	13.6 ± 6.6	−2.2 ± 5.4
					$P = 0.038$
Quality-of-life score					
Saw palmetto	3.3 ± 1.1	3.0 ± 1.4	2.6 ± 1.2	2.6 ± 1.5	−0.7 ± 1.5
Placebo	3.1 ± 1.3	2.8 ± 1.1	2.8 ± 1.3	2.8 ± 1.2	−0.3 ± 1.1
					$P = 0.20$

Data presented as the mean ± SD.

years of age or older and had an International Prostate Symptom Score (IPSS) of 8 or greater. Patients were enrolled in the study from January 1999 through July 2000. Patients were excluded if they had previously undergone prostate surgery, had a history of prostate cancer or urethral stricture disease, or had been treated with finasteride, saw palmetto, or any other alternative therapy for benign prostatic hyperplasia (within 6 months) or any alpha-receptor blocker (within 1 month). The initial evaluation included completion of an IPSS questionnaire[13] and sexual function questionnaire,[14] measurement of urinary flow rate using a standard flow meter, digital rectal examination, measurement of serum prostate-specific antigen level, and urinalysis. Patients with an elevated serum prostate-specific antigen level and/or an abnormal digital rectal examination were allowed to participate if a prostate biopsy demonstrated no evidence of malignancy. The study was conducted at the University of Chicago and the Dekalb Clinic.

During the first month of the study, all patients received a placebo capsule twice daily (placebo run-in period). After 1 month, patients completed the IPSS questionnaire and sexual function questionnaire, and the urinary flow rate was measured. If the IPSS was less than 8, patients were excluded from further participation in the study. After the exclusion of these placebo responders, men were randomized using a computer number table to receive either a commercially available preparation of saw palmetto that did not contain any other active components (160 mg twice daily, Nutraceutical, Ogden, Utah) or placebo for 6 months. The saw palmetto product was standardized to contain 85% to 95% (136 to 152 mg) fatty acids and sterols. The only other ingredients in the saw palmetto and placebo capsules were extra-virgin olive oil, gelatin, and glycerin. Patients noted no difference in the taste and smell of the placebo and saw palmetto capsules. The patients, as well as the physician and research nurse who interacted with the patients at each study visit, were unaware of the results of the randomization. Only the study coordinator, who did not interact with the patients, was aware of the results of the randomization. Patients returned 2, 4, and 6 months after randomization, at which time the IPSS and sexual function questionnaires were completed, the presence of side effects was determined, and the urinary flow rate was measured. The study was designed to detect a three-point difference in symptom score change between the two groups, with an estimated sigma of 5 and power of 80% (alpha = 0.05). On the basis of these estimates, the sample size was calculated to be 45 men in each group. The study was approved by the Institutional Review Board. Statistical comparisons were made using the Mann-Whitney *U* test (symptom score and flow rate) and Student's *t* test (sexual function score and quality of life score) after the data had been entered into the MINITAB computer program. All statistical tests were two-tailed.

RESULTS

Ninety-four men were initially enrolled in the study. After the 1-month placebo run-in period, 9 men were excluded, and 85 men were randomized to receive either saw palmetto (n = 41) or placebo (n = 44) for the remainder of the study. The mean age ± SD of the men in the saw palmetto and placebo groups was 64.6 ± 9.9 and 65.3 ± 9.7 years, respectively. No statistically significant difference was found in the initial flow rate, symptom score, quality-of-life score, or sexual function score between the two groups. Four men in the placebo group and two in the saw palmetto group did not complete the 6-month study. The reasons for this included a failure to return for follow-up visits (one in the saw palmetto group and two in the placebo group), worsening urinary symptoms not responsive to the study medication (two in the placebo group), and the development of diarrhea (one in the saw palmetto group). The only other adverse reaction reported was mild gastric distress by 1 patient in the saw palmetto group.

Men randomized to receive saw palmetto had a mean decrease in symptom score of 4.4 points compared with 2.2 points in the placebo group (Table I). This difference was statistically significant ($P = 0.038$). Although the quality-of-life score also improved to a greater degree in the saw palmetto group (0.7 versus 0.3 in the placebo group), this difference was not statistically significant ($P = 0.20$). No improvement occurred in the sexual function questionnaire results in either group (Table II). The peak urinary flow rate improved slightly in both groups, although no difference in the magnitude of the improvement was found between them (Table II).

COMMENT

Many men with LUTS use saw palmetto and/or other phytotherapeutic agents either alone or in combination with prescription medications to help control their urinary symptoms.[15] Despite their

TABLE II. *Changes in the sexual function questionnaire and peak urinary flow rate in men treated with saw palmetto and placebo for 6 months*

	Initial	2 Months	4 Months	Final	Change
Sexual function questionnaire					
Saw palmetto	20.7 ± 11.3	21.4 ± 10.9	22.1 ± 10.5	20.6 ± 11.2	−0.1 ± 8.0
Placebo	21.7 ± 10.1	22.0 ± 9.6	21.2 ± 10.3	21.6 ± 10.7	−0.1 ± 6.8
					$P = 0.75$
Peak flow rate (mL/s)					
Saw palmetto	10.7 ± 4.7	10.8 ± 5.8	12.6 ± 5.7	11.7 ± 5.8	+1.0 ± 4.9
Placebo	12.9 ± 6.8	14.8 ± 7.1	14.5 ± 7.2	14.3 ± 17.5	+1.4 ± 4.9
					$P = 0.73$

Data presented as the mean ± SD.

popularity, significant skepticism remains regarding the true value of herbal remedies among many physicians.[12] In previously published placebo-controlled trials of saw palmetto, some investigators have noted significant improvement in urinary symptoms and/or urinary flow rates,[5,6,16] and others have reported no advantage with this agent.[7,8,17] However, in several of these studies, patients were treated for only 1 month, with varying methods used to assess the subjective improvement in symptoms. For these reasons, the validity of these trials and the effectiveness of saw palmetto remain unclear. In the largest meta-analysis concerning saw palmetto published to date, the investigators concluded that the use of this agent led to significantly improved voiding symptoms and increased urinary flow rates by 1.93 mL/s compared with placebo.[10] These findings may be questioned, however, because the mean duration of the 18 studies used for the analysis was only 9 weeks, and several of the trials did not include a placebo group or involved the use of saw palmetto in combination with other herbal agents.

In the present study, we have demonstrated a statistically significant improvement in urinary symptoms in men treated with saw palmetto compared with those receiving placebo. Despite this improvement, no appreciable increase in the urinary flow rates occurred. One of the reasons for this finding may have been our inclusion of patients with normal flow rates (greater than 15 mL/s), who most often have been excluded from participating in other studies concerning the treatment of LUTS. As a result, a greater proportion of our patients may not have had bladder outlet obstruction and therefore might not be expected to have a correlation between symptomatic improvement and changes in urinary flow. Overall, 8 (20%) of 41 men in the saw palmetto group and 11 (25%) of 44 in the placebo group had a baseline urinary flow rate greater than 15 mL/s. Our decision to omit the initial flow rates as an exclusion parameter in this study was based on several factors. First, the primary goal of treatment with saw palmetto is improvement in symptoms, not an increase in urinary flow rate. Second, we have previously demonstrated, in a nonrandomized, prospective study that was not placebo controlled, that saw palmetto leads to symptomatic improvement without changes in any urodynamic parameter.[18] Finally, since the mechanism by which saw palmetto might improve urinary symptoms is unclear, it seemed most reasonable to include men with LUTS irrespective of the likelihood that they had bladder outlet obstruction.

An important difficulty in the evaluation of the effectiveness of herbal products is the lack of standardization of these agents. The absence of regulatory control in the United States is likely to cause dramatic differences in purity and content among phytotherapeutic agents.[19] For this reason, the results that we noted in this study may have little bearing on the effects seen with alternative commercially available forms of saw palmetto. This has important implications both for men taking saw palmetto and for health care providers who are advising patients on the use of herbal products. In many cases, saw palmetto is marketed as an herbal blend along with other agents, such as pygeum, vitamins, and others.[9] In an interesting study using one such mix, the histologic analysis after treatment for 6 months demonstrated a significant increase in the percentage of atrophic prostate glands compared with men who received placebo.[9] Although these changes were attributed to saw palmetto, it is difficult to determine which component of the mix was truly responsible for these changes. Therefore, the likelihood that similar histologic effects will be seen with other saw palmetto products is unknown.

CONCLUSIONS

The use of saw palmetto for 6 months led to a statistically significant decrease in the IPSS compared with men treated with placebo. No improvement in sexual function occurred in either group. The peak urinary flow rate increased slightly in the

saw palmetto and placebo groups, but no difference in the degree of improvement was found between the groups.

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EDITORIAL COMMENT

Few topics in the field of LUTS and clinical benign prostatic hyperplasia (BPH) currently generate more interest than phytotherapeutic agents. Among the reasons for this interest are the significant amount of money spent by the taxpayers for over-the-counter drugs, the controversial outcomes of clinical trials, and the ongoing search on the part of patients and healthcare providers for treatments that are both effective, yet free of adverse events. The most popular among the phytotherapeutic agents are the saw palmetto extracts from the fruit of the American dwarf palm tree. More studies using saw palmetto extracts have been reported in the peer-reviewed literature and lay press, and there are more than 30 different compounds available in American health food stores for over-the-counter use. As of today, there is no universally accepted mechanism of action explaining why these compounds should have a beneficial impact on LUTS and men with clinical BPH. Wilt *et al.*,[1] published a systematic review finding that, overall, saw palmetto extracts improve selected urinary symptoms, as well as peak urinary flow rate compared with placebo. Boyle *et al.*[2] published a meta-analysis focusing on Permixon, a single saw palmetto extract, and also found a significant superior quality in terms of nocturia, as well as peak urinary flow rate, compared with placebo. However, all meta-analyses suffer from the data that are entered. In other words, the quality of the trials that are entered into the meta-analysis determines the quality of the output of the meta-analysis. As a matter of fact, there is still a tremendous paucity of well-executed, adequately powered, randomized, and placebo-controlled trials with appropriately chosen outcome parameters in the field of phytotherapeutic agents for the treatment of LUTS and BPH.

The report by Gerber *et al.* is certainly a welcome addition to our knowledge base. In 1998, Gerber *et al.*[3] reported on the outcomes of a nonrandomized trial in which 50 men with LUTS and clinical BPH were treated with 160 mg saw palmetto twice daily during 6 months. The IPSS score dropped from 19.5 to 12.5 points ($P < 0.001$), and the peak urinary flow rate, serum PSA, and urodynamic parameters (Abrams-Griffith number and detrusor pressure [P_{det}] at peak urinary flow rate) remained fundamentally unchanged.

The same authors now present a randomized trial in which 85 patients were given either saw palmetto or a placebo for 6 months. Similar to their previous trial, it should be noted that there were no significant changes regarding peak urinary flow rate (1 ± 1.0 and ± 1.4 for saw palmetto and placebo, respectively), changes in sexual function questionnaire (-0.1 and -0.1, respectively), or the quality-of-life score (-0.7 and -0.3 for saw palmetto and placebo, respectively). However, they did find a significant difference in the reduction of the IPSS score (-4.4 versus -2.2 for saw palmetto and placebo, respectively; $P = 0.038$). Does this mean that this particular saw palmetto extract is now proved superior to placebo, equivalent to perhaps alpha-adrenergic receptor blockers? Should it be used as a first-line therapy for men with LUTS and BPH? The careful reader will note that the study was designed to demonstrate a 3.0 difference in symptom score change between the two groups with a power of 80% and an alpha of 0.05. This led to the sample size calculation of 45 men in each group. However, the study failed to yield a 3-point difference in change—rather, the differences were only 2 points between the active versus the placebo group. Nonetheless, by statistical comparison, a significant difference was obtained ($P = 0.038$). Those familiar with the statistics will note that statistical significance was barely achieved, and even a minor change in one of the two treatment groups might lead to a P value greater than 0.05, the predefined threshold of statistical significance. The reader will also note that the two groups were not perfectly matched in terms of their IPSS score. The saw palmetto group started with the highest score at 16.7 compared with the placebo group at 15.8. This difference did not reach statistical significance, but it indicates that the groups were not perfectly matched at baseline. Is this important? The placebo response