

Long-Term Efficacy of *Serenoa repens* Treatment in Patients with Mild and Moderate Symptomatic Benign Prostatic Hyperplasia

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Key Words

Benign prostatic hyperplasia · Lower urinary tract symptoms · Phytotherapy · *Serenoa repens*

Abstract

Introduction: The study aimed to evaluate the long-term efficacy of treatment with extract of *Serenoa repens* (Prostamol Uno) in patients with lower urinary tract symptoms (LUTS) induced by benign prostatic hyperplasia (BPH). **Patients and Methods:** We studied 120 patients with mild or moderate LUTS induced by BPH, maximal urinary flow (Q_{max}) <15 ml with a voided volume \geq 150 ml, prostate-specific antigen <4 ng/ml, and residual urinary volume <150 ml, treated daily for 24 months with one capsule of 320 mg ethanolic extract of *Serenoa repens*. **Results:** Statistically significant improvements in the International Prostate Symptom Score (5.5 points), quality of life (QoL; 1.8 points), Q_{max} (5.6 ml/s), International Index of Erectile Function (IIEF; 6.4 points) and reduction in residual urinary volume were observed during the study period. The mean prostate volume at 24 months was 36 ml, compared to 39.8 ml at baseline. **Conclusions:** Long-term treatment with 320 mg ethanolic extract of *Serenoa repens*

proved to be efficient in reducing urinary obstruction, improving symptomatology and QoL of BPH patients. It also had a positive effect on sexual function, demonstrated by the statistically significant increase in the IIEF.

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Introduction

It is estimated that by the age of 60 years, nearly 60% of males suffer some degree of clinical benign prostatic hyperplasia (BPH), although its real prevalence is difficult to assess [1]. Nowadays, an increasing proportion of patients with lower urinary tract symptoms (LUTS) associated with BPH benefit from medical treatments. Phytotherapeutic agents, α_1 -blockers and 5α -reductase inhibitors may offer a viable alternative to surgery in a selected subpopulation of cases.

Interest in phytotherapeutic agents is growing in both Europe and North America, especially as a consequence of patients' dissatisfaction due to the adverse effects of other medical alternatives [2, 3]. The most frequently prescribed and studied such agent is *Serenoa repens* extract,

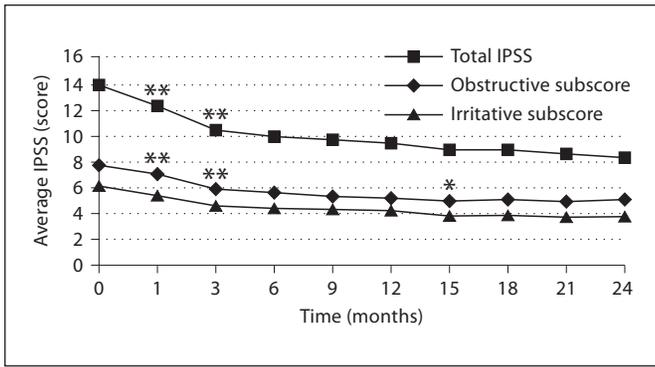


Fig. 1. Evolution of total IPSS, as well as the irritative and obstructive subsets of IPSS, during the study period (* $p \leq 0.05$; ** $p \leq 0.005$).

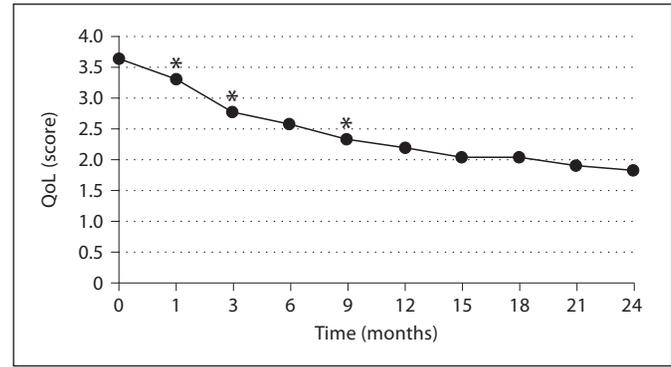


Fig. 2. Evolution of QoL score during the study period (* $p \leq 0.005$).

derived from the berry of the dwarf palm tree. However, the majority of studies were limited by short-term follow-up, reduced number of patients or lack of standardized instruments to evaluate efficacy [4–7]. The aim of our study was to evaluate the long-term efficacy of treatment with extract of *Serenoa repens* (Prostamol Uno) in patients with LUTS induced by BPH.

Patients and Methods

We studied 120 patients with LUTS induced by BPH. The study was approved by the ethics committee of all the participating hospitals. The inclusion criteria were mild or moderate LUTS (IPSS <20) that had been present for at least 6 months, maximal urinary flow (Q_{max}) <15 ml with a voided volume ≥ 150 ml, prostate-specific antigen (PSA) <4 ng/ml and residual urinary volume <150 ml.

Patients were treated daily for 24 months with one capsule of 320 mg ethanolic extract of *Serenoa repens* (Prostamol Uno) per day. International Prostate Symptom Score (IPSS), quality of life (QoL) score and Q_{max} were assessed at each visit (at inclusion, 1, 3, 6, 9, 12, 15, 18, 21 and 24 months). Prostate volume, PSA and International Index of Erectile Function (IIEF) were evaluated at inclusion, 6, 12, 18 and 24 months.

The evolution of IPSS and its two subsets – irritative score (increased frequency, urgency, nocturia) and obstructive score (incomplete emptying, intermittency, weak stream, hesitancy) – were evaluated at all 10 visits. A similar analysis was performed for the QoL score and Q_{max} . The evolution of prostate volume, PSA and IIEF score was also evaluated.

Repeated contrasts were used for statistical analysis (the level of studied parameters at visit 2 compared to the level at visit 1, the level at visit 3 compared to the level at visit 2, and so on). A hierarchical linear model for repeated measures has been chosen as the method for analysis of the point in time when a statistically significant effect is recorded in each of the tracked variables.

Mauchly's test was used to indicate if the sphericity assumption was met. The adapted Greenhouse-Geisser test was applied for cases where nonsphericity was assumed in order to indicate if the impact of time was significant. Wilks' multivariate test was used to evaluate the significance of the effect in relation to the passage of time.

Results

The mean IPSS score improved during the study period by 5.5 points (from 13.8 to 8.3), or by 40%. Repeated contrasts and pairwise comparisons in a multivariate setting statistical analysis demonstrated that the significant improvements occurred during the first 3 months when IPSS decreased by 3.5 points (25.4% of the initial value) (fig. 1, table 1). Patients younger than 60 showed particularly strong symptom improvement, with a total IPSS reduction of 47.1%, compared with those in their 60s and 70s (36.7 and 40.2%, respectively) (data not shown).

At baseline, 6% of patients presented with mild symptoms (IPSS between 0 and 7), while the rest had moderate symptoms. By the end of the study, this proportion increased to 45% (improvement stable for 18 months). Significant changes were also observed in both subsets of IPSS. After 24 months of *Serenoa repens* treatment, a decrease of 2.5 points was encountered with the irritative score (significant at 95% confidence level). Statistical analysis indicated that the significant improvement for this parameter was observed during the first 3 months of treatment and also after 18 months (fig. 1). A similar evolution was observed regarding the obstructive subset, which improved by 2.6 points during the 24-month period.

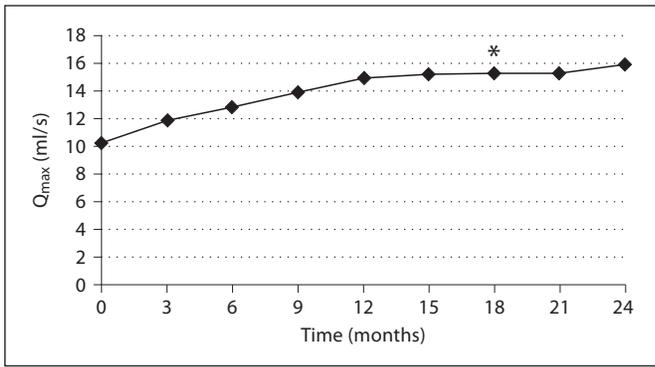


Fig. 3. Evolution of Q_{\max} during the study period (* $p \leq 0.005$).

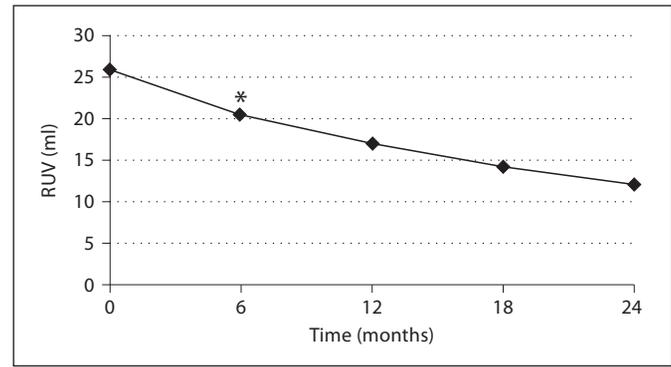


Fig. 4. Decrease in residual urinary volume (RUV) during the study period (* $p \leq 0.005$).

Table 1. Mean values of measured parameters from day 0 (baseline values) to month 24 (endpoint)

Parameter	Baseline values	1 month	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months
IPSS, score	13.8	12.8 ^a	10.3 ^a	9.8	9.5	9.3	8.8	8.8	8.5	8.3
Irritative subscore	6.2	5.3 ^a	4.5 ^a	4.3	4.3	4.2	3.8 ^c	3.8	3.6	3.7
Obstructive subscore	7.6	6.9	5.8	5.5	5.2	5.1	4.9	5.0	4.9	5.0
QoL, score	3.6	3.3 ^a	2.8 ^a	2.6	2.3 ^a	2.2	2.0	2.0	1.9	1.8
Q_{\max} , ml/s	10.3	–	11.9	12.9	13.9	15.0	15.3	15.3 ^d	15.3	15.9
RUV, ml	25.9	–	–	20.4 ^a	–	17.0	–	14.2	–	12.1
PV, ml	39.8	–	–	37.4	–	37.1	–	36.8	–	36.1
IIEF, score	44.4	–	–	48.3 ^a	–	50.3 ^b	–	–	–	50.8
PSA, ng/ml	1.8	–	–	–	–	1.9	–	–	–	2.0

RUV = Residual urinary volume; PV = prostate volume. ^a $p = 0.000$; ^b $p = 0.002$; ^c $p = 0.019$; ^d $p = 0.017$.

The QoL score decreased by 1.8 points during the study period, with the improvement being statistically significant for the first 9 months (fig. 2, table 1). Due to this evolution, the proportion of patients satisfied with their current urinary status increased over 24 months from 14 to 88%, while the proportion of unsatisfied patients decreased from 50 to 2%.

The mean Q_{\max} improved from 10.3 ml/s at visit 1 to 15.9 ml/s 24 months later at visit 10. Statistical analysis demonstrated significant, but not linear, improvement during the first 18 months of treatment (fig. 3, table 1).

The percentage of patients without residual urinary volume increased from 21% at baseline to 43% after 24 months. Residual urinary volume decreased in the rest of the patients, with only 6% of them having more than

40 ml of urine in the bladder at the end of micturition. The results indicate that a significant effect on this parameter score was observed during the first 6 months (fig. 4, table 1).

The mean prostate volume at 24 months was 36 ml, compared to 39.8 ml at baseline. No significant effect on PSA was encountered during the treatment (table 1).

Regarding sexual function, the mean IIEF score improved significantly in the first 12 months (44.4 vs. 50.3). Only a reduced difference occurred during the second year (50.3 vs. 50.8) (fig. 5).

The drop-out rate was 0% during the first 12 months and 19.2% during the second year. Throughout the 24-month treatment period, no patient experienced treatment-related adverse events.

Table 2. Mean changes in efficacy parameters as reported from other studies

	Extraction solution	Treatment duration, months	Number of patients	IPSS change		QoL change		RUV change		Q _{max} change	
				points	%	points	%	ml	%	ml/s	%
Carraro et al. [3], 1996	hexane	6	553	-5.8	-36.9	-1.38	-38	+7.9	+15.2	+2.7	+25.5
Bauer et al. [6], 1999	CO ₂	6	47	-3	-31.3	-0.6	-22.2	-10	-33	+1.8	+15.1
Marks et al. [5], 2000	d.n.s.	6	21	-5.8	-31.5	n.t.	-	+8	+8.8	+2.6	+25.3
Gerber et al. [4], 2001	d.n.s.	6	41	-4.4	-26.3	-0.7	-21.2	n.t.	-	n.t.	-
Giannakopoulos et al. [7], 2002	hexane	6	50	-7.2	-35.4	-0.5	-15.2	-25.2	-38.9	+2.8	+30.1
Pytel et al. [12], 2002	hexane	24	154	-5.3	-41.4	-1.3	-40	n.t.	-	+1.2	+10.6
Debruyne et al [2], 2004	hexane	12	267	-4.5	-29.4	n.t.	-	n.t.	-	+1.8	+16.5
Breza et al. [16], 2005	ethanol ¹	12	596	-5.9	-36	-1.7	-53.6	n.t.	-	+2.3	+19.2
Alyaev et al. [17], 2007	ethanol ¹	12	50	-3	-26.3	-1.8	-42.9	n.t.	-	+1.7	+13.6
Hizli and Uygur [24], 2007	hexane	6	20	-6.1	-33.8	-2.6	-61.9	n.t.	-	+3.2	+34

RUC = Residual urinary volume; n.t. = not tested; d.n.s = data not shown.

¹ Studies on ethanolic extract (Prostamol Uno).

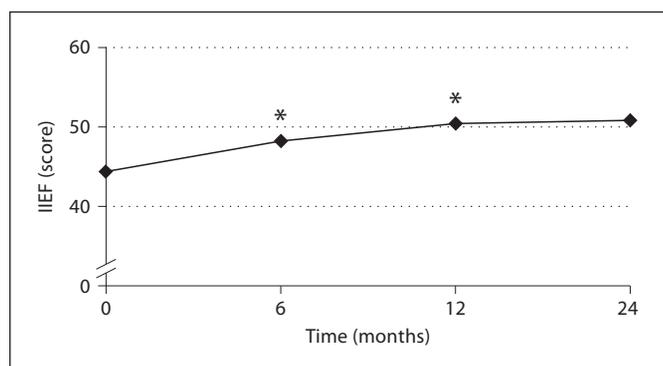


Fig. 5. Evolution of IIEF score during the study period (* $p \leq 0.005$).

Discussion

Worldwide, a significant number of patients are using *Serenoa repens* extracts to control BPH-related LUTS. However, many physicians remain skeptical regarding its mechanism of action or true therapeutic value. In this context, a number of trials evaluating the influence of *Serenoa repens* extracts on LUTS were conducted in recent decades and demonstrated significant improvements of symptoms or urinary flow (table 2). However, the reasons for skepticism persisting are inconsistent outcomes from existing placebo-controlled trials and an insufficient number of long-term treatment studies [8]. For

instance, some of the studies cover only 1- to 6-month therapy periods [9–11].

With the aim of contributing to the growing body of evidence on *Serenoa repens* efficacy and adding information on the results of its long-term use, this observational, multicenter clinical trial aimed to determine the effect of daily intake of 320 mg *Serenoa repens* extract (Prostamol Uno) over 24 months.

In line with several other reports (table 2), we show statistically significant improvement in total IPSS during the first 6 months of therapy, which was sustained for the duration of the study (fig. 1). The effects measured after 6 and 12 months were comparable to those reported by other authors for the same periods of treatment [2, 4]. Similarly, the extent of overall improvement was comparable to that shown by Pytel et al. [12] in another 2-year study. BPH usually combines obstructive and irritative symptoms. Like Debruyne et al. [2], we observed significant decreases in both subscores of IPSS (fig. 1, table 1).

The combined action of *Serenoa repens* extract on both these categories thus offers an advantage over α -blocking therapy, for example. In this context, the symptom category shifted from moderate at baseline to mild at the end of the study in a considerable number of patients (39%). In our study, the quality of life QoL score decreased statistically significantly by 1.8 points during 24 months of treatment. The Gerber trial reported an improvement in the QoL score of only 0.7 points in 6 months, which was not significant [13]. A possible explanation is that, in our study, statistical analysis showed a significant

improvement after the first 9 months, thus demonstrating the importance of long-term treatment trials.

While improvement in symptomatology seems to be more consistent throughout the existing studies, the effects on relevant urodynamic parameters tend to vary more (table 2).

We show that symptomatology as well as urodynamic parameters improved over 24 months. Debruyne et al. [2] reported a Q_{\max} improvement of 1.7 ml/s at 12 months, which proved to be nonsignificant. In our study, a significant ($p = 0.017$; but not linear) improvement took place 6 months later, after the first 18 months of treatment, thus demonstrating the importance of long-term treatment trials.

Some authors have questioned comparability in the efficacy of different *Serenoa repens* preparations depending on the different substrates used for their extraction [14, 15]. Here we contribute current knowledge by showing high efficacy of an ethanolic extract of *Serenoa repens* (Prostamol Uno), recently also reported by other authors [16, 17] (table 2).

Given the long-term nature of therapy, safety aspects of the drug assume the greatest importance. No adverse events were shown in our study. Notably, several recent reports on safety characteristics of long-term use of *Serenoa repens* extensively describe its favorable safety profile, which is comparable to that of placebo [18–20]. Regarding sexual function, the significant improvement of the IIEF score during the first year demonstrated the advantage of phytotherapeutic agents over the other medical treatment alternatives for BPH-related LUTS. If we take into consideration that the retrograde ejaculation and reduced ejaculate volume related to α -blockers, or erectile dysfunction and decreased libido related to 5 α -reductase inhibitors, are frequently associated with medically treated BPH patients' dissatisfaction, *Serenoa repens* extract becomes a viable alternative in selected cases [2, 3, 21, 22].

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However, results from existing placebo-controlled studies are not consistent in showing a significant superiority of *Serenoa repens* therapy over placebo [5, 6, 23]. The issue was recently raised in a meta-analysis of existing data on *Serenoa repens* therapy [8], although the analysis included/considered studies of differing duration, as well as studies on mixed herbal preparations consisting not only of *Serenoa repens* extract. However, not underestimating the importance of more results from placebo-controlled studies, and giving priority to QoL in patients with mild and moderate BPH, the results of our and similar studies clearly suggest beneficial effects of *Serenoa repens* offering very good efficacy combined with excellent safety features.

Nevertheless, more randomized, placebo-controlled, long-term trials are needed in order to eliminate all skepticism related to the use of phytotherapeutic agents in BPH with LUTS.

Conclusions

Twenty-four-month treatment with 320 mg ethanolic extract of *Serenoa repens* (Prostamol Uno) improved in a statistically significant manner IPSS, QoL and Q_{\max} . It also reduced the proportion of patients with residual urinary volume. The improvement of IPSS was associated with a similar evolution of both its subsets – irritative and obstructive scores.

In the 24-month study period, changes in the value of some of the parameters (QoL, Q_{\max}) reached a statistical significance not encountered in some other short-term studies.

The phytotherapeutic agent improved sexual function, with a significant increase in the IIEF score being encountered during the first year of treatment.

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