Multicentre study on the efficacy and tolerability of an extract of Serenoa repens in patients with chronic benign prostate conditions associated with inflammation

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ORIGINAL PAPER

Multicentre study on the efficacy and tolerability of an extract of Serenoa repens in patients with chronic benign prostate conditions associated with inflammation

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Summary

Introduction: *Chronic benign prostate diseases are very common and certainly feature significantly in urological practice.The treatment of chronic benign prostate diseases is a common problem in clinical practice: few studies have been conducted in routine clinical practice to evaluate the efficacy of the treatments for this clinical condition. The objective of this study was to evaluate the efficacy of an extract of Serenoa repens (Permixon®) in the treatment of lower urinary tract symptoms (LUTS) in patients with chronic benign prostate diseases with associated inflammation, also taking into consideration the influence of treatment on sexual function and, therefore, on patients' quality of life.*

Materials and Methods: *All the 591 eligible subjects were evaluated on entering the study; after a screening visit, including medical history, physical examination, physical examination and digital rectal examination (DRE) and laboratory tests, the patients underwent uroflowmetry. The subjects under investigation were also asked to complete the IPSS, NIH-CPSI and IIEF-5 questionnaires, for the purpose of evaluating urinary symptoms and erectile function in relation to sexual activity in the previous 6 months.*

Results: *The analysis of the uroflowmetry results showed that treatment with extract of Serenoa repens distinctly improves bladder voiding and lower urinary tract symptoms, as highlighted also by the improvement in the scores for the IPSS and NIH-CPSI questionnaires which serve as a basis for evaluating the urinary symptoms of patients with prostatic hyperplasia and chronic prostatitis respectively. The results also suggest that using an extract of Serenoa repens for 6 months in patients with chronic benign prostate diseases gives rise to an improvement in erectile function, as demonstrated by the increase in the scores for the IIEF-5 questionnaire after 6 months of treatment.*

Conclusions: *The results of this study demonstrate how treatment for 6 months with an extract of Serenoa repens in routine clinical practice gives rise to a statistically significant improvement in Qmax values and in the IPSS, NHI-CPSI and IIEF-5 questionnaire scores, resulting not only in an improvement in urinary symptoms but also in an overall improvement in patients' quality of life.*

KEY WORDS: *Benign prostatic hyperplasia; Inflammation; Plant extract; Serenoa repens; Lower urinary tract symptoms.*

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Introduction

Chronic benign prostate diseases are very common and certainly feature significantly in urological practice. Prostatitis is a relatively common and widespread condition which affects adults most frequently. It has been estimated that, out of 1,000 male subjects seen for an annual check-up, 76 have genito-urinary conditions, and prostatitis accounts for 25% of these cases. Furthermore, on the basis of recent studies, it would seem that almost 50% of males have at least one episode of prostate inflammation of varying severity in the course of their lives. Benign prostatic hyperplasia (BPH) begins with microscopically small stromal nodules from the age of 35, with an incidence which increases with age throughout the male population. This suggests that almost all men can develop BPH if they live long enough. More than 50% of subjects aged between 60 and 69 have clinically significant BPH. Of these, a significant percentage is at risk of developing acute urinary retention in the absence of appropriate medical and/or surgical treatment.

The treatment of chronic benign prostate diseases is a common problem in clinical practice: few studies have been conducted under routine clinical conditions to evaluate the efficacy of the treatments for this clinical condition.

An extract of *Serenoa repens* (*Permixon®*) has been available for some years for the treatment of benign prostatic diseases. This product is the n-hexane lipidosterolic extract of a dwarf palm known as *Serenoa repens* and represents a complex mixture of various compounds. A number of pharmacodynamic effects have been identified using this product, and multiple mechanisms of action have been suggested. These include in vitro inhibition of type 1 and type 2 isoenzymes of 5α-reductase and interference with the binding of dihydrotestosterone to androgen receptors in prostate cells.

The objective of this study was to evaluate the efficacy of the extract of *Serenoa repens* in the treatment of lower urinary tract symptoms (LUTS) in patients with chronic benign prostate diseases with associated inflammation, also taking into consideration the influence of treatment on sexual function and, therefore, on the patients' quality of life.

Material and methods

Patients

Patients with chronic benign prostate diseases with associated inflammation referred to UROP urology centres in 2009 were enrolled.

Study design

This was an open-label, multicentre study, the primary endpoint of which was to evaluate the efficacy and safety of the extract of *Serenoa repens* in the treatment of lower urinary tract symptoms in patients with chronic benign prostate diseases with associated inflammation. The secondary endpoints comprised:

1) evaluation of the influence of treatment on quality of life in relation to sexual function;
2) evaluation of the change in total PSA values from the start of treatment to the end of the study after six months. The inclusion and exclusion criteria are listed in Table 1.

Table 1.

Inclusion and exclusion criteria.

Inclusion criteria

- Male subjects aged between 35 and 65
- Clinical diagnosis of BPH, chronic prostatitis without infection
- Non-acute irritative dysuric symptoms
- IPSS ≥ 13 at baseline
- Chronic painful prostatitis symptoms index ≥ 2 at baseline
- Q_{max} < 12 ml/sec at baseline
- PVR < 150 ml at baseline
- DRE not suggestive of prostate cancer
- Total PSA ≤ 4 at baseline*

**If PSA > 4, a prostate biopsy had to be performed to rule out the presence of cancer in situ. In the event of a positive result, the patient had to be withdrawn from the study.*

Exclusion criteria

- Previous pelvic surgery
- Urological conditions already diagnosed: neurogenic bladder, bladder outlet obstruction, urethral stricture, bladder tumours, prostate cancer, bladder stones, diabetes mellitus, bladder diverticula, psychiatric disorders, UTI, treatment with: diuretics, androgen antagonists, antidepressants
- Patients under treatment with: finasteride, mepartricin, dutasteride, *Pigeum Africanum*, other adjuvants indicated for BPH may be enrolled in the study after a wash-out period of at least 4 weeks
- Patients diagnosed with irritable bowel disease
- Patients with documented hypersensitivity to one or more ingredients of Permixon®

All the eligible subjects were evaluated on entering the study: after a screening visit, including medical history, physical examination, physical examination and DRE, laboratory tests (total PSA, urinalysis and urine culture, semen analysis with screening for *Chlamydia* and *Mycoplasma*), the patients underwent uroflowmetry.

The subjects under investigation were also asked to complete three questionnaires:

1) the IPSS (*International Prostatic Symptoms Score*) questionnaire, which permits an objective evaluation of the urinary symptoms of the patient with prostatic hyperplasia;
2) the NIH-CPSI (*National Institute of Health - Chronic Prostatitis Symptom Index*) questionnaire for the evaluation of symptoms, divided into three different areas: pain, urinary symptoms and impact on quality of life;
3) the IIEF-5 (*International Index of Erectile Function - 5*) questionnaire, created for the purpose of providing a sensitive and specific questionnaire for evaluating erectile function in relation to sexual activity in the previous six months.

The eligible patients took an extract of *Serenoa repens* 320 mg, one capsule per day, for 6 consecutive months. The subjects were evaluated at baseline [and] after 6

Table 2.

Initial and final values.

Variable	T_0	T_1	Difference T_1-T_0	p value
PSA (ng/ml)	1.9 (0.79)	1.4 (0.71)	-0.6 (0.71)	< 0.0001
Q_{max}	10.7 (4.00)	13.7 (2.37)	2.9 (4.12)	< 0.0001
IPSS	17.8 (4.18)	12.2 (5.28)	-5.6 (3.76)	< 0.0001
NHI-CPSI	13.3 (6.53)	8.2 (5.72)	-5.1 (5.80)	< 0.0001
IIEF	17.6 (4.01)	18.1 (4.65)	0.5 (4.66)	0.0055

Statistically significant differences were observed for all the variables considered.

months. At the final visit, information relating to the total PSA and Q_{max} values was collected again, and the IPSS, NHI-CPSI and IIEF-5 questionnaires were re-administered.

Statistical analysis

For the subjects entered in the study, the mean values, medians, standard deviations and ranges were calculated for the initial and final visit.

The statistical significance of the difference between the initial and final values for the variables under consideration in the subjects who completed the study was determined using a Student's t-test.

RESULTS

The number of patients enrolled in the study was 591. Table 2 shows the initial and final values for the subjects who completed the study, along with the relevant standard deviations and the Student's t-test value on the differences. The patients treated with the extract of *Serenoa repens* experienced a significant reduction in their serum PSA levels compared to baseline, showing a trend which could be maintained, probably even in the long-term. The analysis of the uroflowmetry results showed that treatment with the extract of *Serenoa repens* distinctly improves bladder emptying and lower urinary tract symptoms (Figure 1); an improvement was also observed in the scores for the IPSS and NIH-CPSI questionnaires which serve as a basis for evaluating the urinary symptoms of patients with prostatic hyperplasia and chronic prostatitis respectively (Figures 2, 3).

The results also suggest that using the extract of *Serenoa repens* for 6 months in patients with chronic benign prostate diseases gives rise to an improvement in erectile function, as demonstrated by the increase in the scores for the IIEF-5 questionnaire after 6 months of treatment (Figure 4).

Figure 1.

Uroflowmetry (Q_{max}) at T_0 and after 6 months of treatment with the extract of Serenoa repens.

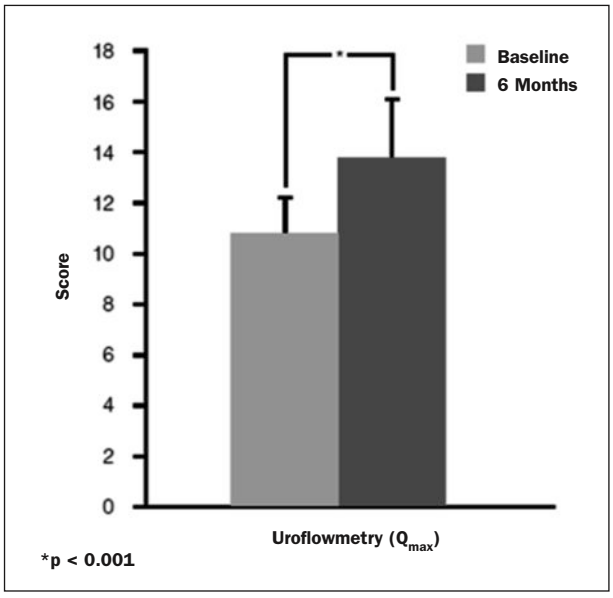


Figure 2.

IPSS score at T_0 and after 6 months of treatment with the extract of Serenoa repens.

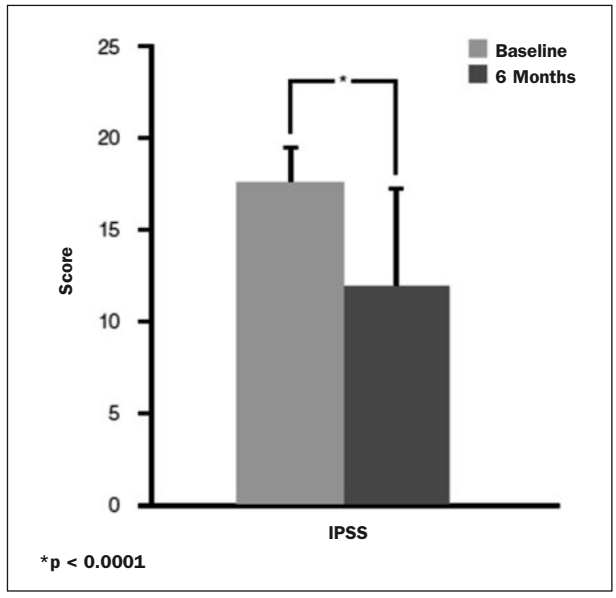


Figure 3.

NIH-CPSI scores at T_0 and after six months of treatment with the extract of Serenoa repens.

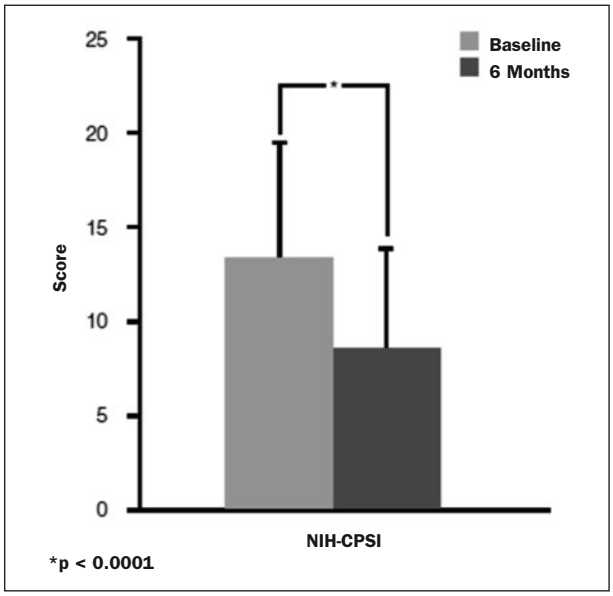
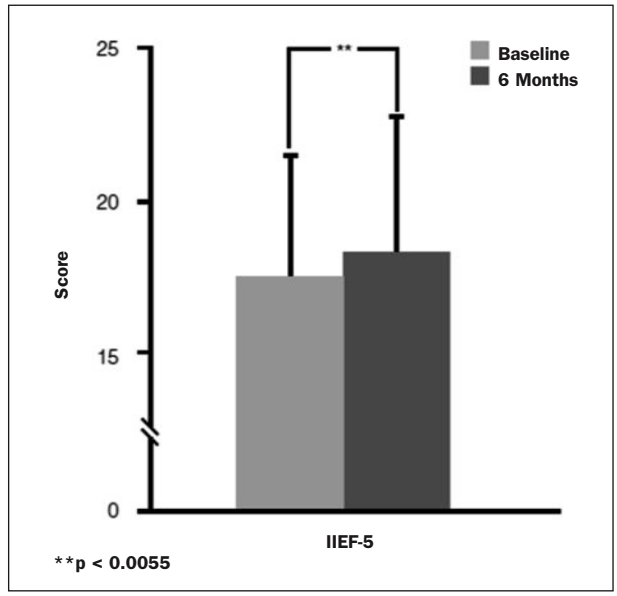


Figure 4.

IIEF-5 scores at T_0 and after six months of treatment with the extract of Serenoa repens.



Discussion

The results of this study demonstrate how treatment for 6 months with a medicinal product based on *Serenoa repens* in routine clinical practice improves Q_{max} values and the scores for the IPSS, NHI-CPSI and IIEF-5 questionnaires, also bringing about a reduction in the total PSA value. The study evaluated the effect of the extract of *Serenoa repens* in respect of urinary and sexual function aspects and finally on the basis of the PSA values.

The strengths of the study include the very large sample size and the fact that the study was conducted as part of routine clinical practice in primary and secondary care centres nationally. The experience of treatment with this medicinal product is wide-ranging (1, 2).

The data in the literature on the efficacy of this medicinal product are numerous (3-5) and the efficacy of the product has been demonstrated in various studies conducted in large populations of patients, including in comparison with other widely used medicinal products such as 5α-reductase inhibitors (finasteride) or alpha blockers (tamsulosin).

In one randomized double-blind study (3) conducted in 1,098 patients with moderate BPH treated for 6 months with the extract of *Serenoa repens* 320 mg (160 mg twice daily) or finasteride 5 mg, for example, both treatments improved the symptoms of BPH in approximately two thirds of the patients. Unlike finasteride, however, the extract of *Serenoa repens* exhibited only a slight effect on the "androgen-dependent" parameters. This is in keeping with what was observed in our study on the basis of the IIEF-5 questionnaire. In this study, in fact, although the improvements in the IPSS score (-37% and -39% for the extract of *Serenoa repens* and finasteride respectively), quality of life (+38% and +41%) and the maximum urinary flow rate (+25% and +30%) were largely similar, the extract of *Serenoa repens* was judged to be superior to finasteride in terms of its effect on sexual function, and it prompted fewer complaints concerning reduced libido and erectile dysfunction. The therapeutic equivalence between the extract of *Serenoa repens* 320 mg/day and pharmacological treatment was also confirmed in the PERMAL study (4), a large-scale European study conducted in 704 patients with BPH (IPSS ≥ 10) to evaluate the effects of the extract and tamsulosin 0.4 mg/day on various clinical efficacy parameters (IPSS, QoL, Q_{max}) and on changes in prostate volume and serum PSA levels. In particular, after 12 months of treatment, the same reduction in the IPSS score (-4.4) was observed in both groups, with no differences in terms of irritative and obstructive symptoms, along with an almost identical improvement in the Q_{max} (1.8 ml/s for the extract of *Serenoa repens* and 1.9 ml/s for tamsulosin): both treatments also maintained stable PSA levels with a slightly better reduction in prostate volume under extract of *Serenoa repens* and a greater incidence of retrograde ejaculation in the tamsulosin group. One subsequent study conducted by the same authors (5) also demonstrated how treatment with extract of *Serenoa repens* can actually give rise to a greater improvement than that achievable with tamsulosin when patients with particularly severe LUTS (IPSS > 19) are taken into consideration. These observations confirmed that the efficacy of extract of *Serenoa repens* can be attributed to its triple mechanism of action, or to its anti-androgen (via inhibition of type 1 and 2 5α-reductase), anti-proliferative (via shrinkage of prostate epithelial cells and reduction of tissue dihydrotestosterone levels) and anti-inflammatory (via inhibition of arachidonic acid metabolites) effects. As such, these may constitute an advantage over alpha blockers in the treatment of BPH with severe symptoms when

obstructive and irritative symptoms are involved at the same time. The use of the extract of *Serenoa repens* has been the subject of numerous pharmacological and clinical investigations in recent years: its equivalent and in some cases superior efficacy in BPH compared with 5α-reductase inhibitors or alpha blockers is closely correlated with the particular product formulation. As already observed in a review published in the *British Journal of Urology* (6), not all *Serenoa repens* extracts have the same composition and consistency, and they cannot therefore be treated as equivalent in terms of their relative therapeutic efficacy. The lack of standardization between the various extracts can actually lead to dosage variations ranging between -97% and +140%, with major implications from the pharmacodynamic and pharmacokinetic viewpoints. In particular, the presence of high levels of unbound fatty acids in the extract of *Serenoa repens* is associated with a greater degree of inhibition of 5α-reductase activity and significant superiority in terms of its effects on symptoms, on urodynamic variables and on quality of life compared with what is observed with other extracts. Another important fact to come out of this study is the effect of *Serenoa repens* in reducing PSA values, which is an important factor in the management of subjects with BPH, particularly with regard to the decision to perform a prostate biopsy. Reducing this value therefore has major clinical implications.

In one randomized, controlled clinical study conducted on *Serenoa repens* versus placebo, the PSA value after one year of treatment was more or less unchanged in the subjects assigned to *Serenoa repens* (-0.005 ng/dl). The baseline value for these subjects was 1-7 (SD 1.4) ng/dl (7), however. In the present study, the reduction was greater in subjects with higher PSA values. In fact, the reduction observed in subjects with a PSA of < 1.7 ng/dl was 0.09 ng/dl. It should be stressed that all the subjects included in the present study had a PSA value of < 4 on inclusion. This reduction in the PSA value can probably be attributed to an anti-inflammatory effect of *Serenoa repens* (8).

Conclusions

In conclusion, the results of this study demonstrate how treatment for 6 months with the extract of *Serenoa repens* under routine clinical conditions gives rise to a statistically significant improvement in Q_{max} values and in the IPSS, NHI-CPSI and IIEF-5 questionnaire scores, resulting not only in an improvement in urinary symptoms but also in an overall improvement in the patient's quality of life.

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