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ORIGINAL PAPER

A prospective study of the efficacy of Serenoa repens, Tamsulosin, and Serenoa repens plus Tamsulosin treatment for patients with benign prostate hyperplasia

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Abstract
Introduction Increasing attention has been focused on the use of phytotherapeutic agents to alleviate the symptoms of benign prostatic hyperplasia (BPH) in recent times. The best described and studied phytotherapeutic agent is Serenoa repens (SR).
Materials and methods This prospective study was designed to have 3 arms including SR 320 mg per day ($N = 20$), Tamsulosin (TAM) 0.4 mg per day ($N = 20$) and SR + TAM ($N = 20$) to reveal the superiority or equivalence between these treatment regimens in BPH.
Results The groups were not statistically different with regard to increase in maximal urinary flow rate (Q_{max}) and decrease in International Prostate Symptom Score (I-PSS) ($P > 0.05$). No adverse effect was detected in SR therapy group.
Conclusion Treatment of BPH by both SR and TAM seems to be effective alone. None of them had superiority to another and additionally, combined therapy (SR + TAM) does not provide extra benefits. Furthermore SR is a well-tolerated agent that can be used alternatively in the treatment of LUTS due to BPH.

Keywords Serenoa repens · BPH · Tamsulosin · Treatment

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Introduction

Lower urinary tract symptoms (LUTS) are frequently associated with benign prostatic hyperplasia (BPH), a non-malignant enlargement of the prostate. Since medical therapy, including 5-alpha-reductase inhibitors, alpha-blockers, and phytotherapeutic agents offer an attractive alternative to surgery, the number of transurethral resections of the prostate has declined in recent years [1–6]. However, the tolerability of these agents varies. Some alpha-1 blockers are associated with postural hypotension and 5-alpha-reductase inhibitors can lead to sexual dysfunction [7]. Therefore, increasing attention has been focused on the use of phytotherapeutic agents to alleviate the symptoms of BPH.

Recent meta-analysis of all published phytotherapy trials revealed it is more efficacious than placebo [8–11] and has equivalent efficacy to Finasteride and Tamsulosin in the treatment of BPH [12, 13]. The most described and studied phytotherapeutic agent for the medical treatment

of symptomatic BPH is the lipido-sterolic extract of Serenoa repens, Permixon® which in Turkey, is known as Prostagood® (Dr. Willmar Schwabe GmbH & Co. Arzneimittel, Karlsruhe, Germany).

This prospective study was designed to evaluate and compare the efficacy and safety of Serenoa repens (SR), Tamsulosin (TAM) and SR plus TAM (SR + TAM) in men with LUTS secondary to BPH during a 6-month period.

Materials and methods

Between May 2005 and November 2005, 60 men between the ages of 43 years and 73 years, with symptomatic BPH were included in the study. This *open-label* prospective 6-month study included 3 protocols: SR, 320 mg/day ($N = 20$); TAM, 0.4 mg/day ($N = 20$); SR + TAM ($N = 20$) 320 mg + 0.4 mg to compare the efficacy of each of these treatment regimens. No placebo protocol was included in the study. Inclusion criteria included an International Prostate Symptom Score (I-PSS) ≥ 10, a maximal urinary flow rate (Q_{max}) of 5–15 ml/s with a postvoiding residual volume (PVR) ≤ 150 ml, a prostate volume ≥25 cc, and a serum prostate specific antigen (PSA) ≤4 ng/ml.

Patients were excluded if they had a history of bladder disease likely to affect micturition, urethral stenosis, prostate cancer, pelvic radiotherapy, repeated infection of the urinary tract or chronic bacterial prostatitis, or any other disease that causes urinary problems. Patients with clinically significant cardiovascular disease, hematuria, insulin dependent diabetes mellitus, a history of severe hepatic failure or abnormal liver function tests, and those receiving concomitant medication likely to interfere with the study medication were excluded from the study. Other exclusion criteria included a known hypersensitivity to one of the study drugs or having participated in another clinical trial in the previous 3 months.

Assessment visits were performed head to head and were scheduled at randomization (Day 0), months 2, 4, 6. At each visit, the I-PSS- and LUTS-related quality of life scores (QL) and uroflowmetry test results were recorded. Values at day 0 were considered as baseline. In addition to these, patients underwent both transrectal ultrasonography (TRUS) to measure prostate volume and blood sampling for serum PSA assay. Adverse effects of study protocol drugs were also recorded.

Kruskal–Wallis H test was used for the comparison of the groups and Wilcoxon signed-rank test was used for the analysis of the baseline and 6th month treatment parameters. A P value <0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS v10.0) software was used for statistical analyses.

Results

A total of 60 men with a mean age of 58.6 ± 6.7 years (range: 43–73 years) were evaluated. The demographic and clinical baseline parameters of the patients are shown in Table 1. There was no statistically significant difference between the three study groups with regard to demographic and clinical baseline parameters.

I-PSS

After 6 months, mean decrease in I-PSS was 6.1, 4.6, and 4.9 in the SR, TAM, and SR + TAM groups, respectively (Table 2). The difference between IPSS values at baseline and 6 months were significant in each group. Patients in the SR group had a greater reduction in symptoms than the other groups. However, statistical analysis did not reveal this expected difference between treatment regimens ($P = 0.1$). The mean decrease of I-PSS scores in the SR group was slightly greater than in the other groups 2 months after the treatment began ($P = 0.7$). Evaluation of mean IPSS values over time is shown in Fig. 1.

Q_{max}

At the 6th month of treatment, mean increase in Q_{max} was similar in both the SR and TAM groups (3.2 ml/s for SR, 3.7 for TAM), but was slightly greater in the SR + TAM group (4.3 ml/s)

Table 1 Demographic and other baseline parameters

	TAM (N = 20)		SR (N = 20)		TAM + SR (N = 20)		P
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	
Age (years)	58.9	±5.7	56.8	±7.8	60.2	±6.3	0.35
Body mass index (kg/m^2)	28.0	±3.4	26.7	±2.5	27.8	±2.3	0.30
I-PSS	16.2	±4.7	18.0	±4.9	15.6	±3.2	0.24
QL	3.5	±1.1	4.2	±1.1	3.5	±1.1	0.09
Q_{max} (ml/s)	10.5	±2.8	9.4	±2.9	9.9	±2.4	0.55
Prostate volume (cc)	38.6	±11.6	35.2	±10.3	31.2	±4.2	0.06
PSA (ng/ml)	2.1	±0.9	1.9	±0.9	1.7	±0.7	0.45
PVR (cc)	65.5	±33.3	67.4	±27.7	63.7	±23.7	0.79

Table 2 Mean changes in efficacy parameters from day 0 to month 6 endpoint

	TAM (N = 20)	SR (N = 20)	TAM + SR (N = 20)	P
I-PSS (Endpoint-Baseline)	–4.6 (3.3)	–6.1 (2.7)	–4.9 (2.3)	0.16
QL (Endpoint-Baseline)	–2.1 (0.8)	–2.6 (0.9)	–2.2 (1.0)	0.14
Q_{max} (ml/s) (Endpoint-Baseline)	3.7 (2.6)	3.2 (2.2)	4.2 (2.5)	0.38
Prostate volume (cc) (Endpoint-Baseline)	–1.0 (2.2)	–0.7 (2.6)	–0.8 (2.0)	0.61
PSA (ng/ml) (Endpoint-Baseline)	–0.1 (0.2)	–2.0 (0.3)	–3.5 (0.2)	0.07
PVR (cc) (Endpoint-Baseline)	–23.6 (20.2)	–28.1 (22.6)	–25.4 (14.8)	0.42

(Table 2) (Fig. 2). Patients in each group had improved flow rates and the difference between Q_{max} values at baseline and 6 months was statistically significant in each group, although the difference was not statistically significant between groups with regard to increase in Q_{max} values (P = 0.3).

Prostate volume

After 6 months of treatment, mean prostate volume had decreased by 0.7 cc in the SR group, 1.0 cc in the TAM group, and 0.8 cc in the SR + TAM group. The difference was not significant (P = 0.6).

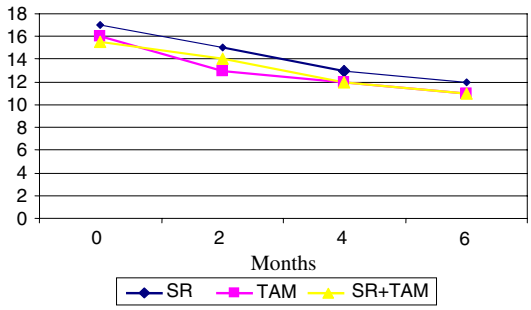

Fig. 1 I-PSS values over time

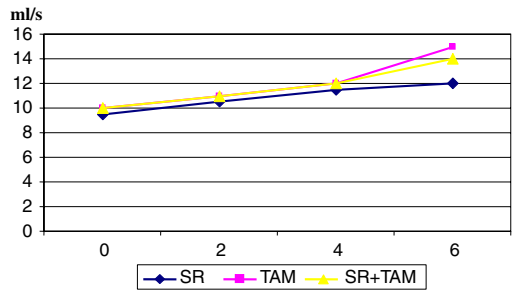

Fig. 2 Q_{max} values over time

PSA

All treatment groups showed similar (0.2 for the SR, TAM, and SR + TAM groups) decreases in PSA levels.

QL

For the QL score, the SR group had an initial mean score of 4.2 (range: 2–6), which decreased to 1.6 (range: 1–3) after 6 months; the TAM group's initial mean score was 3.5 (range: 2–6), which decreased to 1.4 (range: 1–2); the combined therapy group had an initial mean score of 3.5 (range: 0–5), which decreased to 1.3 (range: 1–2) after 6 months (Fig. 3). The 3 groups had lower mean scores after the treatment, but the difference was not significant ($P = 0.1$) (Table 2).

PVR

The improvement in PVR volume was not statistically different between the groups, which had mean decreases of 28.2, 23.6, and 25.4 cc for the SR, TAM, and SR + TAM groups, respectively ($P = 0.4$).

Adverse effects

During the 6-month treatment period, 11 (55%) patients treated with TAM and 4 (20%) with SR + TAM had drug-related adverse reactions, which included postural hypotension, dizziness, libido decrease, dry mouth, ejaculation disorders, rhinitis, fatigue, and asthenia (Table 3). However, these effects did not result in withdrawal from the study. No adverse effect was detected in the SR group.

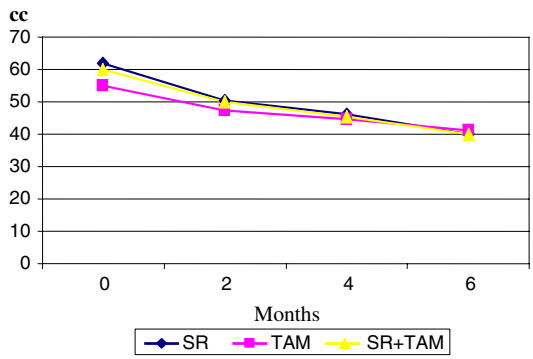

Fig. 3 PVR values over time

Discussion

LUTS associated with BPH are very common in men over the age of 60 years worldwide [14]. Currently, there is no consensus for the management of LUTS due to BPH [14]. Treatment options include watchful waiting, minimally invasive treatments such as transurethral needle ablation of the prostate and transurethral microwave therapy, surgical procedures like transurethral resection of the prostate, and even open enucleation of the prostate. Medical treatment including 5-alpha-reductase inhibitors [15–17] and alpha-blockers are also available for these patients [18, 19].

An alternative treatment of BPH with phytotherapeutic agents seems to be increasing in some European countries. Reasons for the increasing popularity of these agents include dissatisfaction with conventional treatments, the need for personal control of treatment, and a philosophical congruence of alternative therapies and patient values and beliefs [20–22]. The most described and studied phytotherapeutic agent for the medical treatment of symptomatic BPH is the lipidosterolic extract of SR, Permixon®, which is known as Prostagood® in Turkey.

Table 3 Summary of adverse effects

	SR ($N = 20$)	TAM ($N = 20$)	SR + TAM ($N = 20$)
Any	20 (100%)	8 (40%)	17 (85%)
Rhinitis	–	2	–
Asthenia	–	–	1
Fatigue	–	2	–
Dizziness	–	2	1
Postural hypotension	–	3	1
Dry mouth	–	5	1
Libido decrease	–	4	2
Ejaculation disorders	–	7	3

In vitro studies have shown that SR is a non-competitive inhibitor of type I 5-alpha-reductase and non-competitively inhibits the type II isozyme [23, 24]. Another most widely accepted mechanism of action by which SR has been suggested to improve voiding symptoms in men with BPH is through inhibition of dihydrotestosterone binding to the cytosolic androgen receptor in prostatic cells [25–27]. Additionally, anti-proliferative and anti-inflammatory mechanisms have been described [28, 29], while the major mechanism still remains undetermined.

Studies comparing SR with 5-alpha-reductase inhibitors or alpha-blockers have been previously reported [12, 13, 30, 31], but a limited number of studies comparing TAM with SR + TAM were found during our literature review [32, 33].

In most placebo-controlled studies, the efficacy of SR is shown to be greater than placebo [11, 34–37]. Boyle et al. [38] reported a meta-analysis of clinical trials of SR extract in the treatment of BPH and detected a mean increase in Q_{max} of 2.2 ml/s. On the other hand, superiority of SR over placebo was not confirmed by some authors [36, 39]. In the present study, mean increase in Q_{max} of the SR group was 3.2 ml/s.

SR has been compared to other pharmacological agents such as 5-alpha-reductase inhibitors and alpha-blockers [12, 13, 30, 31]. No significant differences between SR and Finasteride in resolving symptoms of BPH have been found in the majority of studies, although SR has been found to cause fewer side effects [12].

It is largely known that TAM is more effective than placebo in patients with LUTS [40–42]. Previous studies have compared TAM with SR and most have found equivalent efficiency in resolving LUTS due to BPH [13, 30]. In a recent study designed by Debruyne, mean Q_{max} increase in the TAM and SR groups was 1.7 ml/s and 1.2 ml/s, respectively. The groups were not statistically different. Conversely, the groups were statistically different with regard to mean decrease in IPSS (–7.8 for SR group and –5.8 for TAM group) [30]. In the present study, mean increase in Q_{max} was 3.2 ml/s for the SR group and 3.7 ml/s for the TAM group. Additionally, mean decrease in IPSS was 6.1 and 4.6 in the SR and TAM groups, respectively. Decrease in IPSS seems to be numerically greater in the SR group, but the difference was not statistically significant for IPSS and Q_{max} values of the SR and TAM groups.

We found improvement in LUTS-related QL in each group; similarly it was reported that SR + TAM resulted in equal improvement in QL compared to TAM [32].

Limited studies have evaluated PVR in measuring response to treatment [43]. We measured PVR to assess the efficacy of treatment regimens and found a mean decrease of 28.2, 23.6, and 25.4 cc for the SR, TAM, and SR + TAM groups, respectively. But the groups were not statistically different.

We have found that SR has no effect on PSA levels, consistent with earlier results [44, 45], and similar results were found in this study. In fact, decreasing PSA would not be a desired result of a BPH medication, because it may mask or delay the detection of prostatic carcinoma. The absence of any effect of SR on serum PSA levels suggest that this agent has little or no effect on androgen-dependent processes. This is in contrast with 5-alpha-reductase inhibitors [46]. Prostate volume was found to be decreased by SR in three uncontrolled studies [44, 47, 48], but this was not confirmed by controlled studies [10, 49]. We found a mean decrease in prostate volume of 0.7 cc and 1.0 cc for the SR and TAM groups, respectively, but they were not statistically significant.

To the best of our knowledge, only two studies have compared SR to combined therapy [32, 33]. Glemain et al. [32] compared TAM alone and SR + TAM in the treatment of BPH and found that the addition of SR to TAM did not provide any significant benefit to the patients. Zlotta et al. [33] compared SR treatment with TAM and Finasteride to evaluate the impact on sexual function and found that SR therapy did not have a negative impact on male sexual function, while Finasteride and TAM had a slight negative impact on sexual function, especially on ejaculation. In the present study, increase in Q_{max}, and decrease in IPSS were not statistically different between the SR, TAM, and SR + TAM groups. These results revealed that combined therapy (SR + TAM) does not provide extra benefits.

Serenoa repens is defined as a well-tolerated agent used in BPH. In clinical trials, side effects from SR, which occur in approximately 2% of patients, are primarily gastrointestinal complaints (nausea, diarrhea, constipation, abdominal discomfort) and, rarely headache, back pain, hypertension, urinary retention, and cholestatic hepatitis [8, 36, 50, 51]. Adverse effects were observed in 15 patients in the present study; none of them was in the SR group, although 12 were in the TAM and 3 were in the SR + TAM groups. Ejaculation disorders have been reported to occur 4–11% of patients treated with TAM (0.4 mg). In the present study, ejaculation disorders were detected in 25% of patients treated with TAM, but not in any patients treated with SR. The ratio seems to be greater than the literature. It may be explained by the small number of patient population. In summary, our results confirm that adverse effects are commonly associated with TAM and SR is a well-tolerated agent used for LUTS in patients with BPH.

Although the efficacy of SR can only be reliably determined with placebo-controlled studies, clinically relevant information can still be gained from comparative trials, and for this reason a placebo group was not included in the present study.

The aim of this study was to compare the efficacy of SR and TAM, and additionally to evaluate if combined therapy was superior to SR or TAM alone in the treatment of BPH. The number of patients randomized was the same in each group (SR, $N = 20$; TAM, $N = 20$; combined therapy, $N = 20$). Due to the absence of a placebo group, this study cannot reveal individual efficacy of SR and TAM or SR + TAM, but can only reveal the relative efficacy of each treatment protocol.

In summary, we found that treatment of BPH with both SR and TAM alone seems to be equally effective, and combined therapy (SR + TAM) does not provide extra benefits. SR is a well-tolerated agent that can be used alternatively in the treatment of LUTS due to BPH. Our analysis has several limitations. First, small sample number reflects this population and second the follow-up of 6 months is relatively short. Large prospective randomized studies with longer follow-up periods are needed to more clearly determine the efficacy of SR in the treatment of BPH.

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