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ORIGINAL PAPER

Efficacy of Serenoa repens lipido-sterolic extract alone or in combination with propolis polyphenols and Boswellia serrata extract suppositories on PSA level and symptoms in patients affected by lower urinary tract disorders

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Summary ***Background: Standard medical treatments for patients with uncomplicated LUTS include alpha-blockers, 5-alpha-reductase inhibitors (5ARIs), phosphodiesterase type 5 inhibitors, antimuscarinics, and beta-3 agonists. The lipido-sterolic extract of Serenoa repens (Sr) is also recommended as a therapeutic option. Our study prospectively evaluated the impact of a 6-month assumption of lipido-sterolic extract of Sr alone or in combination with Phenolmicin P3 and Bosexil medical devices suppositories on symptoms and on PSA levels in patients affected by BPO related-LUTS.***

Methods: We prospectively enrolled 509 patients: 194 (group 1) were prescribed only a 6 months assumption of Sr extract, while 315 (group 2) were also prescribed a 20-day therapy with Phenolmicin P3 and Bosexil medical devices suppositories.

Results: After 6 months, 371 patients' data were registered and analyzed. Furthermore, patients' withdrawal and motivations were also considered.

Conclusions: In our clinical study, the patients treated with Serenoa repens extract (320 mg daily) showed a significant relief regarding LUTS, and the association of a 6-month assumption of Sr extract with a 20-day prescription of Phenolmicin P3 and Bosexil medical device in suppository form seems to significantly improve both efficacy on LUTS and decrease of PSA levels.

KEY WORDS: *Benign prostatic obstruction; Serenoa; LUTS; Symptoms.*

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INTRODUCTION

Benign prostatic obstruction (BPO) is a frequent cause of *lower urinary tract symptoms* (LUTS) in adult men. LUTS can be highly bothersome, impairing the quality of life of men and that of their partners (1, 2). The prevalence of BPO increases substantially with age, reaching 90% in men aged 81-90 years (3). Likewise, the prevalence of LUTS ranges from 44% in men aged 40-59 years, increasing to 70% in men aged > 80 years (3, 4). LUTS have been shown to cause significant debility and have greater impacts on anxiety and depression than similar chronic illnesses such as diabetes, gout and hypertension (3). Standard medical treatments for patients with uncomplicated LUTS include alpha-blockers, 5-alpha-reductase inhibitors (5ARIs), phosphodiesterase type 5 inhibitors, antimuscarinics, and beta-3 agonists. The lipido-sterolic extract of *Serenoa repens* (Sr) is also recommended as a therapeutic option in the EAU Guidelines on non-neurogenic LUTS (1).

The mechanisms underlying the pharmacological effects of Sr in BPO are still far from being completely identified (11). It has been suggested that Sr may inhibit 5ARI and may have an anti-androgenic, antiproliferative, anti-inflammatory and anti-edema activity (11, 12). These effects are obtained with high doses of Sr and therefore it has been questioned whether these effects have a therapeutic relevance (12). Furthermore, it has been demonstrated that Sr may exert anti-adrenergic receptors activity (13). Sr interacts with the adrenergic and muscarinic receptors localized in the lower urinary tract lessening the obstructive symptoms following BPO (14).

Medical treatments are usually prescribed as monotherapy in patients with mild to moderate LUTS, though in patients showing insufficient improvement and/or more severe symptoms, treatments may be combined (1, 3). The most widely used combination therapy is an alpha-blocker with a 5ARI (4), although it has been reported that adverse events are significantly more common with this combination than during monotherapy (5). Sr has proven as effective as alpha-blockers (6) and 5ARIs when used as a monotherapy over a 6-month period (7, 8), although it has a significantly superior tolerability profile (6-9), which makes it a valid alternative as a treatment option for LUTS. As a persistent prostatic inflammatory state plays a role in the development and progression of LUTS (10), the anti-inflammatory effect of Sr might contribute to greater relief of LUTS symptoms than when using an alpha-blocker alone (10). Irritative symptoms and lower urinary tract infections play a significant role

on LUTS progression and suppository corticosteroids therapy is often prescribed as first line treatment, though its role is limited by relevant side effects, especially on diabetes affected patients. As an alternative, a medical device, in form of suppositories, based on propolis polyphenols (*Phenolmicin P3*) and Boswellia serrata extract (*Bosexil*), has been reported to possess an anti-inflammatory property, due to its antioxidant and mucoadhesive capacity, in a variety of inflammatory diseases whose physio-pathological pathways are shared with those of prostatitis.

Our study prospectively evaluated the impact of a 6-month assumption of lipido-sterolic extract of Sr alone or in combination with *Phenolmicin P3* and *Bosexil* suppositories on symptoms and on PSA levels in patients affected by BPO related-LUTS.

Materials and methods

We prospectively enrolled at our Institution between January and December 2023, patients who presented for outpatient visit for LUTS with or without symptoms of acute prostatitis, and an enlarged prostate of 25 ml or more on transrectal or transabdominal ultrasonography. Exclusion criteria were any history of other urologic disorders; history of bladder-neck or prostate surgery, transurethral incision of the prostate, balloon dilation, or thermotherapy; suspected prostate cancer.

Age, symptoms, prostate volume, PSA level and side effects were registered in our database. After a complete urological examination, including digital rectal examination and PSA level evaluation, all included patients were prescribed a 6-month daily assumption of 320 mg lipido-sterolic extract of Sr (*Saba®*). Patients were also randomly assigned to a 20-day prescription of *Phenolmicin P3* and *Bosexil* suppositories (*Mictalase®*). Patients were evaluated at 6 months by physical examination and serum PSA level measurement. Changes in symptoms or in PSA level, as also patients' withdrawal and their motivations were registered.

Comparisons between the two groups (*Saba® + Mictalase® vs Saba® alone*) were assessed by means of the Student's t test. All statistical tests were two-sided, and significance was declared at the 5% level.

Results

509 patients were enrolled in the present study, 194 (38%, group 1) were prescribed only a 6-month course of *Saba®*, while 315 (62%, group 2) were also prescribed a 20-day therapy with *Mictalase®*; 138 patients were subsequently excluded because they had not completed the 6 months of therapy or were not available at the time of the 6 months visit. Overall median age was 67 years, Overall PSA level was 1.47 ng/ml in the entire population (1.6 *vs* 1.42 in group 1 and group 2 respectively), while prostate volume was 42 ml (42 ml *vs* 43 ml in group 1 and group 2 respectively). LUTS were registered in 68 (35%) and 85 (27%) patients in group 1 and group 2. No statistically significant differences were observed between the two groups concerning age, PSA level, prostate volume and presence of LUTS.

At the 6 months scheduled visit, 371 patients were still following the prescription, and their data were registered and analyzed. Furthermore, patients who withdrawal and motivations for withdrawal were also taken into account. In total 138 (27.1%) patients dropped off the study because of epigastric pain (n = 16; 11.6%), therapy cost (n = 62; 44.9%), nausea (n = 25; 18.1%), or other causes including unavailability at the time of the visit (n = 35; 25.4%).

Table 3 resumes patients' characteristics at the time of follow up. Median PSA level after 6 months of Saba assumption was 1.42 ng/ml, with no differences with patients treated also with *Mictalase®*. PSA level decrease, on the other side, was significantly more frequent in group 2

Table 1.
Overall characteristics of the entire population.

	Overall (n = 509)	SABA alone (n = 194)	SABA+MICTALASE (n = 315)	p-value
Age, years				
Median (IQR)	67 (42-83)	66 (42-83)	68 (51-80)	0.76
PSA, ng/ml				
Median (IQR)	1.47 (1.0-2.54)	1.6 (1.09-2.31)	1.42 (1.0-3.01)	0.14
Prostate volume, ml				
Median (IQR)	42 (25-87)	42 (25-77)	43 (25-87)	0.47
LUTS				
Yes	154 (30.3%)	68 (35.0%)	85 (27.0%)	0.11
No	355 (69.7%)	126 (65.0%)	230 (73.0%)	

Table 2.
Patients' withdrawal causes.

	Overall (n = 138)
Cause of drop-off, n (%)	
Epigastric pain	16 (11.6%)
Nausea	25 (18.1%)
Therapy Cost	62 (44.9%)
Other causes	35 (25.4%)

Table 3.
Patients' follow up data at 6 months.

	Overall (n = 371)	SABA alone (n = 157)	SABA+MICTALASE (n = 214)	p-value
PSA at 6 months, ng/ml				
Median (IQR)	1.42 (1.01-2.3)	1.42 (1.13-2.11)	1.42 (0.61-2.31)	0.97
PSA level decrease, n (%)				
Yes	258 (69.5%)	97 (61.8%)	161 (75.2%)	0.03
No	113 (21.5%)	60 (38.2%)	53 (24.8%)	
LUTS improvement, n (%)				
Yes	338 (91.1%)	131 (83.4%)	207 (96.4%)	< 0.01
No	33 (8.9%)	26 (16.6%)	7 (3.6%)	

patients (161 patients *vs* 97; p = 0.03). Moreover, 91.1% of patients declared a certain grade of improvement of their LUTS, with a significantly higher rate of improvement in group 2 compared to group 1: 207 (96.4%) *vs* 131 (83.4%) (p < 0.001).

Discussion

Patients with symptomatic BPO are usually treated with alpha-blockers as a first-line therapy option. However, alpha-blockers are drugs with significant adverse effects in a considerable percentage of patients. In our study, we have enrolled a population of men presenting with LUTS and/or acute prostatitis and divided them into two groups: group 1 was treated with Sr extract (*Saba*®) and group 2 with Sr extract and *Phenolmicin P3* and *Bosexil* suppositories (*Mictalase*®). Clinical and laboratory examinations were performed at the beginning of the study, and 6 months later. We observed that serum PSA levels were significantly reduced by therapy in both groups, with a significantly higher rate of patients with decrease in group 2, which is comparable to some previous studies (15). However, in a recent randomized, placebo-controlled, trial conducted on 369 men with BPO, Sr extract does not affect serum PSA levels more than placebo (15). On the contrary, the prostate size increase during the 1-year follow-up and the proportion of patients with prostate volume > 40 ml was significantly higher in the control groups than in the Sr group indicating a measurable effect on this important BPO parameter. We observed significant improvements of LUTS in both groups, with a decrease of symptoms of more than 83% in group 1 and 96% in group 2. This indicates that there is clinically evident improvement in the patients' symptoms related to BPO with a therapy not based on alpha-blockers or 5ARIs. Although the changes in urological symptoms were highly significant (p < 0.01) in favor of group 2, results are certainly encouraging for both groups. Our results are consistent with some of the previously published studies in which a noticeable reduction of LUTS associated with BPO and significant improvement of life quality were observed (16). The clinical responses to phytotherapy with Sr repens extracts are also found to be very promising in other studies (17, 18). Moreover, EAU guidelines state that these herbal extracts significantly reduce nocturia in comparison with placebo (19). On the contrary, some authors described that Sr have not shown more effectiveness than placebo in the treatment of BPO (20, 21). However, more recent data favor the use of Sr extracts in milder BPO cases with promising results (22). It also has been proved that the extraction methods also have an impact on the pharmacological action of *Saba*®, in BPO and this may be one of the major reasons for studies' inconsistencies (23). No serious adverse events or interactions with co-administered drugs have been described during the use of Sr and this treatment is associated with less sexual dysfunction-related side effects than the usual drug therapy for BPO as tamsulosin or finasteride (24).

On the other hand, the medical device in the form of suppositories, we have studied, contain different functional principles, as *Bosexil* and *Phenolmicin P3*. The first is a derivative of Boswellia serrata while the second is a derivative of propolis; their combined functional actions allow to obtain multiple effects at the same time: mucoadhesion, antioxidant effect and creation of a microenvironment not suitable for the proliferation of pathogenic bacteria. The effectiveness of this medical device has been tested, by another research group, through the evaluation of a standardized questionnaire (25), showing that the medical device, in the form of a suppository, is able to reduce genitourinary pain and improve the quality of life in men affected by symptoms similar to prostatitis (26, 27). It is therefore conceivable that this medical device supports the main action of *Saba*®, with non-pharmacological mechanisms.

In evaluating a large-scale applicability of these treatments, causes of abandonment of therapy were registered and costs represented the main reason for renunciation. In Italy, this could represent a disadvantage regarding patients' compliance, compared to alpha-blockers and 5ARIs, because the latter are provided by Italian healthcare system with no further costs for the patient.

A limitation of the present study is that it was not randomized because our protocol only aimed to observe patients with BPO under strict inclusion and exclusion criteria. Also, improvements were not registered based on a standardized questionnaire for LUTS (such are IPSS score system) or on an objective instrumental exam such as uroflowmetry. Larger studies with longer follow-up are needed to further evaluate the potential efficiency of this treatment for BPO as an alternative to the established pharmaceutical agents and to evaluate the possible side effects due to the long-term use.

Conclusions

In our clinical study, the patients treated with Serenoa repens extract (320 mg daily) showed a significant relief regarding LUTS, and the association of a 6-month assumption of Sr extract (*Saba*®) with a 20-day prescription of *Phenolmicin P3* and *Bosexil* suppositories (*Mictalase*®) seems to have a significantly higher efficacy on both LUTS and PSA levels decrease.

Declarations

Ethical approval: *Not applicable because the study is based on herbal products of well-established use. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.*

Availability of data and material: *The datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.*

Competing interests: *The authors declare that they have no competing interests.*

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Authors' contributions: *Barbaresi U, DiCuio M: conception or design of the work, acquisition, analysis and interpretation of data; Mineo Bianchi F, Marini M, Quadrini F: acquisition, analysis and interpretation of data; Lupo S, De Stefano R: Final approval of the version to be published.*

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