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ORIGINAL PAPER

The association of Boswellia resin extract and propolis derived polyphenols can improve quality of life in patients affected by prostatitis - like symptoms

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Summary

Objectives: *Chronic prostatitis syndrome is a bothering and poorly understood condition. Many patients report genitourinary pain and Lower Urinary Tract Symptoms as a main complaint. Many different pharmacological or behavioural therapies are prescribed in daily clinical practice, but efficacy data are still lacking. The aim of our study was to test the efficacy and safety of a transrectal delivered association of Boswellia resin extract and propolis derived polyphenols for the relief of prostatitis - like symptoms.*

Materials and methods: *Patients affected by chronic/recurrent prostatitis - like symptoms were prospectively enrolled in our study from December, 2016 to December, 2018. Patients were screened at baseline through clinical examination and validated questionnaires administration: Chronic Prostatitis Symptom Index (CPSI), International Prostate Symptom Score (IPSS), International Index of Erectile Function (IIEF). Inclusion criteria were: age ≥ 18; prostatitis symptoms persisting for at least 3 of the last 6 months; CPSI pain domain score ≥ 5; previous negative Meares-Stamey test. Treatment consisted on the administration of 1 suppository containing Boswellia resin extract and propolis derived polyphenols, once a day for 20 days. The primary endpoint of the study was the improvement of quality of life after treatment, defined by a reduction of ≥ 2 points, or ≥ 25%, of mean CPSI pain domain score, compared to baseline. Secondary endpoints were the improvement of post-treatment CPSI total score and the analysis of treatment - related adverse events. All patients were re-evaluated 1 month after treatment.*

Results: *40 patients were enrolled in our study. Median age (Inter - Quartile Range IQR) was 51.5 (41.5-63.2) years. Mean baseline CPSI scores were: 22.15 (total score), 9.67 (pain domain), 5.15 (micturition domain) and 7.35 (quality of life domain), respectively. No significant adverse events were reported. At 1 month follow-up, CPSI scores appeared modified as follows: 16.40 (total score, p = 0.001); 6.92 (pain domain; p = 0.001; 4.02 (micturition domain, p = 0.09); 5.45 (quality of life domain, p = 0.002). Mean CPSI pain domain score reduction was -2.75 points (-28.5%). Mean CPSI total score reduction was -5.75 points (-26%).*

Conclusions: *The association of Boswellia resin extract and propolis derived polyphenols can reduce genitourinary pain and then improve quality of life of men affected by bothersome prostatitis - like symptoms.*

KEY WORDS: *Prostatitis; Pain; Boswellia serrata; Propolis; Quality of life.*

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No conflict of interest declared.

INTRODUCTION

Prostatitis syndrome is characterised by genitourinary pain and *Lower Urinary Tract Symptoms* (LUTS).

According to different studies, the prevalence of prostatitis in the male population ranges between 2.2% and 13.8% (1), and it is estimated that at least 50% of men have suffered from at least one episode of prostatitis in their lifetime (1). Moreover, this disease can account for up to 10% of all urological consults (2). The *National Institute of Health* (NIH) differentiates prostatitis into several etiologic categories. Acute bacterial prostatitis (NIH type 1) is characterized by fever and acute onset of LUTS. Conversely, asymptomatic inflammatory prostatitis (NIH type 4) is characterized by the absence of symptoms and its diagnosis is usually occasional (3). Chronic prostatitis is a pathological entity lying between the two categories, and it is basically defined as a clinical syndrome whose manifestations are prolonged over time. The aetiology of chronic prostatitis may be infectious (*Chronic Bacterial Prostatitis*, CBP, NIH type 2), or merely inflammatory (*Chronic Prostatitis/Chronic Pelvic Pain Syndrome*, CP/CPPS, NIH type 3). Nevertheless, at least from a clinical point of view, the two conditions appear to be largely overlapping (3). Chronic prostatitis remains one of the most common urologic disorders. It is often poorly understood in its causative mechanisms and usually complex to manage. Due to a lack of standardized therapeutic protocols, it is often treated with empirical pharmacological therapies, including prolonged antibiotic courses. Despite a microbiological evidence of infection is often unavailable, in fact, antibiotics are prescribed up to a third of all patients (4). Several alternative therapies have been also evaluated over time, including anti-inflammatory medications, neuromodulators, alpha-blockers, physical and cognitive - behavioural therapies, and phytotherapy. However, reliable efficacy data are still lacking. *Bosexil®* is a vegetal extract derived from the resin of *Boswellia serrata*, a plant native to *India*. *Boswellic acids* (BAs) already showed anti-inflammatory and antioxidant properties in a variety of inflammatory diseases, including rheumatoid arthritis, osteoarthritis, and asthma (5, 6), whose physio-pathological pathways could be shared with those of chronic prostatitis. On the other

hand, *Fenolmicina P3®*, a polyphenolic extract derived from beehive propolis, demonstrated anti-inflammatory, anti-microbial and antioxidant properties in several preclinical reports (7-9). The aim of our study was to test the efficacy and safety of the association of *Bosexil®* and *Fenolmicina P3®* in relieving prostatitis - like symptoms in an adult male, prospective cohort.

Materials and methods

Study design and sample size definition

Our study was conceived as a pilot study, characterised by an observational, non-randomized, prospective approach. The required sample size for this study was determined on the basis of the expected variation of mean *Chronic Prostatitis Symptom Index* (CPSI) pain domain score, compared to baseline. A size of 40 patients was needed to detect a 2 points difference, with an 80% power and a 0.05 alpha error level.

Patients selection

Male patients, attending our outpatient service for chronic/recurrent prostatitis - like symptoms were prospectively evaluated from December 2016 to December, 2018. A key point for the diagnosis of prostatitis was the presence of chronic perineal or genital pain, exacerbated by micturition or ejaculation. According to current *European Association of Urology* (EAU) Guidelines, prostatitis syndrome was suspected when symptoms persisting for 3 months or more were reported (10). Moreover, we included in the study patients with both recurrent symptoms and previous negative Meares-Stamey test. Once screened, patients' general and urological history was investigated, and a complete urological examination, including a *Digital Rectal Examination* (DRE) was carried out for all candidates to enrolment, in order to confirm prostatic pain and exclude synchronous prostatic diseases, like *Prostate Cancer* (PCa). Moreover, they were all administered three validated questionnaires: NIH-*Chronic Prostatitis Symptom Index* (NIH-CPSI), *International Prostate Symptom Score* (IPSS) and *International Index of Erectile Function* (IIEF).

Validated questionnaires

Three international validated questionnaires were used to evaluate patients at baseline and at follow-up:

- CPSI: it is an international, validated questionnaire proposed by the NIH *Chronic Prostatitis Collaborative Research Network* in 1999 to objectively assess prostatitis symptoms (3). It has been validated in Italian in 2005 (11). It is composed of three parts, or "*individual domains*": a) pain domain, assessing the localization and amount of painful urogenital symptoms; b) micturition domain, focused on LUTS; c) quality of life domain.
- IPSS: it is an international, validated questionnaire aiming to assess LUTS. It is composed of 7 questions about LUTS, plus 1 question about Quality of Life. Symptoms are classified as: mild (0 to 7 points); moderate (8 to 19 points); severe (20 to 35 points) (12).
- IIEF: it is composed of 15 questions about several aspects of sexual function. It is divided into 5 domains: 1) erectile function; 2) orgasmic function; 3) sexual desire; 4) intercourse satisfaction; 5) overall satisfaction. It allows a minimum of 5 points and a maximum of 75 (13).

Inclusion criteria

Inclusion criteria were: age >=18; diagnosis of chronic prostatitis-like symptoms, prolonged for >=3 months over the last six (10); CPSI pain domain score >=5; previous negative Meares-Stamey test. We excluded from the study patients affected by acute bacterial prostatitis, asymptomatic prostatitis, *Benign Prostatic Hyperplasia* (BPH), PCa, *Inflammatory Bowel Diseases* (IBD), previous intra-vesical therapies (mitomycin, BCG), recent (< 1 month) systemic antibiotic therapies or ongoing specific therapies for chronic prostatitis (including phytotherapy).

Study schedule

At baseline, general medical information and baseline characteristics were recorded. Moreover, NIH-CPSI, IPSS and IIEF questionnaires were administered.

Subsequently, patients underwent a 20 days therapy with *Bosexil®* and *Fenolmicina P3®* suppositories (*MICTALASE®*). Standard therapeutic regimen was one suppository, once a day, for 20 days.

Every administration (2 g suppository) contained:

1. *BOSEXIL® - Boswellia Fitosoma®*
2. *Fenolmicina P3®* - propolis derived polyphenols
3. Silicon Dioxide, lecithin, cellulose, silica and solid glycerides.

All patients were re-evaluated after 30 days. At follow-up, they were re-administered the CPSI, IPSS and IIEF questionnaires. Results were recorded by using a dedicated database.

Analysis of results

Analysis of the results was based on the comparison of pre and post-treatment mean scores of the CPSI (total score and pain, micturition and quality of life domain scores), IPSS and IIEF questionnaires. The primary endpoint of the study was the improvement of quality of life, defined by a statistically and clinically significant reduction of symptoms after treatment. A reduction of at least 2 points or ≥ 25% of pain domain CPSI score was considered clinically significant. Secondary endpoints were: 1) total CPSI score statistically and clinically significant reduction, defined by at least 5 points or ≥ 25% reduction of the score after treatment. 2) evaluation of treatment's safety. For this purpose, adverse events of any type were investigated and reported.

Statistical analysis

The t-test was used to compare the distribution of continue variables. The $\chi 2$ test was used to compare categorical variables. The statistical significance was obtained when a $p < 0.05$ value was reached. The statistical analysis was performed with SPSS version 20.0 (*IBM Corp, Armonk, NY, USA*).

The study was conducted according to the statements of the Helsinki Declaration and the Good Clinical Practice Guidelines.

Results

Baseline

40 patients were enrolled in the study. The median (IQR) age was 51.5 (41.5-63.2) years. As concerns descriptive statistics, 2 (5%) patients were cigarette smokers; 1 (2.5%) was affected by diabetes mellitus; 8 (20%) were affected by hypertension (Table 1).

Baseline data were collected for all patients through the CPSI, IPSS and IIEF questionnaires administration. Mean (SD) CPSI total score was 22.15 (6.02). Mean (SD) CPSI pain domain score was 9.67 (2.77). Mean (SD) CPSI micturition and quality of life domain scores were 5.15 (3.17) and 7.35 (2.2), respectively. Mean (SD) IPSS score was 15.55 (8.8). Mean (SD) IIEF score was 62.6 (16.5).

Adherence to therapy and adverse events

All patients underwent a standard therapeutic regimen. We did not register any case of withdrawal from the study.

Moreover, we did not register any significant, treatment - related adverse event.

Follow-up

Follow-up was carried out at 1 month. Mean (SD) CPSI pain domain score was 6.92 (4.50), p = 0.001. Mean (SD) CPSI total score was 16.40 (8.97), p = 0.001. Mean (SD) CPSI micturition and quality of life domain scores were 4.02 (2.71), p = 0.09 and 5.45 (3.21), p = 0.002 respectively. Mean CPSI pain domain score reduction was -2.75 points (-28.5%). Mean CPSI total score reduction was -5.75 points (-26%). Mean (SD) post-treatment IPSS score was 12.5 (7.97), p = 0.10, while mean (SD) IIEF score was 63.85 (16.45), p = 0.74 (Results are summarized in Table 2).

Table 1.

Baseline characteristics of patients included in the study.

Age, years, median (IQR)	51.5 (41.5-63.2)
Cigarette smoke, n (%)	2 (5)
Diabetes, n (%)	1 (2,5)
Hypertension, n (%)	8 (20)
Coronary Artery Disease, n (%)	0 (0)

Age is expressed as median and Inter Quartile Range (IQR). Total sample number (N) = 40.

Table 2.

Baseline and post-treatment (1 month) results of validated questionnaires measuring prostatitis - like symptoms.

	Baseline	1 month follow-up	p value
CPSI total score	22.15 (6.02)	16.40 (8.97)	0.001
CPSI pain domain score	9.67 (2.77)	6.92 (4.50)	0.001
CPSI micturition domain score	5.15 (3.17)	4.02 (2.71)	0.09
CPSI quality of life score	7.35 (2.20)	5.45 (3.21)	0.002
IPSS	15.55 (8.8)	12.5 (7.97)	0.10
IIEF	62.60 (16.5)	63.85 (16.45)	0.74

Results are expressed as: mean (standard deviation, SD). CPSI: Chronic Prostatitis Symptom Index; IPSS: International Prostate Symptom Score; IIEF; International Index of Erectile Function.

Discussion

Chronic prostatitis still remains a poorly understood condition. Many of the underlying pathological patterns of this disease are yet to be enlightened. On the other hand, prostatitis prevalence is not negligible and its symptoms can sometimes be very bothering and negatively affecting patients' quality of life. Poor knowledge and limited therapeutic options often make chronic prostatitis a true urological challenge. Despite microbiological definition of the disease is often lacking, prolonged antibiotic administration is still considered a gold standard treatment (10). On the other hand, due to the lack of standardized therapeutic protocols, many other pharmacological or non-pharmacological therapies, including phytotherapy, are often considered by physicians as part of a multimodal treatment, even though evidences about effectiveness and safety of these products are limited (1, 14, 15).

Our study aimed to test the efficacy and safety of a transrectal delivered association of *Bosexil®* and *Fenolmicina P3®* for the treatment of chronic prostatitis symptoms. Among a wide range of other products, *Boswellia serrata* derivatives, like BAs and, specifically, *Bosexil®*, have been traditionally attributed a therapeutic potential against several chronic inflammatory diseases. More specifically, literature reports show *in vitro*, preclinical efficacy data concerning the use of *Boswellia* in different contexts as an antioxidant, revealing a positive effect on the reduction of oxidant species and inflammation (5, 6, 16). Besides propolis, rich in polyphenols, is the object of several preclinical reports that have confirmed its anti-inflammatory and antioxidant activity. Moreover, propolis shows a strong antioxidant effect, generating a synergistic effect when linked to the activity of *Boswellia* (7-9, 17). As concerns systemic bioavailability of this constituents after oral or transrectal administration, we still undoubtfully reckon with inconclusive data. Moreover, no comparative data between the oral and transrectal administration of *Boswellia* resin extracts and propolis are available to our knowledge, but the use of the transrectal way, which allows antioxidant substances to be in contact with the mucosa and antagonize oxidant species thus reducing painful symptoms, appears reasonable. Data from our study, which is the first, to our knowledge, addressing the therapeutic role of this association of compounds for the treatment of prostatitis - like symptoms, showed some significant results. First, we reported a significant post-treatment reduction of prostatitis - like symptoms, which we considered an index of quality of life improvement, as demonstrated by a statistically and clinically significant reduction of both the NIH-CPSI total score (p = 0.001) and pain domain score (p = 0.001). Moreover, we also registered a significant improvement of the CPSI quality of life domain (p = 0.002). On the other hand, we did not appreciate a similar effect against those symptoms more related to bladder outlet obstruction and BPH. In fact, the improvement of the CPSI micturition domain did not reach statistical significance (4.02 *versus* 5.15 p = 0.09).

Our results, the most interesting of which is the significant improvement of CPSI pain domain score, find confirmation in previously published, high quality studies.

As a matter of fact, the use of an NIH-CPSI based evaluation of the response to treatment is a common finding in chronic prostatitis trials, even though reference levels are not clearly established and can vary highly between different studies. For example, *Cai and colleagues* (18) demonstrated the superiority of flower pollen extract in association with vitamins over ibuprofen, considering a ≥ 25% reduction in the NIH-CPSI total score as clinically significant. Similarly, *Wagenlehner* (1) and *Elist* (19) showed a significant improvement of the CPSI total score, CPSI "*pain*" domain score and QoL score as indicative of efficacy of another pollen extract, compared to placebo. In most cases, a reduction > 25-50% or > 2-5 points in NIH-CPSI total score or pain domain score, was considered significant (20).

As a second strength of our study, we particularly focused on the selection of our sample. In fact, we aimed to differentiate patients affected by prostatitis - like symptoms from pure BPH or mixed patients.

Considering that the two conditions, despite sometimes overlapping symptoms, can be differentiated on a clinical basis through accurate anamnestic data collection ad clinical examination, we relied on this to segregate the ones from the others, being the prostatitis patients those characterized by prevalent genitourinary pain compared to the IPB ones affected by prevalent unpainful micturition symptoms. Moreover, we used the instrument of the validated questionnaires to obtain an even more accurate patient selection, including only CPSI pain domain ≥ 5 subjects. Reflecting the good selection of the included patients and meeting our expectations, patients in our sample referred a better response of the painful, inflammatory symptoms than those more typical of non-inflammatory BPH.

Finally, treatment with *Bosexil®* and *Fenolmicina P3®* demonstrated completely safe. No major nor minor adverse side effects were registered. Moreover, we did not report any case of withdrawal from the study and no patients were lost to follow-up, even though longer follow-up should be advisable.

Nonetheless, our study is not devoid of limitations, the major of which is the lack of randomisation and a control group. Without any doubt, the absence of a control group makes our results, showing a strong positive effect of the treatment against prostatitis symptoms, susceptible to overestimation, due to possible placebo effect.

For this reason, we interpreted our data in the light of other previously published, randomized, controlled trials concerning the same issues, particularly those addressing the use of *Boswellia* resin extracts (21). As we found our results consistent with those reported by randomized controlled trials investigating similar compounds, we judged them highly suggestive of a real therapeutic effect. However, since our study was conceived and has to be considered as a preliminary investigation, the need for further studies concerning these compounds is to be underlined.

Conclusions

The association of *Bosexil®* and *Fenolmicina P3®* can reduce genitourinary pain and then improve quality of life of men affected by bothersome prostatitis - like symptoms.

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