A Prospective Interventional Study in Chronic Prostatitis with Emphasis to Clinical Features

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Purpose: Chronic bacterial prostatitis displays a variety of symptoms (mainly local pain exhibiting variability in origin and intensity). These symptoms often persist despite bacterial eradication. The purpose of this article is to exam the role of phytotherapeutic agents as complementary treatment in patients with bacterial prostatitis.

Materials and Methods: The material consisted of individuals with reported pelvic discomfort and genital pain with or without lower urinary tract symptoms (LUTS) and sexual dysfunction visiting our department from March 2009 to March 2011. Patients underwent Stamey-Meares test (several cases underwent the two glass test). Depending on history and specific symptoms urethral smear and semen cultures were additionally obtained from several patients. All patients were randomized into two groups. Subjects in the first group (72 patients) received appropriate antibiotic (according to the sensitivity test) for 15 days, while subjects in the second group (72 patients) received phytotherapeutic agents for 30 days, additionally the conventional 15 days antibiotic treatment. The response was tested using laboratory and clinical criteria.

Results: We found no statistically significant differences between the two groups regarding bacterial and symptom persistence rate, however, symptoms burden was lower in patients receiving combinational treatment.

Conclusion: Phytotherapeutic agents may improve pain and prostatitis related difficulty in urination. Further randomized, placebo-controlled studies are needed to substantiate safer conclusions.

Keywords: administration; oral; phytotherapy; plant preparations; therapeutic use; prospective studies; prostate; pathology; prostatitis; drug therapy.

INTRODUCTION

The incidence of chronic prostatitis is around 3/1000 and peaks between the ages of 20-49 years. Moreover, chronic prostatitis constitutes a frequent diagnosis in men aged over 65 years primarily as a histological finding or in relation to benign prostatic hyperplasia (BPH) symptoms.[1-3] Between 1990 and 1994, there were more than 2 million outpatient visits in the USA related to chronic prostatitis cases, whereas currently 15% of men who visit a doctor due to lower urinary tract symptoms (LUTS) are diagnosed with prostatitis.[4] This particular disease has been characterized as a significant and developing clinical enigma given that its etiopathogenesis remains to a great extent unclear. Its presentation is related to an infective focus in the distant -mainly- prostatic glandular element and ducts involving gram-negative uropathogens and less frequently gram-positive bacteria.[5] It exhibits an array of symptoms, most notably pelvic pain (at various sites and of varying intensity), urinary symptoms (obstructive and irritative) as well as erectile and sexual dysfunction. Similar symptoms are also encountered in BPH and are attributed to both obstruction and secondary inflammation. The effectiveness of phytotherapeutic agents used for symptoms related to BPH justifies their use in the treatment of chronic prostatitis.[6] The aim of the study is to assess the effectiveness of phytotherapeutic agents in the management of these symptoms.

MATERIALS AND METHODS

From a pool of 234 patients with reported pelvic discomfort and genital pain with or without LUTS and sexual dysfunction visiting our department from March 2009 to March 2011, those found with chronic bacterial prostatitis confirmed by the Stamey-Meares test (a few cases underwent the two glass test), consisted the subjects of this study. In this particular study the encountered situation was a two treatment comparison in an undetermined sample size of patients. Given that the overall 2 numbers of patients was small, equal sample sizes had to be formed in order to obtain a precise comparison. For this reason, patients were randomized into two groups depending on the date of attendance (odd/even day of the month).

Subjects in the first group (72 patients) received the appropriate antibiotic treatment for 15 days, while subjects in the second group (72 patients) received phytotherapeutic agents for 30 days, additionally to the conventional 15 days antibiotic treatment. The choice of antibiotic for both groups was based on antibiotic sensitivity testing while the choice of phytotherapeutic for group 2 was based on the price of the least expensive product in the category at the time of enrolment. Microbial response was assessed by the Stamey-Meares test and the response to symptoms by the patients report at 4 and 8 weeks from the beginning of the study (15 after the completion of antimicrobial therapy). The final clinical evaluation was assessed by National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) questionnaire, the ultrasonography (US) and digital rectal examination (DRE) findings 8 weeks from the beginning of the study.

Patients suffering from neurological disorders, those with anatomic abnormalities of the urinary tract and immunosuppressed patients were excluded from the study, as these are all conditions which can affect the clinical manifestation of the disease and could alter the outcome of the study.

Depending on history and specific symptoms urethral smear and semen cultures were additionally obtained from several patients.

Microbiological Assessment

The Stamey-Meares test was deemed positive if: 1) bacteria were cultured in the expressed prostatic secretion (EPS) and the VB3 urine specimens (or post prostate massage) and were not cultured in the VB1 and VB2 (or prostate massage) specimens, 2) bacterial colony count in the VB3 specimen was 10 times that in the VB1 and VB2 specimens and 3) leukocyte numbers in the EPS and VB3 were 10 times those in the VB1 and VB2. No lower cut-off value for the number of colonies was set. Cultures for gonococcus, mycoplasma and ureaplasma and the semi-quantitative assessment were performed using bioMerieux reagents (Biomerieux, Canada Inc., 4535 Rue Dobrin, Saint-Laurent, Québec H4R 2L8, Canada). Chlamydia trachomatis were detected using direct immunofluorescence (Kallestad anti-membrane lipopolysaccharide monoclonalantibodies). Urine specimens were centrifuged and cultured in blood and MacConkey agar for aerobic and anaerobic Gram-positive and negative bacteria (bioMerieux culture media). All processing and final assessment of samples in this study were performed by the same specialist microbiologist to whom the medical history of the patients was not disclosed.

Questionnaire

The chronic prostatitis NHI-CPSI questionnaire includes 9 questions in 3 sections [character-site of pain, urinary symptoms and effect on quality of life (QoL)]. The resultant sum ranges from 0 to 43 (character-site of pain: 0-21, urinary symptoms: 0-10 and QoL: 0-12). The greater the resulting sum the greater the disturbance.

Ultrasound Evaluation

Prostatic volume and echo pattern (unequal echogenicity, hypo echogenicity, hyper echogenicity) as well as the presence and the pattern of calcifications (diffuse or periurethral) were assessed with a GE Logiq 3 Pro ultrasound machine (Ultraschall Deutschland GmbH & Co. KG. Beethovenstr. 239, 42655 Solingen. Germany) with convex array (2-5 MHz) and a 10 MHz frequency transrectal probe.

Statistical Analysis

Statistical Analyses were performed with the Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 15.0. Descriptive statistics were used to estimate the frequencies, means and standard deviations of the study variables. Differences between study groups in baseline characteristics and clinical outcomes were assessed with the use of chi-square test for categorical variables and Student's *t* tests for continuous variables. The accepted statistical significance cut-off value was P value < .05.

RESULTS

The most prominent symptoms (as reported by the patients) were chronic suprapubic, scrotal, perineal and penile pain (and feeling of burning as well) alone or in combination with a variety of symptoms. In most of the cases, symptoms lasted more than three months; however many patients (especially those experiencing frequent recurrences) were able to recognize them earlier. Interestingly, only 12 out of the 155 subjects had recurrent episodes of acute infection (epididymitis and prostatitis). Sexual and erectile dysfunctions were reported by only 6 patients. More precisely, 46 patients of the group 1 and 54 of the group 2 had a history of prostatitis or associated conditions; the mean age was the 45.45 years for group 1 and 40.98 years for group 2, while the mean NIH-CPSI score was 26.62 for group 1 and 25.78 for group 2. No statistically significant differences in history, age and NIH-CPSI score at baseline were found between the two groups (**Table 1**). On clinical examination, 76 prostates (39 of the group 1 and 37 of group 2) were abnormal in palpation-suggestive of prostatitis. Forty one out of the 144 patients (22 of the group 1 and 19 of the group 2) had abnormal prostate US. No statistically significant differences in abnormal DRE and US findings at baseline were found between the two groups.

The most common microorganisms were Escherichia coli (E. coli) and Enterococcus faecalis. While most E. coli isolates (almost 79%) were sensitive to a wide range of antibiotics, Enterococcus faecalis and Proteus isolates were so in only half of the cases (55% and 50% respectively). Almost 36% of the bacterial cultures revealed Gram (+) bacteria other than Enterococcus faecalis, with coagulase-negative Staphylococcus being the most common.

Twenty seven out of the 72 patients of the group 1 received pluri-floxacin, 33 ciprofloxacin, 6 levofloxacin, 2 trimethoprim/sulfamethoxazole (TMP-SMX), 2 tetracycline and 2 azithromycin. A few patients additionally received aminoglycosides for up to 5 days. Thirty two of the group 2 received combination of plurifloxacin and saw palmetto, 6 levofloxacin and saw palmetto, 11 ciprofloxacin and saw palmetto, 10 ciprofloxacin and pygeum africanum, 4 plurifloxacin and pygeum africanum, 4 roxithromycin and pygeum africanum, 2 TMP-SMX and saw palmetto and 5 levofloxacin and pygeum africanum. The dosage for pygeum africanum was 200 mg daily while that for saw palmetto was 320 mg daily.

At the first follow up visit, 44 patients of the group 1 who reported complete or near complete symptom relief were bacterial free. In contrast, 2 patients of the same group were found with bacterial persistence despite absence of symptoms. Seventeen patients of the group 1 reported symptom persistence despite bacterial eradication and 9 patients of the same group had both symptom and bacterial persistence. Similarly, 49 patients of the group 2 were asymptomatic and bacterial free, 16 reported symptom persistence despite bacterial eradication and 7 were found with bacterial persistence despite absence of symptoms. There was no statistically significant difference in the overall outcome between the two groups at the first follow-up visit (**Table 2**).

At the second follow-up visit, 47 patients of the group 1 were asymptomatic and bacterial free, 15 were found with symptom or bacterial persistence while 10 patients were lost to follow up. Similarly, 54 patients of the group 2 were asymptomatic and bacterial free, 14 were found with symptom or bacterial persistence while 4 patients were lost to follow-up. There was no statistically significant difference in the overall outcome between the two groups at the second follow-up visit (**Table 2**). Of note, there was discordance between subjective self-reported symptoms relief and documentation of symptoms in the NIH-CPSI report, since most patients who reported symptoms regression had NIH-CPSI score between 2-12 (20 of the group 1 and 11 of the group 2). Similarly, several patients who reported symptom persistence had lower NIH-CPSI scores in the follow-up period than that at baseline. Of note only 35 patients of both groups provided a completed NIH-CPSI score at endpoint. Similarly, data on variations in DRE findings were available in 133 cases and data on variations in prostate US were available in 50 patients. Difference in mean NIH-CPSI score at the second follow-up between group 1 and group 2 was statistically significant ($P < .05$). No statistically significant differences in US and DRE findings ($P > .05$) were found between the two groups. Differences in the side effects rate between the two groups were not statistically significant ($P > .05$).

DISCUSSION

The herbs saw palmetto and pygeum africanum have been used to treat men with BPH, to help relieve some of the bothersome symptoms of BPH, including nocturia and difficulty urinating. Lately they have been the object of focused research into the treatment of infections of the urinary tract, having been used as a sole agent, combined with antibiotics, with alpha-blockers, anti-inflammatory agents and 5-alpha reductase inhibitors. However, their precise mechanism(s) of action on prostatic inflammation remain partly explained.[7] In addition, it is unclear whether they potentiate the effect of antibiotics. Actually, the active ingredient of both herbs is the beta-sitosterol complex. This includes beta-sitosterol, campesterol, stigmasterol and brassicasterol. All these phytosterols exhibits an anti-androgenic activity, related to the inhibition of conversion of testosterone to the more potent androgen dihydrotestosterone at the level of androgen receptors. This is particularly important given that androgen receptor enhance the migration of macrophages and macrophage-mediated stromal cell proliferation.[8] Inhibition of conversion of testosterone results in a reduction of the hormonal response of macrophages and leukocytes and the inhibition of their migration to the site of inflammation. As a consequence there is a reduction in the release of myeloperoxidase which causes destruction of the inflamed tissue and of platelet-derived growth factor and growth factor-beta which induce inflammation.[9-11] Recently it has been demonstrated that atraric acid isolated from bark material of pygeum africanum exhibits an indirect anti-androgenic anti-inflammatory activity by inhibiting the transac

Table 1. Difference between groups 1 and 2 with regard to age, prostatitis related history and NIH-CPSI score upon introduction into the study.

Variables	Number		Mean		Standard Deviation		*P* Value
	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	
Age (years)	72	72	45.4583	40.9861	11.43375	12.46346	.176
History of prostatitis	72	72	0.56940	0.65280	0.498630	0.47943	.707
Baseline NIH-CPSI score	72	72	17.9306	20.5000	12.93573	2.15162	.659

Abbreviation: NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index.

tivation mediated by the ligand-activated human androgen receptor.[12] On the other hand, serenoa repens (isolated from saw palmetto extract) exhibits a direct androgen-independent anti-inflammatory activity by inhibiting epidermal growth factor-dependent growth and proinflammatory responses of the prostate epithelial cells.[13,14]

Only a few clinical trials examining the effect of complementary phytotherapeutic agents administration to the conventional antibiotic treatment of chronic bacterial prostatitis exists. Most of them have shown impressive clinical effects, a finding which is not in accordance with our results.

In a small study, pygeum africanum extract (200 mg/daily for 60 days) was used either alone or in combination with antibiotics to treat 18 patients suffering from sexual disturbances due to chronic prostatitis. Pygeum improved all the urinary parameters investigated by medical history and prostatic transrectal US, and improved sexual function despite the fact that there were no significant differences between hormonal levels and nocturnal penile tumescence and rigidity monitoring before and after therapy.[15] Cai and colleagues in a prospective randomized trial examined whether a combination of saw palmetto extract with other phytotherapeutics is able to improve the efficacy of prulifloxacin in bacterial prostatitis patients. One month after treatment, 89.6% of patients who had received prulifloxacin associated with phytotherapeutics were free of symptoms, whilst only 27% of patients who received antibiotic therapy alone were recurrence-free. Significant differences were also found between groups in terms of symptoms and QoL.[16] Similarly, Pavone and colleagues administered to 320 patients suffering from prostatitis related LUTS a combination of saw palmetto extract with other phytotherapeutics for a minimum duration of 30 days to a maximum of a year, either alone or in association with antibiotics or alpha-blockers. Variations in symptom score could be fully evaluated only in 80 of 320 patients (25%), of whom 68 (85%) reported a significant benefit, with special reference to an improvement of pain, urgency, strangury and nocturia. Data on variations in prostate volume, as measured by DRE were available in 84 (26.5%) patients. No significant change was observed. Maximum urinary flow rate (Qmax) after treatment was measured in 83 (26%) patients. It did not show significant changes from the baseline. No untoward side effect was reported in any case.[17] Aliev and colleagues examined retrospectively the efficacy of serenoa repens extract in the prevention of chronic prostatitis recurrences as an adjuvant to standard antibiotic therapy. According to their results serenoa repens extract improved both subjective [International Prostate Symptom Score (IPSS) and QoL scale] and objective symptoms (absence of the disease progression and adverse effects and enhancement of the erectile function).[18]

Magri and colleagues found a 94% symptoms regression rate and improved QoL in patients who underwent one or more cycles of combination therapy (ciprofloxacin/ azithromycin, alpha-blocker and serenoa repens extract) after an extended follow-up of 30 months.[19] The cumulative eradication rate of this study - calculated on a total of 137 enrolled patients - was 83.9%, however it is unknown to which extend this result is due to serenoa repens extract administration. Of note, Kulchavenia and colleagues found a 4-fold microbiological eradication rate for E. coli in the combination treatment group (sparfloxacin and serenoa repens extract) versus control (sparfloxacin only), and a 2-fold microbiological eradication rate for chlamydia and ureaplasma.[20]

Based on the above we expect the effectiveness of phytotherapeutics in an array of symptoms related to prostatitis to depend on the presence of prostatic hypertrophy, any preexisting obstruction, co-administered treatments and the duration of treatment. This hypothesis explains the differences between the present study and what has been discussed above. However, the small number of patients included in the above mentioned studies as well as differences in methodology

Table 2. Differences in overall outcome between study groups in first and second follow-up visits.

Follow-up Visits	Number		Mean		Standard Deviation		*P* Value
	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	
First	72	72	0.5139	0.56940	0.919170	0.81925	.342
Second	72	72	0.3056	0.3750	0.57259	0.63772	.375

and outcomes render the drawing of conclusions problematic.

This study has some limitations. The most prominent one is the relatively small sample size and this is probably the reason why we found no significant relationships from the data. In fact statistical tests normally require a larger sample size to ensure a representative distribution of the population and to be considered representative of groups of people to whom results will be generalized or transferred. Another limitation of this study is the use of various antimicrobial agents and of two different phytotherapeutic agents. However; there is no evidence of synergistic antibacterial effect of phytotherapeutic agents while both saw palmetto and pygeum africanum have similar properties and comparable efficacy. Therefore it is not expected that this limitation eventually matter and, if so, to a limited extent.

In this study we haven't associate the bacterial virulence with the outcome, however currently there is no evidence of an association between bacterial virulence and phytotherapeutic agents' effect. In the light of lack of prior research studies on the topic, this limitation can serve as an important opportunity for further research.

CONCLUSION

Although, phytotherapy seems to be effective in the treatment of pain symptoms in chronic bacterial prostatitis, results from the existent studies are conflicting. On the other hand, conditions such as chronic bacterial and chronic non-bacterial prostatitis and prostatic hypertrophy overlap, many of the symptoms are common, while conditions and diseases of organs other than the prostate can contribute towards the presentation or deterioration of these symptoms. More randomized placebo-controlled studies are required to substantiate safer conclusions.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Cheah PY, Liong ML, Yuen KH, et al. Chronic prostatitis: symptom sur-vey with follow-up clinical evaluation. Urology. 2003;61:60-4.
2. Nickel JC, Elhilali M, Vallancien G. ALF-ONE Study Group. Benign prostatic hyperplasia (BPH) and prostatitis: prevalence of painful ejaculation in men with clinical BPH. BJU Int. 2005;95:571-4.
3. Fall M, Baranowski AP, Elneil S, et al. EAU guidelines on chronic pelvic pain. Eur Urol. 2010;57:35-48.
4. Collins MM, Stafford RS, O›Leary MP, Barry MJ. How common is prostatitis? A national survey of physician visits. J Urol. 1998;159:1224-8.
5. Nickel JC, Moon T. Chronic bacterial prostatitis: an evolving clinical enigma. Urology. 2005;66:2-8.
6. Levin RM, Das AK. A scientific basis for the therapeutic effects of Pygeum africanum and Serenoa repens. Urol Res. 2000;28:201-9.
7. Dreikorn K, Berges R, Pientka L, Jonas U. Phytotherapy of benign prostatic hyperplasia. Current evidence-based evaluation Urologe A. 2002;41:447-51.
8. Wang X, Lin WJ, Izumi K, et al. Increased infiltrated macrophages in benign prostatic hyperplasia (BPH): role of stromal androgen receptor in macrophage-induced prostate stromal cell proliferation. J Biol Chem. 2012;287:18376-85.
9. Hill B, Kyprianou N. Effect of permixon on human prostate cell growth: lack of apoptotic action. Prostate. 2004;61:73-80.
10. Marks LS, Hess DL, Dorey FJ. et al. Tissue effects of saw palmetto and finasteride: use of biopsy cores for in situ quantification of prostatic and rogens. Urology. 2001;57:999-1005.
11. Latil A, Libon C, Templier M. et al. Hexanic lipidosterolic extract of Serenoa repens inhibits the expression of two key inflammatory mediators, MCP-1/CCL2 and VCAM-1, in vitro. BJU Int. 2012;110:E301-7.
12. Papaioannou M, Schleich S, Prade I, et al. The natural compound atraric acid is an antagonist of the human androgen receptor inhibiting cellular invasiveness and prostate cancer cell growth. J Cell Mol Med. 2009;13:2210-23.
13. Wadsworth T, Carroll J, Mallinson R. et al. Saw Palmetto extract suppresses Insulin-Like Growth Factor-I signaling and induces stress-activa ted protein kinase/c-Jun N-terminal kinase phosphorylation in human prostate epithelial cells. Endocrinology. 2004;145:3205-14.
14. Iglesias-Gato D, Carsten T, Vesterlund M, Pousette A, Schoop R, Norstedt G. Androgen-independent effects of Serenoa repens extract (Prostasan®) on prostatic epithelial cell proliferation and inflammation. Phytother Res. 2012;26:259-64.
15. Carani C, Salvioli V, Scuteri A, et al. Urological and sexual evaluation of treatment of benign prostatic disease using Pygeum africanum at high doses. Arch Ital Urol Nefrol Androl. 1991;63:341-5.
16. Cai T, Mazzoli S, Bechi A. et al. Serenoa repens associated with Urtica dioica (ProstaMEV) and curcumin and quercitin (FlogMEV) extracts are able to improve the efficacy of prulifloxacin in bacterial prostatitis patients: results from a prospective randomised study. Int J Antimicrob Agents. 2009;33:549-53.
17. Pavone C, Abbadessa D, Tarantino ML, et al. Associating Serenoa repens, Urtica dioica and Pinus pinaster. Safety and efficacy in the treatment of lower urinary tract symptoms. Prospective study on 320 patients. Urologia. 2010;77:43-51.
18. Aliaev IuG, Vinarov AZ, Demidko IuL, Spivak LG. Treatment of chronic prostatitis in prophylaxis of prostatic adenoma. Urologiia. 2012;2:39-40.
19. Magri V, Trinchieri A, Pozzi G. et al. Efficacy of repeated cycles of combination therapy for the eradication of infecting organisms in chronic bacterial prostatitis. Int J Antimicrob Agents. 2007;29:549-56.
20. Kulchavenia EV, Breusov AA, Brizhatiuk EV, Kholtobin DP. Approaches to raising efficacy of treatment of patients with chronic prostatitis associated with intracellular infections. Urologiia. 2010;6:55-8.