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ORIGINAL PAPER

Efficacy of Palmitoylethanolamide, Epilobium and Calendula suppositories for the treatment of patients with chronic prostatitis/chronic pelvic pain syndrome type III

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Summary *Objective: The management of chronic prostatitis/chronic pelvic pain syndrome type III (CP/CPPS) has been always considered complex due to several biopsychological factors underlying the disease. In this clinical study, we aimed to evaluate the efficacy of the treatment with Palmitoylethanolamide, Epilobium and Calendula extract in patients with CP/CPPS III.*

Materials and methods: From June 2023 to July 2023, we enrolled 45 consecutive patients affected by CP/CPPS type III in three different institution. We included patients aged between 18 and 75 years with symptoms of pelvic pain for 3 months or more before the study, a total National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) score ≥ 12 point and diagnosed with NIH category III, according to 4-glass test Meares-Stamey test. Patients were then allocated to receive rectal suppositories of PEA, Epilobium and Calendula, 1 suppository/die for 1 month. All patients have been tested with standard urinalysis in order to assess urinary leukocytes (U-WBC).

The primary endpoint of the study was the reduction of NIH-CPSI. The secondary outcomes were the change of peak flow, post-void residual (PVR), IIEF-5, VAS score, PSA and decrease of U-WBC.

Results: A total of 45 patients concluded the study protocol. At baseline, the median age of all the patients included in the cohort was 49 years, the median PSA was 2.81 ng/ml, the median NIH-CPSI was 18.55, the median IIEF-5 was 18.27, the median U-WBC was 485.3/mmc, the median VAS score was 6.49, the median PVR was 26.5 ml and the median peak flow was 16.3 ml/s. After 1 month of therapy we observed a statistically significant improvement of NIH-CPSI, U-WBC, PSA, IIEF-5, peak flow, PVR and VAS.

Conclusions: In this observational study, we showed the clinical efficacy of the treatment with PEA, Epilobium and Calendula, 1 suppository/die for 1 month, in patients with CP/CPPS III. The benefits of this treatment could be related to the reduction of inflammatory cells in the urine that could imply a reduction of inflammatory cytokines. These results should be confirmed in further studies with greater sample size.

KEY WORDS: *Chronic prostatitis; Chronic pelvic pain syndrome; Palmitoylethanolamide; Epilobium; Calendula*

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INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) stands as one of the prevalent conditions affecting men, often related with *benign prostatic hyperplasia* (BPH), posing significant financial burdens on healthcare systems (1-4). Despite its prevalence and the progress in treatment of BPH (5), the understanding of CP/CPSS underlying mechanisms remains incomplete due to diverse risk factors and associated conditions. Psychological factors and various triggers, such as infection or inflammation, can exacerbate CP/CPPS mechanisms, ultimately impacting patients' *quality of life* (QoL) and psychological well-being (6). Consequently, treatment approaches vary and may not consistently yield clinical efficacy, as shown by the variability in reported treatment effects across case series and controlled trials, often influenced by placebo effects or publication biases (7). Among the spectrum of therapies, some new treatments emerged in last years, such low-intensity shockwave therapy and acupuncture (8, 9) although there is not enough strong evidence to adopt these therapies in clinical practice. The core of treatment of CP/CPSS is still phytotherapy, or herbal medicine, particularly in alleviating pain and enhancing QoL, alongside mild anti-inflammatory effects.

Additionally, rectal therapies involving corticosteroids have shown promise in CP/CPPS patients, with beclomethasone di-propionate suppositories demonstrating a favorable safety profile and efficacy in ameliorating storage symptoms and clinical findings associated with lower urinary tract inflammation (10). In a previous study we demonstrated the efficacy of *Curcumina* and *Calendula* suppositories for the treatment of patients with chronic prostatitis/chronic pelvic pain syndrome type III (11). However, there is a growing body of evidence regarding the therapeutic benefits of Palmitoylethanolamide and *Epilobium* on BPH and CP/CPSS, due their anti-inflammatory effect and inhibition on NF-KB (12, 13). Based on these premises, the aim of this study is investigating the efficacy of *Palmitoylethanolamide*, *Epilobium*, *Curcumina* and *Calendula* suppositories for the treatment of patients with chronic prostatitis/chronic pelvic pain syndrome type III.

Materials and methods

From June 2023 to July 2023, we enrolled 45 consecutive patients affected by CP/CPPS III in three different institutions. Inclusion criteria were age between 18 and 75 years old, symptoms of pelvic pain for 3 months or more before the study according to *European Association of Urology* (EAU) guidelines, a negative 4-glass test Meares-Stamey test and a total *National Institutes of Health Chronic Prostatitis Symptom Index* (NIH-CPSI) score ≥ 12 point. Patients diagnosed with NIH category IIIA and IIIB using the PPMT (pre- and post-massage test) have been enrolled. Category IIIA refers to the presence of *white blood cells* (WBC) after a prostate massage urine specimen (VB3) (WBC in VB3 > 10/hps). Category IIIB refers to patients with pelvic pain with no evidence of inflammation on VB3. Exclusion criteria were urinary tract infection, urethritis, *sexually transmitted disease* (STD), treatment with phytotherapeutic agents, alpha-blockers or antibiotics, urogenital cancer. At baseline subjects underwent uroflowmetry to evaluate the peak flow and the *post void residual* (PVR), they filled out the *International Index of Erectile Function* questionnaire (IIEF-5), the NIH-CPSI and the *visual analogue score* (VAS). PSA test and *urinary white blood cells count* (U-WBC) have also been performed. All subjects gave written informed consent before entering the study, which was conducted in accordance with the Declaration of Helsinki.

Patients underwent treatment consisting of rectal suppositories of PEA, *Epilobium* and *Calendula* (Riflog CM), 1 suppository/die for 1 month.

Statistical analysis

The primary endpoint of the study was the reduction of NIH-CPSI. The secondary outcomes were the change of U-WBC, peak flow, IIEF-5 and VAS. The Student T-Test was used for comparisons in the distribution of nonnormal variables between baseline and follow-up. A two-sided p-value < 0.05 was considered statistically significant in all the tests used. Statistical analyses were performed using STATA®16 software (*StataCorp LLC, US*).

Results

We enrolled 45 patients in study, at baseline, average age was 48.75 (S.D. 13.44; IQR 29-68), average NIH-CPSI score was 18.55 (S.D. 3.71; IQR 12-24), average IIEF5 score was 18.27 (S.D. 5.18; IQR 11-25), average peak flow was 16.3 ml/s (S.D. 7.78; IQR 8.6-31), average PVR was 26.5 ml (S.D. 29.5; IQR 0-70), average VAS score was 6.49 (S.D. 1.55; IQR 4-8), average U-WBC was 485.3/mmc (S.D. 407.98; IQR 0-1153), average PSA was 2.81 ng/ml (S.D. 1.76; IQR 0.57-5.4). After 1 month of follow-up, average NIH-CPSI score reduced to 9.36 (S.D. 4.63; IQR 2-15), average IIEF5 score augmented to 19.53 (S.D. 5.46; IQR 11-25), average VAS score reduced to 2.84 (S.D. 1.75; IQR 0-5) and average PSA reduced to 1.74 ng/ml (S.D. 1.26; IQR 0.4-3.8) (Figure 1).

Furthermore, at follow-up average peak flow augmented to17.63 ml/s (S.D. 7.63; IQR 9.4-32), average PVR reduced to 19.48 ml (S.D. 26.83; IQR 0-50), average U-WBC reduced to 306.85/mmc (S.D. 359.65; IQR 0-837) (Figure 2). All the changes were statistically significant since the mean difference in NIH-CPSI score was -9.2 (95%CI -7.57; -10.82, p < 0.05); the mean difference in IIEF5 score was 1.27 (95%CI 0.67; 1.85, p < 0.05); the mean difference in VAS score was -3.65 (95%CI -4.23; -3.07, p < 0.05); the mean difference in peak flow was 1.34 (95%CI 0.52; 2.15, p < 0.05); the mean difference in PVR was -7.05 (95%CI -9.92; -4.17, p < 0.05); the mean difference in U-WBC score was -178.45 (95%CI -225.39; -131.52, p < 0.05); the mean difference in PSA score was -1.06 (95%CI -1.40; -0.72, p < 0.05).

Figure 1.
NIH-CPSI score, IIEF-5 score, VAS score and PSA at baseline and follow-up.

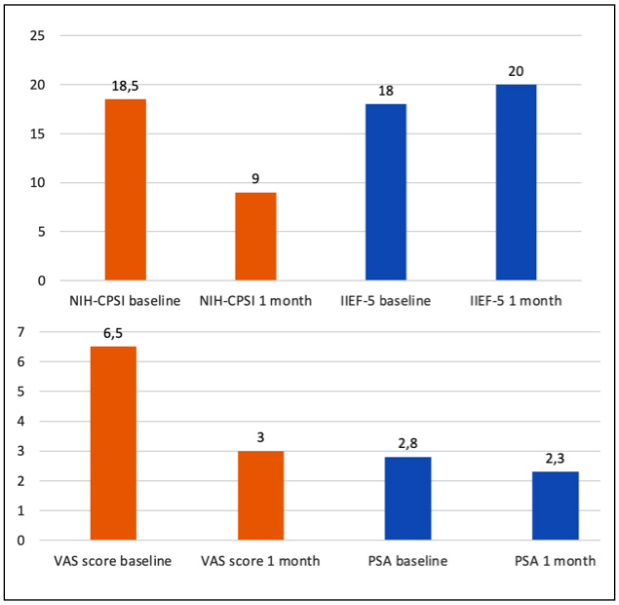
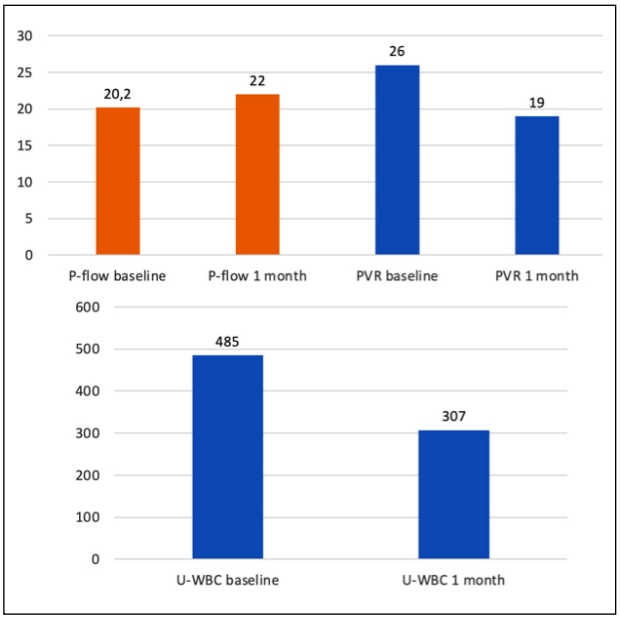


Figure 2.
Peak flow, post-void residual and U-WBC at baseline and follow-up.



Discussion

CP/CPPS stands as one of the most common ailments affecting males under the age of 50. It is distinguished by a diverse range of risk factors and subsequent clinical presentations. Various treatments, such as alpha-blockers, antibiotics, anti-inflammatory drugs, and other agents like finasteride, phytotherapy, and gabapentinoids, are regularly employed. Nonetheless, the effectiveness of these treatments remains contentious due in part to the limited size and statistical power of many clinical trials assessing their efficacy (14).

In this study, we demonstrated that the utilization of rectal suppositories containing of PEA, *Epilobium* and *Calendula* (Riflog CM) proved to be clinically effective in alleviating pain, improving voiding symptoms, and enhancing urinary flow after one month of treatment; on the other hand, we demonstrated the reduction of U-WBC and PSA values, as an effect of reducing inflammation. The underlying rationale behind such therapy likely stems from its anti-inflammatory properties, which could exert multiple beneficial effects.

The extract from *Calendula* officinalis flowers demonstrated significant anti-inflammatory properties. In a chronic inflammation model using formalin, administration of *Calendula* extract at doses of 250 and 500 mg/kg body weight resulted in inhibitions of 32.9% and 62.3%, respectively, compared to control groups. Additionally, *Calendula* extract significantly suppressed TNF-alpha production by macrophage cultures treated with *lipopolysaccharide* (LPS). Furthermore, the extract significantly inhibited the elevated levels of pro-inflammatory cytokines IL-1beta, IL-6, TNF-alpha, and IFN-gamma, as well as the acute phase protein *C-reactive protein* (CRP) induced by LPS injection in mice. Treatment with the extract also led to inhibition of LPS-induced *cyclooxygenase-2* (Cox-2) levels in mice spleens (15).

The analgesic effects of PEA are exerted through various pathways. PEA directly targets PPARα and GPR55 receptors and indirectly influences CB1, CB2, and TRPV1 receptors. It suppresses inflammation by hindering MC activation, downregulating mediators like NGF, COX-2, TNF-α, and iNOS, and inhibiting microglia and astrocyte activation. In chronic inflammatory conditions, this enables PEA to maintain peripheral nerve structure, decrease endoneural edema, and mitigate macrophage infiltration.

Currently, PEA has a recognized role as an analgesic in various clinical conditions, such as headache and menstrual pain (16).

Epilobium has a recognized role in BPH treatment due to his anti-inflammatory effects inhibiting COX and NF-kB (12, 17). Some bias of our study are that it is not a randomized trial, the small sample size and the lack of comparison with placebo, however our previous randomized trial has demonstrated the superiority of phytotherapy versus placebo in similar setting; some strengths are the investigations of new compounds for CP/CPPS treatment, the "*real life*" design and the consideration of objective indicators of urinary inflammation such as U-WBC.

In conclusion we demonstrated the efficacy of rectal suppositories with PEA, *Epilobium* and *Calendula* (Riflog CM) for the treatment of CP/CPPS, in terms of pain and urinary symptoms; these results should be confirmed in further studies with, perhaps, greater sample size and randomized placebo-controlled trial design.

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