

Cannabidiol-hyaluronic acid combination delivered rectally for attenuating abacterial prostatitis symptoms: Single-arm open-label pilot clinical trial

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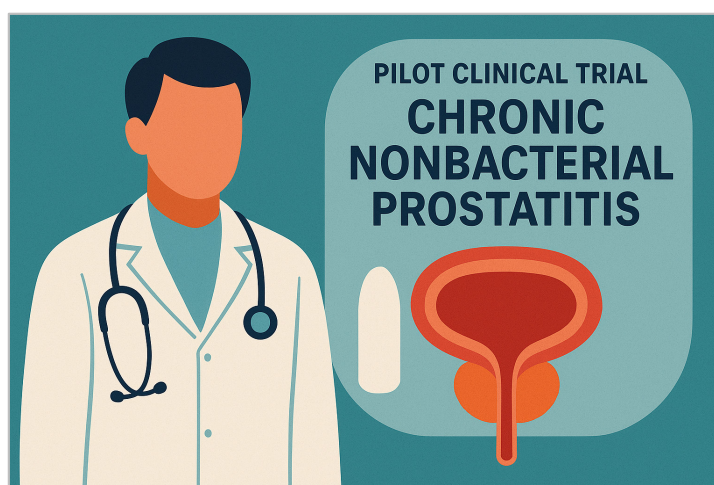
Background. Chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a prevalent urological disorder with a significant impact on quality-of-life. This study assessed the effects of rectal administration of dual cannabidiol (CBD)/hyaluronic acid (HA)-based therapy in men with CP/CPPS.

Methods. A single-arm, open-label pilot trial on 16 men (24–49 years) with CP/CPPS (NIH Chronic Prostatitis Symptom Index [NIH-CPSI] >10, pain subscore ≥4). The participants self-administered rectal CANNEFF® suppositories containing CBD (100 mg) and HA (6.6 mg) as active ingredients, nightly for 30 days. Outcome measures included changes in NIH-CPSI total score, International Prostate Symptom Score (IPSS), and International Index of Erectile Function (IIEF-5). Safety and tolerability were also assessed.

Results. The median baseline NIH-CPSI score was 24.5 points (range 11, 39) decreasing to a median 20.0 (range 2, 26) at day 30 ($P=0.003$), with a median reduction of 7.0 points (range –20.0, 6.0). Symptom improvement was found in 81.3 % (13/16) of participants. The IPSS total score decreased from a median of 14.0 points (range 4, 32) to a median 12.0 (range 3, 18) ($P=0.033$), with voiding symptoms showing the largest improvement. The IIEF-5 score increased modestly but without statistical significance. No adverse events were reported.

Conclusions. The administration of the suppositories with CBD/HA action demonstrated potential symptom relief in CP/CPPS with a favourable tolerability profile. A more nuanced analysis of NIH-CPSI changes and IPSS and IIEF-5 data suggests a clinically meaningful benefit for most participants.

THE EFFECTS OF RECTAL ADMINISTRATION OF DUAL CANNABIDIOL (CBD)/HYALURONIC ACID(HA)-BASED THERAPY IN MEN WITH CHRONIC ABACTERIAL PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME (CP/CPPS)



The administration of the suppositories with CBD/HA action demonstrated potential symptom relief in CP/CPPS with a favourable tolerability profile.

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Graphical Abstract

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INTRODUCTION

Chronic non or abacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS), classified as National Institutes of Health (NIH) category III prostatitis, International Classification of Diseases, 10th revision code N41.1, is the third most common urogenital diagnosis in men, following benign prostatic hyperplasia and prostate cancer, with an estimated prevalence of up to 8.2% (ref.¹). Clinically, CP/CPPS presents with persistent pelvic pain, the hallmark symptom, but patients also report lower urinary tract symptoms (LUTS) and sexual dysfunction. These factors collectively have a negative impact on quality of life². Psychological sequelae, include anxiety, stress and depression exacerbating the patient burden.

Despite its considerable socioeconomic impact, no definitive treatment consensus exists for CP/CPPS. Standard interventions (antibiotics, alpha-blockers, non-steroidal anti-inflammatory drugs) frequently yield only partial or inconsistent responses, prompting investigation of new approaches that address the condition's multifactorial pathogenesis and reduce reliance on antibiotics³. Evidence suggests that inflammation and oxidative stress contribute to the pathogenesis, supporting the potential utility of antioxidant and barrier-forming therapies⁴.

Cannabidiol (CBD), a phytocannabinoid from *Cannabis sativa*, has demonstrated anti-inflammatory and analgesic properties in preclinical models⁵. However, its oral bioavailability is limited (~6%) due to extensive hepatic first-pass metabolism⁶. Despite promising findings, there is a paucity of relevant research on CBD, particularly for standardized pharmaceutical formulations. Most existing studies have focused on *cannabis flos* or extracts, which exhibit batch-to-batch variability common in natural products. As a result, studies using non-standardized products have limited reproducibility and translational value. Second, hyaluronic acid (HA), a sugar molecule naturally found in the skin, forms a mucosal barrier that reduces local irritation and inflammation⁷. CBD and HA delivered together and transrectally offer a unique approach targeting directly, pelvic tissues and bypassing the hepatic metabolism.

We carried out a single-arm pilot study using rectal CANNEFF[®] suppositories containing CBD and HA in men with diagnosed CP/CPPS to assess their clinical efficacy and tolerability.

MATERIALS AND METHODS

Study design

This was a prospective, single-centre, open-label pilot trial conducted at the Department of Urology, University Hospital Olomouc Czech Republic between December 2022 and April 2024. The institutional ethics committee approved the protocol (No. 176/22) before patient enrolment, and the study was registered at ClinicalTrials.gov (NCT06968910). All participants provided a priori written informed consent. The trial conformed to the latest

Declaration of Helsinki and adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for single-arm pilot studies. A CONSORT-style flow diagram is presented in Fig. 1.

Participants

Men aged 18–50 years were eligible if they reported pelvic pain for ≥ 3 months in the past 6 months, had a National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) total score > 10 with a pain subscore ≥ 4 , and clinically and laboratory diagnosed CP/CPPS. Exclusion criteria included confirmed genitourinary infections (e.g., *Escherichia coli*, *Enterococcus faecalis*, *Chlamydia spp.*), recent antibiotic use (within 6 months), cannabis use, alpha-blockers or phytotherapeutics in the preceding 4 weeks, history of pelvic trauma, surgery or radiotherapy, neurogenic bladder, post-void residual > 50 mL, or psychiatric disorders.

Participant recruitment and screening

Potential participants were primarily referred from outpatient clinics or through general urology consultations at the University Hospital Olomouc, Czech Republic. Upon expressing interest, individuals underwent a preliminary screening to ensure eligibility. Following informed consent, they received a comprehensive medical history review, physical examination (including digital rectal examination), laboratory and microbiological tests (urinalysis, urine and semen culture and serologic testing, urethral swab test was used in case of prevalent urethral symptoms such as burning during micturition, itching in the penis). Blood biochemistry, including C-reactive protein, and complete blood count, were performed. Pelvic and kidney ultrasound was carried out to exclude other confounding urological conditions.

Intervention

Participants self-administered rectal suppositories (CANNEFF[®] SUP, CB21 Pharma Ltd. manufacturer) containing 100 mg CBD and 6.6 mg of HA nightly for 30 consecutive days. They were given verbal and written instructions on correct insertion techniques, including: washing hands before and after administration, adopting a comfortable position (e.g., lying on one side), inserting the suppository 2–3 cm into the rectum, remaining recumbent for a few minutes post-insertion to aid dissolution. Compliance was monitored at follow-up visits by direct questioning about usage frequency and any difficulties encountered.

Outcome measures

Primary endpoint

The primary outcome was the change NIH-CPSI (ref.^{8,9}) total score between baseline (Day 0) and Day 30. The NIH-CPSI is a validated questionnaire assessing three domains relevant to CP/CPPS: pain, urinary symptoms, and quality of life¹⁰. In addition, changes in the NIH-CPSI pain subscore were evaluated to capture the specific impact on pelvic pain.

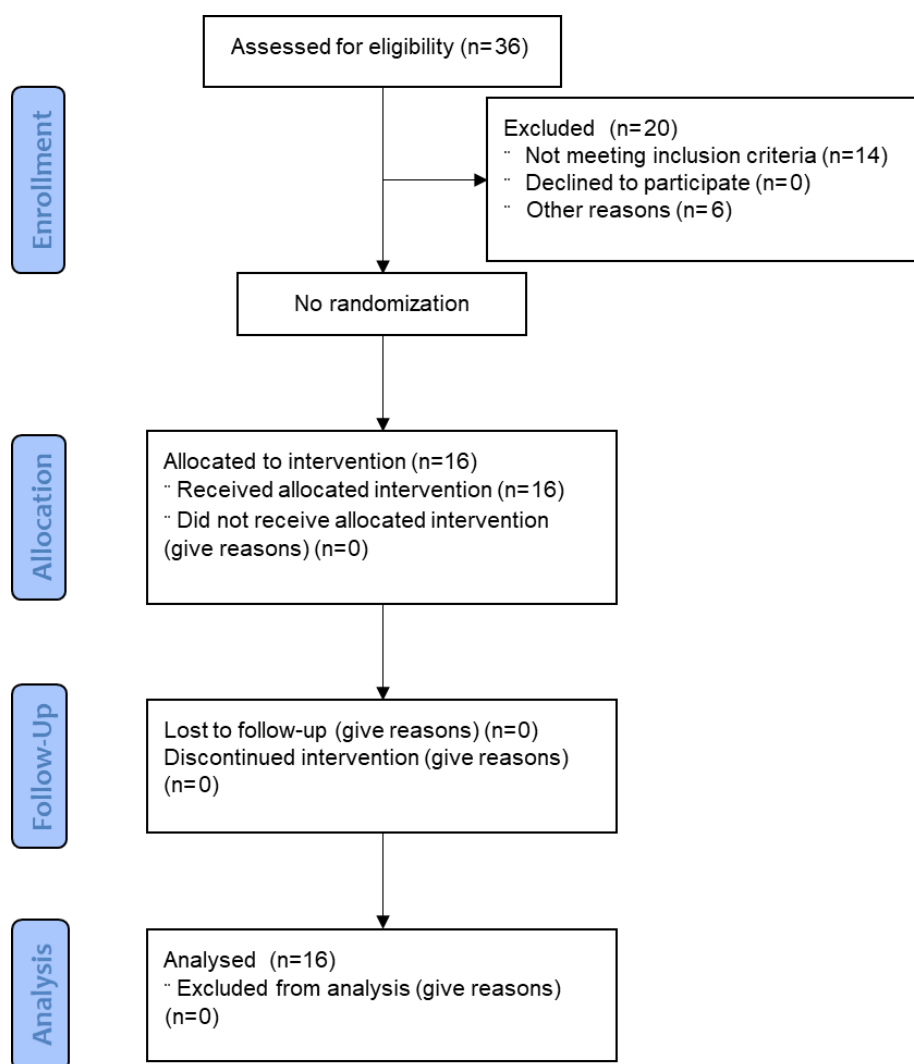


Fig. 1. CONSORT flow diagram on subject enrolment, allocation, follow-up and analysis.

Secondary endpoint

Secondary outcome measures included the International Prostate Symptom Score (IPSS) (ref.^{11,12}) and the five-item International Index of Erectile Function (IIEF-5) (ref.¹³). The IPSS evaluates lower urinary tract symptoms (both storage and voiding), whereas the IIEF-5 provides a brief assessment of erectile function. All questionnaires were administered at baseline and again on Day 30.

Laboratory tests

The standard blood biochemistry (including C-reactive protein) and blood count analysis were conducted at the Department of Clinical Biochemistry and the Department of Haemato-Oncology (University Hospital Olomouc, Czech Republic) to monitor systemic status or pathologies at baseline. Urine and semen cultures were taken in the morning and evaluated at the Department of Microbiology (University Hospital Olomouc, Czech Republic). Semen was obtained by masturbation. Serological tests aiming at determining levels of IgA, IgG, and IgM antibodies against *Chlamydia trachomatis*; *Chlamydia* species were assessed using immunoenzymatic

assay, and levels of IgG and IgM anti-*Mycoplasma pneumonia* antibodies were evaluated by chemiluminescence immunoassay.

Statistical analysis

Data were analysed using software R, ver. 4.5.1 (www.r-project.org). NIH-CPSI, IPSS and IIEF-5 scores were compared between baseline and Day 30 (after treatment) using a two-tailed one-sample non-parametric Wilcoxon test with the significance level set at 5%. Values at the baseline, Day 30 as well as their differences (after treatment; baseline) are presented as medians (ranges) and the differences also graphically as boxplots with horizontally jittered data points. Missing values were not imputed, and all participants who completed the 30-day intervention were included in the final analysis.

RESULTS

Patient flow and baseline characteristics

Thirty-six men were screened for the study. Fourteen were excluded because of confirmed infections. Of

Table 1. Questionnaire results before and after 30-day treatment using suppositories containing CBD and HA for participants with CP/CPPS.

	Before treatment	After treatment	Difference	<i>P</i>
NIH-CPSI total	24.5 (11, 39)	20 (2, 26)	–7 (–20, 6)	0.003
NIH-CPSI pain subscore	12 (6, 20)	8.5 (0, 14)	–4.5 (–13, 4)	0.009
IPSS score	14 (4, 32)	12 (3, 18)	–3.5 (–14, 7)	0.033
IPSS storage subscore	5.5 (0, 13)	5 (1, 8)	–1 (–5, 3)	0.226
IPSS voiding subscore	9.5 (3, 19)	6.5 (0, 12)	–3 (–9, 4)	0.009
IPSS QoL	3.5 (1, 6)	3 (0, 6)	–0.5 (–2, 2)	0.094
IIEF-5	20 (8, 25)	23 (10, 25)	1 (–3, 4)	0.114

Data are presented as median (min, max); NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index; IPSS, International Prostate Symptom Score; IIEF-5, International Index of Erectile Function; QoL, quality of life.

these, seven tested positive for *Escherichia coli*, seven for *Enterococcus faecalis*, three for *Chlamydia* spp., two for *Gardnerella vaginalis*, one for *Gemella haemolysans*, one for *Facklamia hominis*, and one for *Pseudomonas montei*. Some patients had multiple pathogens, accounting for a total organism count exceeding 14. These patients were treated with long-term antibiotics according to the pathogen susceptibility. An additional six men were excluded for not meeting eligibility criteria (two had low pain score, three refused treatment and one had complications associated with surgery for hydrocele). Thus, 16 participants, median age 38 completed the trial. For all of them, the blood biochemistry, blood count analysis and other parameters described in the section Laboratory tests (see above) were within physiological (normal) ranges at baseline.

Primary and secondary outcomes

The primary outcome of the study was the change in the total score of the NIH-CPSI from baseline to Day 30 (Table 1). At baseline, participants had a median NIH-CPSI total score of 24.5, which significantly decreased to 20 by Day 30 ($P=0.003$), corresponding to a median reduction of 7.0 points. The pain subscore also showed significant reduction, with the median score decreasing from 12 (range 6, 20) at baseline to 8.5 (range 0, 14) at Day 30 ($P=0.009$). These improvements are visually represented in Fig. 2A, which includes boxplots for both total and pain scores. Most subject (13/16 = 81.3%) achieved the primary endpoint of reduction in their total NIH-CPSI score. However, three showed either no change or only minor symptom improvement.

Secondary outcomes included changes in the IPSS, the IIEF-5, and treatment safety. The median IPSS decreased from 14.0 at baseline to 12.0 at Day 30 ($P=0.033$).

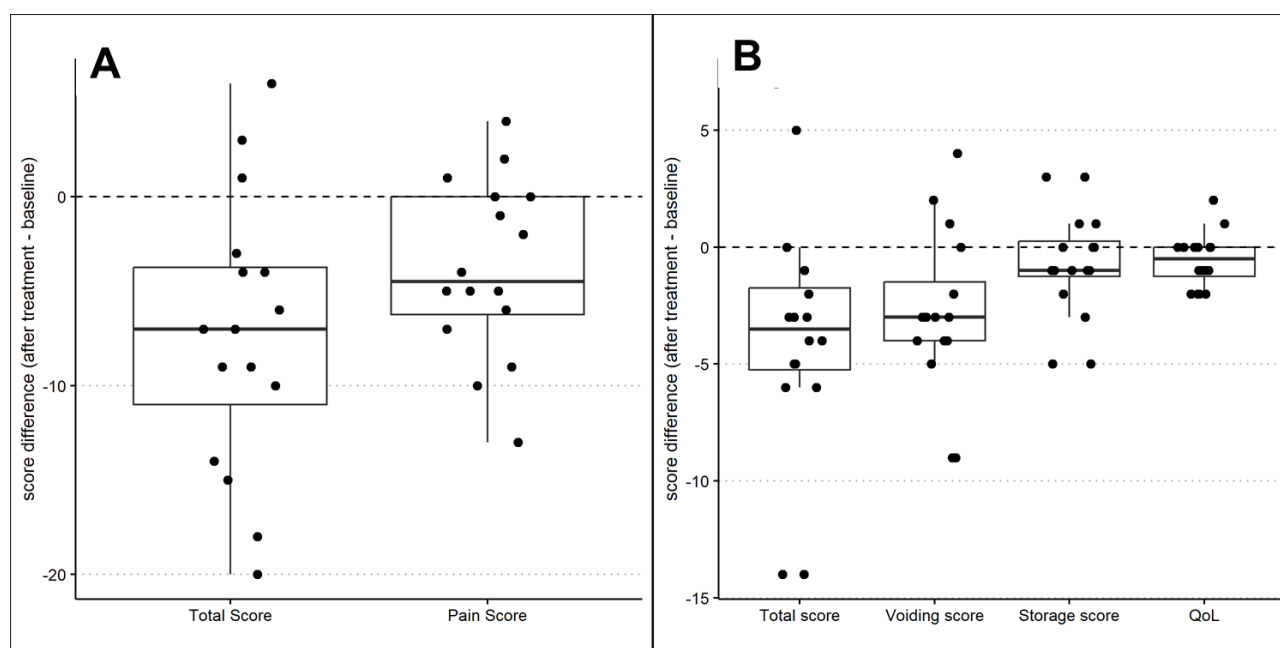


Fig. 2. Box plots showing score differences before and after treatment for (A) NIH-CPSI total and pain NIH-CPSI scores (B) and total and subscores for IPSS; dashed lines represent zero change.

The boxplot depicts five summary statistics – the median, the first and third quartiles and whiskers which extend no further than 1.5 * IQR from the hinge. All values are presented as individual points.

Improvement was most pronounced in the voiding subscale (e.g., weak stream, straining) (Fig. 2B). The median IIEF-5 increased non-significantly from 20 at baseline to 23 at Day 30.

Safety and tolerability

No adverse events were reported throughout the 30-day treatment period. All participants tolerated the suppositories well, with no instances of local irritation, systemic side effects, or withdrawal due to the intervention. Compliance was uniformly high, as all 16 men completed the regimen and reported consistent adherence.

DISCUSSION

The major finding of the study was that the CBD/HA combination delivered rectally was able to improve the quality of life in a sample of men with CP/CPPS.

There was a median 7-point reduction in the overall NIH-CPSI total score, which aligns with improvements ranging from 4 to 7 points that have been reported for other CP/CPPS interventions, such as phytotherapeutics (e.g., quercetin, pollen extracts) or alpha-blockers^{14–16}. For instance, Shoskes et al. demonstrated a 6-point mean drop with quercetin, whereas certain alpha-blocker studies achieved approximately 5–6-point reductions¹⁷. Anti-inflammatory strategies have also been explored, as demonstrated by Zhao et al., who reported that a 6-week course of celecoxib (200 mg/day) led to an approximately 8-point decrease in total NIH-CPSI scores in men with difficult Category IIIA CPPS, although the benefits diminished shortly after discontinuation of therapy¹⁸. Our data not only fall within this range but also highlight the potential efficacy of a non-systemic, intrarectal approach.

The NIH-CPSI pain subscore decreased by a median 4.5 points (baseline median 12; post-treatment median 8.5; $P=0.009$), indicating clinically meaningful relief. This aligns with a meta-analysis of 390 patients with interstitial cystitis/painful bladder syndrome (IC/PBS), where intravesical HA reduced pain by 3.65 points on a 10 cm VAS (95% CI –3.81 to –3.50) (ref.¹⁹). Given the overlap in symptoms and pathophysiology between IC/PBS and CP/CPPS, these findings support the use of HA in urological pain syndromes. Further, CBD provides anti-inflammatory and neuromodulatory effects^{20,21}, while HA restores the urothelial barrier and reduces fascial friction, helping to relieve myofascial pain²². Though not yet tested in combination, their complementary actions suggest at least additive analgesic potential.

In addition to improvements in pain scores, we noted a statistically significant decrease in the IPSS, particularly in the voiding subscale. This suggests that the combination of CBD and HA may also alleviate lower urinary tract symptoms (LUTS), another prominent aspect of CP/CPPS. Similar effect on IPSS score was reported using phytotherapeutics in studies by Presicce et al.¹⁶ and Macchione et al.¹⁴. Although the 5-item IIEF-5 increased modestly from baseline, showing improved erectile functions, it did not reach statistical significance. We can

speculate that larger studies may be needed to clarify whether intrarectal CBD/HA might benefit erectile function. Studies on phytotherapeutics showed only minor improvement in IIEF-5 despite their reported effect on alleviating the symptoms of CP/CPPS (ref.¹⁶).

One of the key considerations in our study was delivering CBD *via* the rectal route, which bypasses extensive first-pass hepatic metabolism and the variable absorption seen with oral administration²³. By minimizing systemic exposure, rectal delivery not only enables higher concentrations of active ingredients to reach the pelvic region but also reduces the likelihood of systemic side effects⁶. In comparison, oral CBD suffers from low (~6%) bioavailability due to hepatic metabolism, often complicating dosing regimens and achieving therapeutic levels.

The suppositories contained water-solubilized HA within the emulsion matrix. HA is widely recognized for forming a local mucosal barrier, reducing friction, and facilitating tissue repair²⁴. By creating a more stable, hydrated environment, HA may alleviate mechanical irritation that contributes to pelvic discomfort in CP/CPPS. Meanwhile, the well-documented antioxidant and cytoprotective properties of CBD can mitigate oxidative stress, downregulate local inflammation, and modulate membrane-bound ion channels^{5,25–27}. Also, previous studies demonstrated the safety of CBD (ref.^{28,29}) and HA (ref.²⁴) in medical applications, suggesting that dual application of these agents may yield additive benefits.

CONCLUSION

In conclusion, rectal CANNEFF[®] suppositories with dual CBD/HA action led to symptom improvement in men with CP/CPPS, with no adverse events observed over 30 days of treatment. Although these findings are encouraging, the single-arm, open-label design with a modest sample size limits definitive conclusion regarding long-term efficacy and comparative advantage. Larger, randomized, double-blind trials with control groups are warranted to confirm these preliminary findings, refine dosing strategies, and explore possible synergy with existing therapies³⁰. As with other new approaches for CP/CPPS, a comprehensive, phenotype-oriented treatment algorithm may ultimately prove most effective³¹.

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Author contributions: VS: conceptualization, methodology, investigation, writing-original draft; VR: methodology; JVR: methodology; JVa: conceptualization, resources, writing-review and editing. All authors read and approved the final manuscript.

Conflict of interest statement: JVa is involved in the scientific board of CB21 Pharma Ltd. The authors have scientific collaboration and financial support from CB21 Pharma Ltd.

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