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CLINICAL TRIAL STUDY

Flower Pollen Extract in Association with Vitamins (Deprox 500®) *Versus Serenoa repens* in Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Comparative Analysis of Two Different Treatments

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Abstract: ***Objective*:** Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) is reported in the literature ranging from 1 to 14.2%. The aim of the present study was to assess the impact on patient's quality of life and symptoms of Flower pollen extract in association with vitamins (Deprox 500®) in comparison with *Serenoa repens* 320 mg (Permixon 320 mg® by Pierre Fabre) in patients with CP/CPPS.

***Methodology*:** All consecutive patients, with a diagnosis of CP/CPPS, referred to our center from January to August 2016, were screened to be enrolled in this single-center, randomized, controlled trial. The main outcome measure was the evaluation of IPSS/NIH-CPSI (International Prostatic Symptom Score/NIH-Chronic Prostatitis Symptom Index) score variation and the assessment of the quality of life and symptoms at the end of the therapy. The second outcome measure was the evaluation of the comorbidity role in the CP/CPPS therapy. 63 patients were analyzed; patients were randomized into two groups: 29 patients were treated with Deprox 500® 2 tablets/day for 6 weeks and 34 patients with *Serenoa repens* 320 mg, 1 tablet/day for 6 weeks.

***Results*:** The mean score variation for IPSS was -12.7 ± 4.3 in the Deprox 500® group and -7.8 ± 4.7 in the *Serenoa repens* group (p=0.0005) while for NIH-CPSI was -17.3±3.1 in the Deprox 500® group and -13.6±4.8 in the *Serenoa repens* group (p=0.0016). By accounting only the symptoms part of NIH-CPSI questionnaire, the mean score variation reported was -11.5±2.5 in the Deprox 500® group and -9.02±4.0 in the *Serenoa repens* group (p=0.009321). Furthermore, analyzing the comorbidity subgroups, in patients with hypertension, the mean IPSS score variation was -14.3±3.2 in the Deprox 500® group and -9.02±4.0 in the *Serenoa repens* group.

***Conclusion*:** In conclusion, in patients with CP/CPPS, Deprox 500® improves IPSS and NIH-CPSI scores up to 74.5% and 84.5% respectively. Furthermore, in patients with hypertension, the antioxidant effect of Deprox 500® reduces the mean IPSS score of 82.7%.

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1. INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome are reported in literature ranging from 1 to 14.2% [1-3]. It is clear that those data do not represent the true prevalence of this clinical condition, due to the significant overlap of symptoms with other diseases, such as benign prostate syndrome or the bladder pain syndrome [4]. The lack of reported data is also related to the unclear classification of this condition not properly defined in the past years [5]. Currently, according to

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the National Institutes of Health [6], prostatitis are classified into four distinct entities. Category I is reported as acute bacterial prostatitis; category II is defined as chronic bacterial prostatitis; category IV is reported as asymptomatic inflammatory prostatitis; category III is called chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and by definition, it is characterized by pelvic pain for more than 3 of the previous 6 months, urinary symptoms and painful ejaculation, without documented urinary tract infections from uropathogens [7].

Based on the fact that there is a proven bacterial infection in only 10% of the cases described as prostatitis [8], most of the remaining 90% should be classified as category III and IV, according to the absence of infection or other pathologies [9]. The pathogenesis of CP/CPPS is still unclear, and until today no single explanation has been found. It seems that many factors are involved in the development of CP/CPPS, such as a single or multiple expositions to initiating factors in susceptible men. Those factors include infectious, genetic, neuromuscular, endocrine, anatomical, immune or psychological mechanisms [10]. An important role seems to be played by the involvement and the chronic damage of the peripheral neuronal system that results in pelvic floor dysfunction in the form of increased pelvic muscle tone [11, 12]. The focus of therapy is pain relief, and many therapeutic measures have been suggested: the use of antibiotics (fluoroquinolones), NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) or alpha-blockers. Although the use of those drugs is associated with a good rate of pain relief (almost 50% after 4 weeks of antibiotics) [13] they are also related to a considerable percentage of side effects. For this reason, in the last years, the research was addressed to find some phytotherapic solutions and, recently, according to the EAU (European Association of Urology) Guidelines, many therapeutic alternatives are recommended [14]. Recently, Cai *et al*. demonstrated that pollen extract in association with vitamins significantly improved the symptoms in patients with non-inflammatory CP/CPPS without severe side-effects [15], even when compared with ibuprofen [16]. From another Italian multicentric study published by Morgia *et al*. [17] the same results regarding the quality of life and pain relief in patients affected by CP/CPPS were shown using *Serenoa repens* extract. The aim of the present study was to assess the impact on the patient's quality of life and symptoms of Flower pollen extract in association with vitamins in comparison with *Serenoa repens*.

2. MATERIALS AND METHODS

This is a single center prospective randomized controlled trial, comparing the efficacy of Flower pollen extract in association with vitamins (Deprox 500®) versus *Serenoa repens* 320 mg in chronic prostatitis/chronic pelvic pain syndrome. All consecutive patients, with a diagnosis of CP/CPPS, referred to our center from January to August 2016 were screened to be enrolled in this study. The trial was performed in accordance with Good Clinical Practice guidelines [18] and with the ethical principles of the Declaration of Helsinki [19]. Written informed consent was obtained from all patients prior to treatment and the diagnosis of the CP/CPPS was done according to the EAU Guidelines 2016 and to the National Institutes of Health (NIH). A placebo arm was not included in this trial, and the lack of placebo-arm was evaluated in the results analysis. The first outcome was the evaluation of IPSS/NIH-CPSI score variation and the assessment of the quality of life and symptoms at the end of the therapy. The second outcome was the evaluation of the role of comorbidity in the CP/CPPS therapy. All adverse events, all the complications and the suspension of therapy were recorded by the authors at follow-up. A clinical failure was defined as persistence of symptoms at the end of therapy and was reported as absence of variation at IPSS/NIH-CPSI. All male patients referred to our center with a CP/CPPS between 18 and 70 years old were evaluated to be enrolled in this trial. They underwent baseline questionnaires (IPSS/NIH-CPSI), urine culture, semen culture, urological examination and uroflowmetry in order to exclude other urological diseases. Patients with medical treatment for LUTS (Lower Urinary Tract Symptoms) such as alpha-blockers or 5-ARIs (5α-Reductase Inhibitors), with major concomitant diseases and with residual urine volume >50 mL were not included in this study. Uroflowmetry was performed at the day one, and all patients with an altered urinary

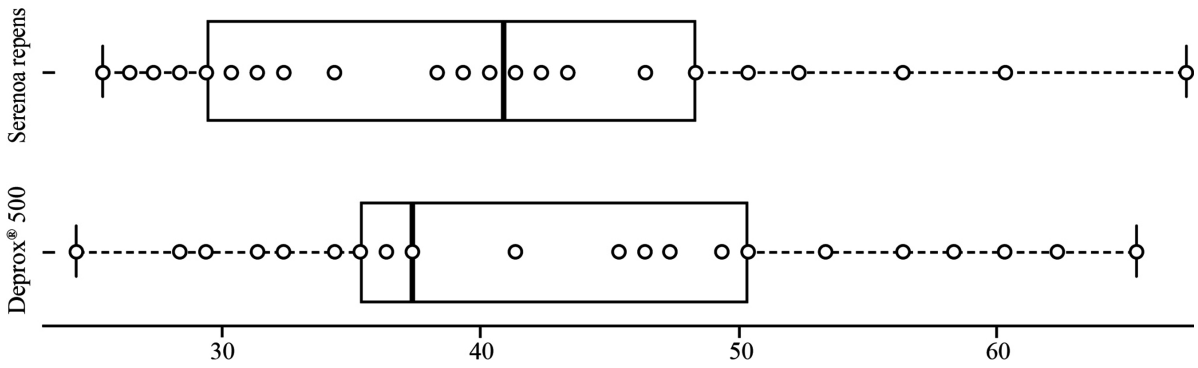

Fig. (1). Age distribution.

flow were excluded from the trial. All patients enrolled in this trial were randomized using a defined schedule and they were assigned at one of the two groups. The first group was treated with Deprox 500® 2 tablets/day for 6 weeks and the second group was treated with *Serenoa repens* 320 mg 1 tablet/day for 6 weeks. According to the company (IDI Integratori Dietetici Italiani) data, Deprox 500® contains Flower pollen extract (500 mg per tablet) in association with vitamins B_1, B_2, B_6, B_9, B_{12} and PP and the efficacy of those components was already shown by several studies (15,16). *Serenoa repens* 320 mg (Permixon 320 mg® by Pierre Fabre) are tablets with fatty acids (laurate, myristate, palmitate, stearate, oleate, linoleate) and phytosterols (campesterol, stigmasterol, β-sitosterol) of the saw palmetto as LSESr (lipidosterolic extract of *Serenoa repens*) [20]. The efficacy and the benefits of using this supplements are shown in many studies [21]. For all patients, a follow-up at 2 and 6 weeks was planned. At first follow-up the patients underwent a clinical examination and presented the results of urine and semen culture. The patients with a positive culture, reporting adverse events or intolerance to the phytotherapy were excluded from the trial. After 6 weeks' follow-up, a post-therapy IPSS/NIH-CPSI score was recorded. For each patient, a folder was created in order to collect all the data regarding demographics, comorbidities, symptoms, culture results, IPSS/NIH-CPSI score at day 1 and IPSS/NIH-CPSI score at the end of therapy. In order to avoid to collect bad quality data, at the diagnosis of the CP/CPPS and at the follow-up validated Italian versions of IPSS and of NIH-CPSI questionnaires were collected by the urologists (Fig. **1**).

2.1. Statistical Analysis

The primary target of the study is the comparison between the reported improvements after treatment with Deprox 500® or *Serenoa repens* in patients affected by CP/CPPS. To quantify the improvements, IPSS and NIH-CPSI surveys were administered and related scores registered.

2.2. Sample Size

The required sample size for the present study was calculated under the following conditions: difference between the groups, 2 ± 1 score points; α error level, 0.05 two-sided; statistical power, 80%. The calculation yielded 2 x 28 individuals per group, but more patients were enrolled to prevent dropouts. Randomization based on order of enrollment associated with a single sequence of random assignments (simple randomization) was performed using a pseudo-random number generator software (R statistical software, version 3.2.5).

2.3. Homogeneity of the Groups

Normality of data was assessed through Shapiro-Wilk normality test. The data resulted, in general, were not normally distributed and therefore comparisons were performed by Two-sample Kolmogorov-Smirnov test or Kruskal-Wallis rank sum test accordingly to applicability. Categorical data were evaluated by Pearson's Chi-squared test or Fisher's Exact test accordingly to applicability.

2.4. Data Analysis

Data were analyzed based on the Intention-to-treat approach, however, no drop out occurred and the excess patients remained in the study. Statistical significance was achieved when $p<0.05$. All

reported *p*-values are two-sided. All calculations were performed using R version 3.2.5 (2016-04-14) - Copyright (C) 2016 The R Foundation for Statistical Computing.

3. RESULTS

A total of 86 patients were enrolled and randomized for this trial. Of those, 3 patients refused to be treated with phytotherapic drugs, 8 patients were lost and 12 patients showed positive semen culture (9) and positive urine culture (3) at first follow-up (2 weeks). A total of 63 patients concluded the therapy and were included in the data analysis. Among those, 29 patients were treated with Deprox 500® and 34 with *Serenoa repens* (Fig. **2**). Patients from 24 to 67 years old were enrolled (mean age was 41.2 years old) and both groups were similar according to age distribution and to all the demographic data recorded. For both groups the presence of the following comorbidity and risk factors were recorded: diabetes, hypertension, obesity, smoke and history of sexual transmitted diseases. For all the comorbidities and risk factors evaluated no differences were reported in both groups (Table **1**). No side effects or intolerance were recorded; only in one patient treated with *Serenoa repens* a case of nausea was registered, and most likely was not related to the therapy. All patients reported at the end of therapy an improvement of the symptoms and Quality of life. In all cases for both groups a pain relief was obtained, recorded as IPSS/NIH-CPSI scores variation. The mean scores recorded in the group treated with Deprox 500® were at enrollment for IPSS 16.3 ± 3.5 and for NIH-CPSI 20.4 ± 2.1. The group treated with *Serenoa repens* reported the following mean scores: IPSS of 13.7 ± 3.8 and NIH-CPSI of 19.6±2.4 at enrollment. At the end of therapy, the mean scores were IPSS of 4.1 ± 2.1 in the group of patients treated with Deprox 500® and IPSS of 5.8 ± 2.3 in the *Serenoa repens* group while the NIH-CPSI mean score was 3.1 ± 3.8 for the Deprox 500® group and 6.0 ± 5.3 for the *Serenoa repens* group. The mean score variation from the start to the end of therapy was for IPSS -12.7 ± 4.3 for Deprox 500® and -7.8 ± 4.7 for *Serenoa repens* (*p*-value=0.0005) while for NIH-CPSI was -17.3 ± 3.1 for Deprox 500® and -13.6 ± 4.8 for *Serenoa repens* (*p*-value= 0.0016) (Fig. **3**). Those data showed a statistically significant difference between the IPSS/NIH-CPSI score variation of the group of patients treated with Deprox 500® compared to the other group treated with *Serenoa repens*. By evaluating singularly the symptoms section of the NIH-CPSI a mean scores of 13.5 ± 1.7 and 12.9 ± 2.0 were recorded at day one in the Deprox 500® and *Serenoa repens* groups respectively. A mean score of 1.9 ± 2.7 and 3.9 ± 3.7 were reported for the same NIH-CPSI section at the end of the therapy in Deprox 500® and *Serenoa repens* group respectively. The mean score variation reported was -11.5 ± 2.5 for Deprox 500® group and -9.02 ± 4.0 for *Serenoa repens* group (*p*-value=0.009321) (Fig. **4**). In order to assess an eventual role of the comorbidities and risk factors on the CP/CPPS therapy we evaluated the same scores variations in all the subgroups, and no differences were recorded for STDs history, diabetes, smoke and obesity. In the sub-group of patients with hypertension the mean IPSS score was 17.3 ± 2.6 at start of therapy and 3.0 ± 1.1 after 6 weeks-treatment in the Deprox 500® group (mean score variation: -14.3 ± 3.2) and 12.6 ± 3.1 and 5.9 ± 2.4 (mean score variation: -6.75 ± 4.0) in the *Serenoa repens* group (*p*-value= 0.0003861) (Fig. **5**). According to the results after six weeks of treatment with Deprox 500® an IPSS score improvement of 74.5% and a NIH-CPSI score improvement of 84.5% was recorded. In the *Serenoa repens* group the score variation was reported as 57.5% for IPSS and 69.2% for NIH-CPSI. Furthermore, in patients with hypertension, the IPSS reduction was of 82.7% in the group treated with Deprox 500® and of 53.3% in the *Serenoa repens* group ($p<0.001$) (Table **2**).

4. DISCUSSION

According to our results, Deprox 500® compared to *Serenoa repens* 320 mg improves the IPSS/NIH-CPSI mean scores when patients are well selected, in fact with the first follow-up at 2 weeks of treatment we excluded from the trial all the patients with bacterial prostatitis and UTIs (Urinary Tract Infections). Furthermore, by analyzing the IPSS/NIH-CPSI variation in all comorbidity sub-groups it was revealed that in patients with hypertension treated with Deprox 500® the IPSS mean score was statistically reduced up to

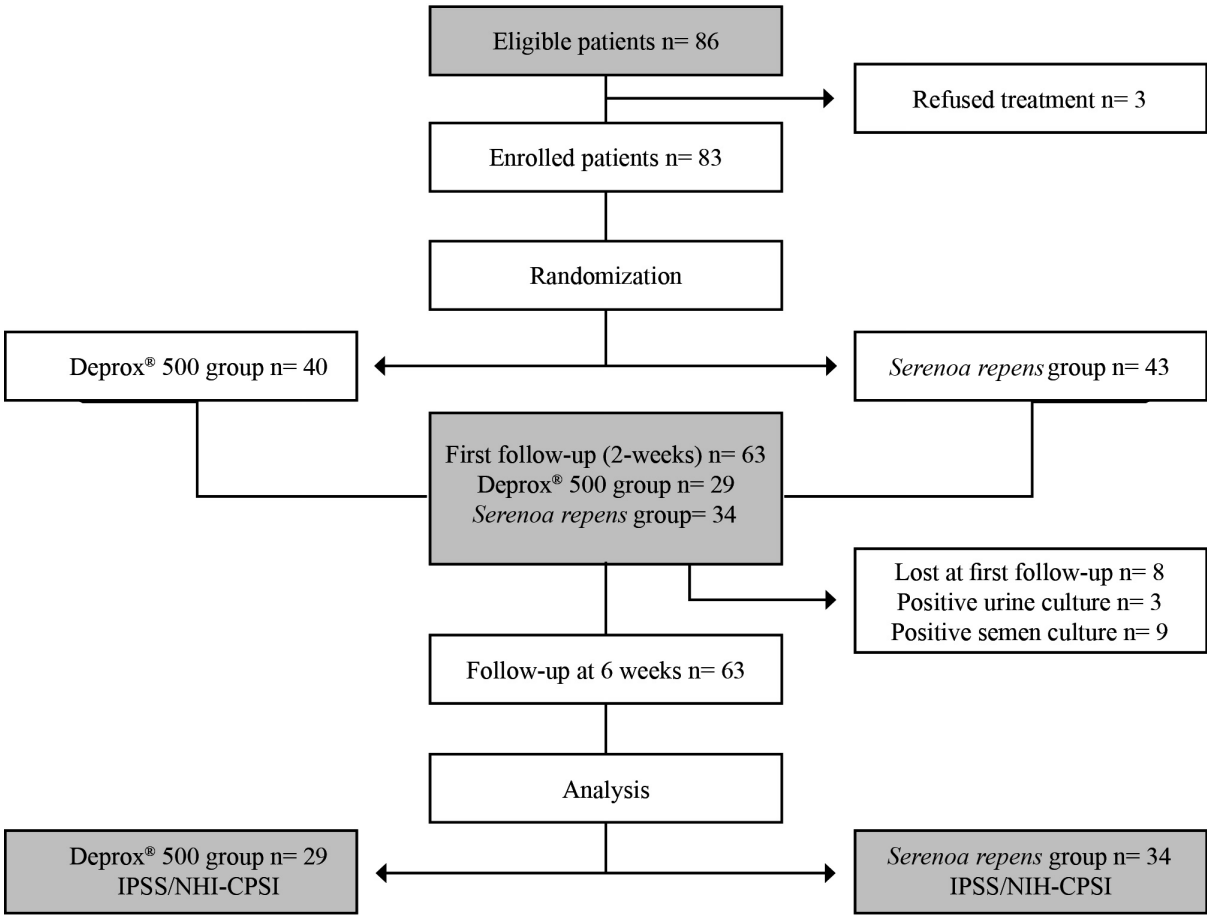

Fig. (2). Study flow-chart.

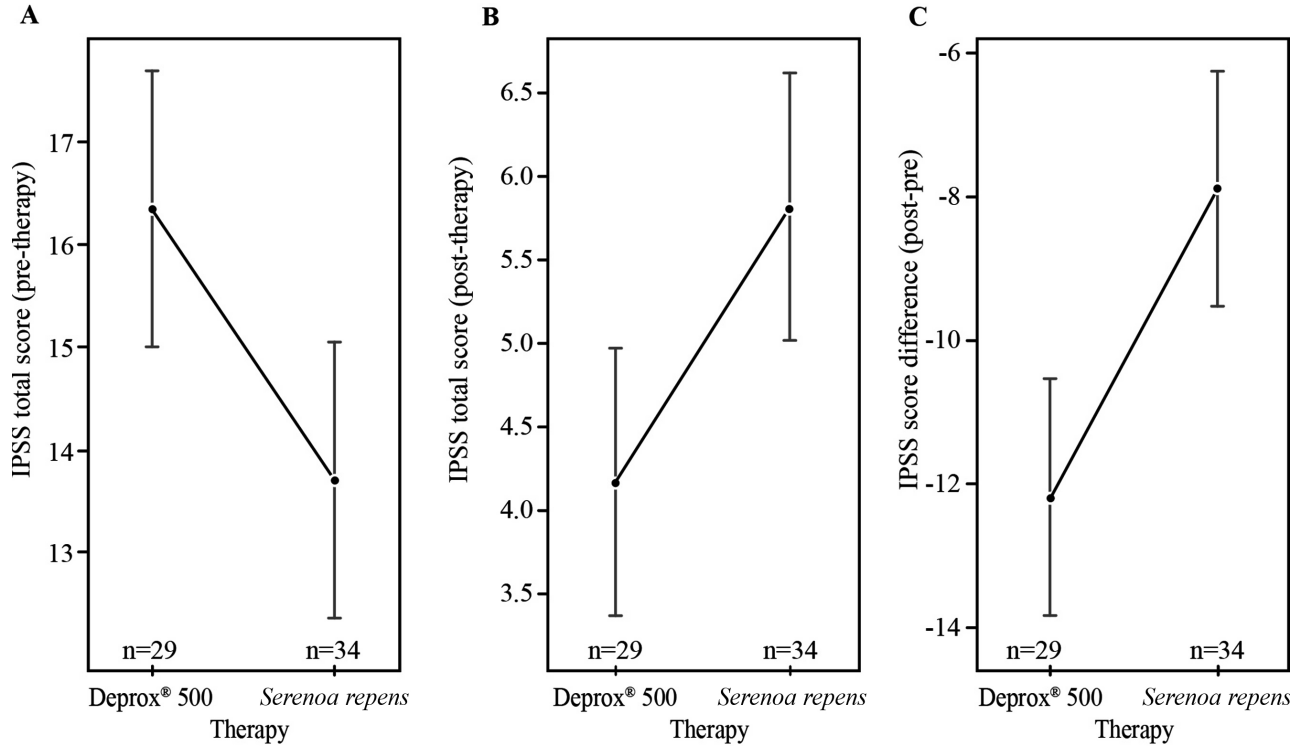

Fig. (3). IPSS score at day one (**A**); IPSS score post-therapy (**B**) and IPSS score variation (**C**).

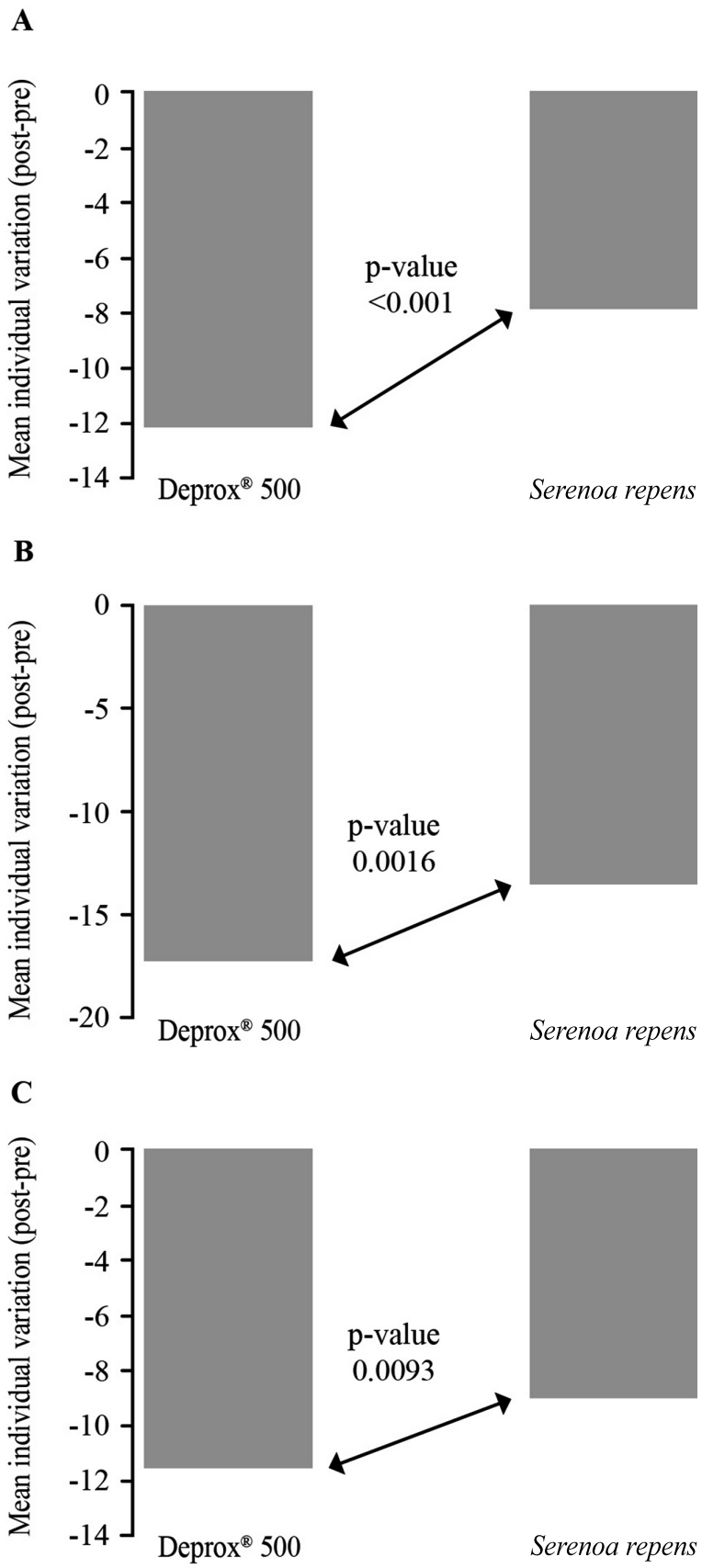

Fig. (4). IPSS score variation (**A**); NIH-CPSI variation (**B**) and NIH-CPSI symptoms variation (**C**).

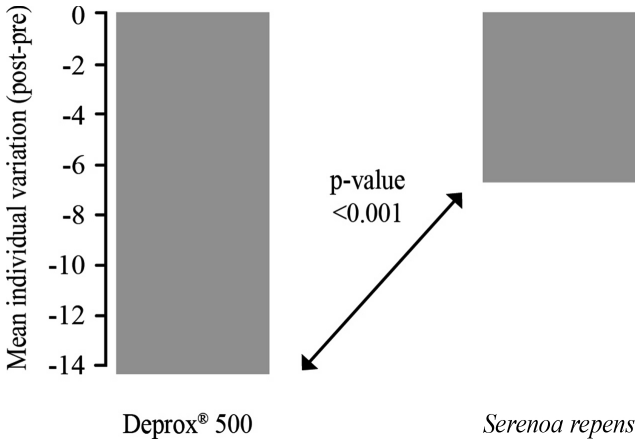

Fig. (5). IPSS score variation in Deprox® 500 hypertension sub-group.

Table 1. Patient's data.

Patient's Data	Deprox® 500	*Serenoa Repens* 320 mg
Mean age[a]	42.7 ± 11.6	39.9 ± 11.6
Diabetes mellitus	2	2
Obesity	4	4
Hypertension	11	12
STDs history	3	7
Smokers	12	13
IPSS day one[a]	16.3 ± 3.5	13.7 ± 3.8
IPSS post-therapy[a]	4.1 ± 2.1	5.8 ± 2.3
NIH-CPSI day one[a]	20.4 ± 2.1	19.6 ± 2.4
NIH-CPSI post-therapy[a]	3.1 ± 3.8	6.0 ± 5.3

[a]Data are presented as the mean ± standard deviation. STD, Sexually Transmitted Diseases; IPSS, International prostatic symptom score; NIH-CPSI, National Institute of Health-Chronic Prostatitis Symptom Index.

Table 2. Results of the IPSS/NIH-CPSI variation in both groups.

Mean Score Variation	Deprox® 500	*Serenoa Repens* 320 mg	p-value
IPSS[a]	-12.7± 4.3	-7.8 ± 4.7	0.0005
NIH-CPSI[a]	-17.3 ± 3.1	-13.6 ± 4.8	0.0016
NIH-CPSI symptoms[a]	-11.5 ± 2.5	-9.02 ± 4.0	0.009321
IPSS hypertension[a]	-14.3 ± 3.2	-6.75 ± 4.0	0.0003861

[a]Data are presented as the mean ± standard deviation. IPSS, International prostatic symptom score; NIH-CPSI, National Institute of Health-Chronic Prostatitis Symptom Index.

82%. In both groups we reported an improvement in QoL and symptoms, analyzing IPSS/NIH-CPSI score, but the mean score variation at the end of the therapy was statistically higher in the Deprox 500® group up to 75% for IPSS and 84% for NIH-CPSI. In literature there are similar trials comparing pollen extract with vitamins versus other drugs or even versus placebo. Rugendorff *et al*. [22] in 1993 showed QoL and LUTS improvements in a group of patients treated with pollen extract up to 78%, and demonstrated a tolerability rate of 97%. A recent review involving 444 men was published

by MacDonald *et al*. [23] and showed that pollen extract is well tolerated and improves overall urological symptoms. Similar results were shown by Iwamura *et al*. [24] in a recent trial reporting a NIH-CPSI reduction in 78% of the patients and an improvement of QoL, pain and symptoms. Wagenlehner *et al*. [25] showed that pollen extract improved symptoms, pain and quality of life after 3 months of treatment compared with the placebo. In 2006 Elist [26], using a double-blind study comparing pollen extract versus placebo, also demonstrated the superiority of pollen extract in terms of improvement in pain score and symptoms. Consistent with all the previous studies Deprox 500® in this trial improved the QoL and symptoms in a therapy protocol of 6 weeks-treatment when compared with *Serenoa repens*. This effect seems to be related to the antioxidant role of the pollen extract and the nerves protection activity of vitamins. As shown in several studies, B vitamins including thiamine (B_1), pyridoxine (B_6) and cyanocobalamin (B_{12}), are effective to cause anti-nociception in experimental animals with acute and chronic pain [27, 28]. In addition, vitamins B_6 and B_{12}, are able to protect neurons from certain injuries [29, 30]. The B vitamins, B_1, B_6 and B_{12} are clinically useful in the treatment of certain painful conditions associated with diabetic polyneuropathy [31]. With those data we hypothesized that the significant symptoms and QoL improvement reported in the Deprox 500® group is due to the protective effect on nerves and the antioxidant activity of pollen extract. This hypothesis is already reported by Cai *et al*. in a study comparing Deprox 500® and Ibuprofen in patients with CP/CPSI (16). Furthermore, in a recent comprehensive analysis including all published clinical trials regarding Deprox 500® the authors collected 6 clinical, non-controlled studies including 206 patients, and 4 RCTs including 384 patients. They showed that the mean response rate in non-controlled studies was 83.6% (62.2-96.0%) and also they demonstrated with the meta-analysis, that flower pollen extract could significantly improve patients' quality of life [OR 0.52 (0.34-0.81); $p = 0.02$] [32]. IPSS/NIH-CPSI also improved in the *Serenoa repens* group, and as reported for Deprox 500®, those results are related to the antioxidant activity of this phytotherapic drug. In 2010, Morgia *et al*. demonstrated the efficacy of *Serenoa repens* plus lycopene and selenium versus *Serenoa repens* alone in patients with CP/CPSSI. They showed a NIH-CPSI score decreasing of 51% in the group treated with *Serenoa repens*, lycopene and selenium versus a decrease of 26% in the group treated only with *Serenoa repens*. Again in this study the significant difference of improvement recorded for both groups was reconducted at the antioxidant activity of selenium and lycopene [17]. Consistent with these results in our study *Serenoa repens* was able to improve the IPSS/NIH-CPSI mean scores, but not as much as Deprox 500®. Most likely this difference is due to the treatment duration, as we know from studies regarding the use of *Serenoa repens* alone in BPH (Benign Prostatic Hyperplasia) treatment, the therapy duration is longer than 6 weeks [33, 34]. In addition to the previous studies, our results demonstrated that hypertension could have a role in treatment of CP/CPSI. In fact, in the group of patients treated with Deprox 500® IPSS is reduced of 82.7% versus the 53.3% recorded in the other group ($p< 0.001$). At present, there are no studies in literature with similar results, and apparently there are no clear hypothesis to explain the enhanced efficacy of Deprox 500® in patients with hypertension. It was demonstrated in several studies that the hypertension associated with diabetes mellitus may accelerate the clinical progression of BPH [35] and the main role seems to be linked to chronic inflammation, that is a candidate mechanism at the crossroad between MetS (Metabolic Syndrome) and BPH/LUTS [36]. Most likely, these patients may obtain greater advantages from this therapy with the antioxidant effects of pollen extract and vitamins B, reducing the general chronic inflammation and improving more the QoL. Recently, in an *ex vivo* study some authors showed the activity of pollen on immortalized prostate cells (PC3), and in rat prostate specimens challenged with *Escherichia coli* lipopolysaccharide (LPS). They found that Graminex pollen was able to reduce radical oxygen species (ROS) production by PC3 cells and MDA, NFkB mRNA and PGE2 levels in rat prostate specimens [37]. This trial presents few limitations that should be considered in order to have a wider perspective of the results; the most important one is represented by the small number of patients enrolled and by the

selected patient populations. The other limitations were the lack of a control group, the single center experience and the fact that it was not a blind study.

CONCLUSION

In conclusion, by taking into account all the limitations of this trial, Deprox 500® when compared to *Serenoa repens* 320 mg, appears to be more effective in patients with CP/CPSI; improving IPSS and NIH-CPSI scores up to 74.5% and 84.5% respectively, after 6 weeks-treatment. Furthermore, in patients with hypertension the antioxidant effect of Deprox 500® on IPSS mean score seems to be enhanced compared to the results with *Serenoa repens*, demonstrating an IPSS score reduction of 82.7%. Larger and multicentric RCTs (Randomized Controlled Trials) are needed to confirm those data.

LIST OF ABBREVIATIONS

5-ARIs	=	5α-Reductase Inhibitors
CP	=	Chronic Prostatitis
CPPS	=	Chronic Pelvic Pain Syndrome
CPSI	=	Chronic Prostatitis Symptom Index
EAU	=	European Association of Urology
IPSS	=	International Prostatic Symptom Score
LUTS	=	Lower Urinary Tract Symptoms
NIH	=	National Institutes of Health
NSAIDs	=	Nonsteroidal Anti-Inflammatory Drugs
QoL	=	Quality of Life

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was not requested for the study because of the fact that we were using already accepted therapy which is performed routinely by all the urologists in absence of new substance but well known phototherapy.

HUMAN AND ANIMAL RIGHTS

No animals were used for the study. All the reported experiments on humans were in accordance with Good Clinical Practice Guidelines and with the ethical principles of the Declaration of Helsinki.

CONSENT FOR PUBLICATION

Written informed consent was obtained from all patients prior to the treatment.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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