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Clinical evaluation of patients with benign prostatic hyperplasia, treated with the natural product Calprost®: a randomized, controlled study

[Evaluación clínica de pacientes con hiperplasia prostática benigna, tratados con el producto natural Calprost®: estudio aleatorizado, controlado]

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Abstract

Context: Benign Prostatic Hyperplasia (BPH) is a common disease that course with Lower Urinary Tract Symptoms (LUTS), mainly in over 50 years-old men. Commonly indicated drugs such as alpha adrenergic-blockers are life-treatment with some adverse reactions. Center for Drug Research and Development produce a microencapsulated lipophilic extract of pumpkin seed oil (Calprost®) with anti-androgenic, anti-inflammatory, antioxidant, antiproliferative and diuretic properties.

Aims: To evaluate the effect and safety of Calprost® in patients with BPH and LUTS.

Methods: A multicenter, randomized, controlled, open exploratory clinical trial was conducted. Two experimental groups, study group (Calprost®, 140 mg daily) (n=81), and control group (terazosin, 2 mg daily) (n=50) were conformed. All the patients were treated during three months. Efficacy was evaluated through International Prostate Symptoms Score (IPSS), residual bladder volume and prostate volume.

Results: Most of the included patients (74.0%) were white skin color and their mean age was 66 yrs. Fifteen patients, nine of them from terazosin group, withdraw the trial voluntarily. A significant reduction in the overall IPSS scale was obtained for both groups. Nevertheless, some obstructive (intermittency, straining) and irritative (frequency, urgency) urinary symptoms decreased more markedly in the Calprost® group being milder. Median residual and prostatic volumes decreased significantly (p=0.048 and p=0.002, respectively) only into the Calprost® group. Most of the adverse events were recorded in the terazosin group (79.4%), where postural hypotension prevailed.

Conclusions: The natural product Calprost® was probed as a successful treatment of patients with BPH/LUTS, being also well-tolerated.

Keywords: Benign prostatic hyperplasia; Calprost®; IPSS; lower urinary tract symptoms, pumpkin seed oil, terazosin.

Resumen

Contexto: La Hiperplasia Prostática Benigna (HPB) es una enfermedad común en hombres mayores de 50 años de edad, que cursa con Síntomas del Tracto Urinario Bajo (STUB). Los tratamientos de por vida con medicamentos bloqueadores alfa-adrenérgicos producen algunas reacciones adversas. El Centro de Investigación y Desarrollo de Medicamentos produce un extracto lipofílico microencapsulado de aceite de semillas de calabaza (Calprost®) con propiedades anti-androgénicas, anti-inflamatorias, antioxidantes, antirproliferativas y diuréticas.

Objetivos: Evaluar el efecto y seguridad del Calprost® en pacientes con BPH/STUB.

Métodos: Se realizó un estudio exploratorio, multicéntrico, aleatorizado, controlado y abierto. Se conformaron dos grupos experimentales, estudio (Calprost®, 140 mg diarios) (n=81), y control (terazosina, 2 mg diarios) (n=50). Todos los pacientes fueron tratados durante tres meses. La eficacia se evaluó mediante la sintomatología urinaria (escala IPSS), volumen vesical residual y volumen prostático.

Resultados: La mayoría de los pacientes (74.0%) fueron blancos, con edad promedio de 66 años. Quince pacientes, nueve de ellos del grupo terazosina, abandonaron el estudio voluntariamente. Hubo disminución significativa de la escala global de síntomas en ambos grupos, aunque algunos de ellos se redujeron notablemente solo en el grupo Calprost®, llegando a ser más ligeros. La mediana tanto del volumen residual (p=0.048) como del prostático (p=0.002) disminuyó de manera significativa solo en el grupo tratado con Calprost®. El porcentaje de eventos adversos presentados fue mayor con la terazosina (79.4%), prevaleciendo la hipotensión postural.

Conclusiones: El producto natural Calprost® fue efectivo en el tratamiento de la HPB/STUB, siendo además bien tolerado.

Palabras Clave: Aceite de semilla de calabaza; Calprost®; hiperplasia prostática benigna; IPSS; síntomas del tracto urinario bajo; terazosina.

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INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is the benign growth of the prostatic gland. BPH is one of the adult man's more frequent pathologies. It is characterized by the presence of obstructive and irritative symptoms of the lower urinary tract that can alter individual's quality of life and to limit their daily activities. The histological prevalence increases from 1/5 men with 50-60 yrs. to 4/5 men with 80 yrs or more (Bushman, 2009; Roehrborn et al., 2011; Roehrborn and McConnell, 2012).

Current pharmacological treatment includes alpha adrenergic-blockers (tamsulosin, doxazosin, alfuzosin, terazosin) since the contractile properties of the prostate are mediated by the activation of alpha 1 adrenergic receptors. Their results are encouraging, although long-term benefits are ignored, and they are not exempt of adverse effects as postural hypotension (Edwards, 2008). On the other hand, 5-alpha reductase inhibitors as finasteride are targeted to decrease epithelial hyperplasia degree, related to the androgens level, but undesired effects as decrease of the libido and impotence could occur. When these treatments are discontinued symptoms usually reappear (Helling, 2008). Finasteride was effective reducing prostate size and its complications, although its impact on symptoms was modest and relatively slow (Tarter and Vaughan, 2006).

Phytotherapy has been used thoroughly in the treatment of BPH. Particularly extracts from herbal medicines *Pygeum africanum*, *Urtica dioica*, *Bixa orellana*, *Curcubita pepo* and *Serenoa repens* (saw palmetto) report successful results in the relief of the prostatic symptoms, and good tolerability (Morán et al., 2013). In the medical practice urologists and Natural and Traditional Medicine specialists frequently indicate ingestion of pumpkin seeds for this affection; most of the times lacking to consider an exact dosage. A Cuban microencapsulated lipophilic extract of pumpkin seed oil (Calprost®) was obtained in the Center for Drug Research and Development (CIDEM, in Spanish) (López-Hernández et al., 2009) and its biological effects were well-proven in experimentation animals (Bellma-Menéndez et al., 2006; Tillán-Capó et al., 2009). The present investigation aims to evaluate the effect and safety of Calprost® in patients with HPB, using as control group patients treated with terazosin.

MATERIAL AND METHODS

A multicenter, randomized, controlled, open-label exploratory study was carried out at the Urology Services of the Clinical-Surgical Hospitals "Dr. Luis Díaz Soto", Havana, Cuba and "Iván Portuondo", Artemisa, Cuba. Another participant institution was the "Joaquín Albarrán" Hospital, Havana, Cuba, where the trial was conducted under uncontrolled conditions since only patients treated with Calprost® were included.

The clinical protocol was approved by the Ethics Committees from each clinical site and by the Cuban Regulatory Authority for this type of products, Institute of Nutrition and Hygiene of Foods (INHA, in Spanish), Havana, Cuba. The study complied with the ethical standards included in the 1964 Helsinki declaration and its later amendments. All patients prior to study enrollment provided their written informed consent to participate.

Patients

Patients to be included in the trial must have been Cuban citizens, between 50 and 80 years-old, with clinical diagnosis of mild or moderate BPH. The diagnosis comprised the presence of Lower Urinary Tract Symptoms (LUTS), either obstructive or irritative, using the International Prostate Symptoms Score (IPSS), physical examination including rectal tact, and ultrasound. Exclusion criteria were: history of allergy, idiosyncrasy or hypersensibility to drugs, acute or uncompensated chronic diseases at entry and history or clinical evidence of some of the following pathologies: urethral stenosis, bladder litiasis, prostate cancer, bladder cancer, bladder diverticulis, neurogenic bladder, neurological disease, diabetes mellitus and medullar lesion. Patients could withdraw the trial voluntarily, due to occurrence of severe adverse reactions, lack of treatment adhesion (>30 doses), by appearance of any exclusion criteria or if they received some disease-modifier drugs concomitantly with Calprost®.

Study design and treatment

Patients where corresponded were distributed according to a computer-generated random number list, stratified by center, to receive, orally, 140 mg of Calprost® (70.0 mg *Cucurbita pepo* L. capsules, excipient, CIDEM, Havana, Cuba) (study group) or daily 2 mg (one tablet) of terazosin (Novatec Laboratories, Medsol Group, Havana, Cuba) (control group). Calprost® dose was chosen based on the whole pharmacological data (see Discussion section) from which the minimum effective dose extrapolated to humans was calculated in a range between 100-150 mg per 70 kg.

Both treatments were given ambulatorily during three months. Patients included in the study group should receive daily, one capsule of Calprost® at 8:00 am and the other at 8:00 pm. Those patients included under uncontrolled conditions received the tested medication with the same schedule. Terazosin was taken at night before bedtime.

The study was open-label since Calprost® and terazosin presentations were not similar. Other treatments could be administered to mitigate adverse events, after medical consent. None of them could affect the results because interactions neither direct effects on the tested variables.

Evaluation

The main efficacy outcome was the presence and severity of urinary symptoms using the IPSS questionnaire (Cam et al., 2003). It is based on the answers to seven questions concerning urinary symptoms; obstructive (incomplete emptying, Intermittency, weak stream, straining) and irritative (frequency, urgency, nocturia). The doctor completed the questionnaire by each question with the patient answer at each visit. Each question allowed the patient to choose one out of six answers (¿how often?) indicating increasing severity of the particular symptom. Answers for the six first symptoms were: not at all, less than 1 in 5 times, less than half the time, about half the time, more than half the time and almost always. Regarding nocturia, possible answers were: none, 1 time, 2 times, 3 times, 4 times and 5 times. The answers were assigned points from 0 to 5. Total score could therefore range from 0 to 35 as follows: mild (symptom score less than or equal to 7), moderate (symptom score range 8-19) and severe (symptom score range 20-35). See Fig. 1 for English version of the Spanish questionnaire applied.

Secondary variables included residual bladder volume, prostate volume and patients' quality of life. Residual urine volume (post-void residual urine) was determined by means of bladder ultrasonography (Aloka ProSound Alpha 5, Tokyo, Japan) after voiding. Residual urine volume reflects bladder and outlet activity during the emptying phase of micturition. The volume of 50 mL constitutes the lower threshold defining abnormal residual urine volume. Meanwhile, prostatic volume was estimated by abdominal ultrasound (Aloka ProSound Alpha 5, Tokyo, Japan). The common procedure one-dimensional measurement was used to calculate the prostatic volume. The prolate ellipsoid formula, multiplying the largest anterioposterior (Height), transverse (Width) and cephalocaudal (Length) prostate diameters by 0.524 ($H \times W \times L \times \pi/6$) was used (Eri, 2002).

Patient's perceived quality of life was classified according to IPSS guideline as: delighted, pleased, mostly satisfied, mixed, mostly dissatisfied, unhappy or terribly wrong (Fig. 1). All these evaluations were done in both groups at entry and at the end of treatment (month 3). Rectal tact was only done for diagnosis purposes.

Additionally patients were classified as responders (therapeutic success) or non-responders (therapeutic failure). Responders were who achieved a decrease in prostate symptoms score and decreased prostate volume and residual urine volume at the end of the study. Patients who experienced an increase in prostate symptoms score, prostate volume and residual urine volume were non-responders. Those patients that voluntarily discontinued treatment, had disease worsening or severe adverse events were also considered as failures.

Safety and tolerability were monitored during the study by means of adverse events control. Events were severe if produce patient's death, threatens patient's life, requires or prolongs hospitalization or produce a significant or persistent disability. The medical terminology for adverse events and their intensity classification (in 5 grades) was applied according to the Common Terminology Cri-

teria for Adverse Events (CTCAE, 2010). The causal relationship was classified as very probable (definitive), probable, possible or remote (doubtful) (Naranjo et al., 1998).

International Prostate Symptom Score (I-PSS)

Patient Name: _____ Date of birth: _____ Date completed _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladders?	0	1	2	3	4	5	
2. Frequency How often have you had to urinary less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

Figure 1. International Prostate Symptoms Score (IPSS) questionnaire, based on American Urological Association (AUA) Symptom Index.

Additionally, blood samples were taken for routine hematological and biochemical determinations before and after treatment. Hematological counts (hemoglobin, hematocrit, leukocytes) and blood chemistry (glycemia, cholesterol, triglycerides, creatinine, urea, liver enzymes, serum albumin, and total protein) were done according to usual clinical laboratory procedures, using advanced automated analyzers (Elimat, Hitachi, Tokyo, Japan; Inlab 158, CPM, Milan, Italy). Imagenological and laboratory evaluations were done blindly regarding the patients' group allocation.

Statistical analysis

Sample size was calculated using the equation $n = [(Z\alpha + Z\beta)\sigma/\delta]^2$ assuming 0.05 and 0.85 for type I and II errors. The "2N" Program for Design of Clinical Trials was used (Hauer-Jensen, 1990). A 15% excess was considered to compensate withdrawals. This yielded a range of 130-150 patients for this trial.

Data were double entered and validated and then imported into SPSS for Windows (version 15.0, IBM Analytics 2006, Armonk, North Castle, NY, USA) and Epidat (version 3.1, Directorate General of Public Health (Xunta de Galicia) 2006, Santiago de Compostela, Spain) for further analysis. Continuous variables were expressed as mean ± standard deviation (SD) or median ± interquartile range (QR) and minimum and maximum values (range). With these variables a normality analysis (Kolmogorov-Smirnov's test or Shapiro Wilk's test) and homogeneity of variance (Levene's test) were carried out. Groups were compared at the beginning and at the end of treatment using the Student's t-test (parametrical) or the Mann-Whitney's U test (non-parametrical), depending on the normality assumption. These variables were also analyzed using paired analysis (Student's t test or Wilcoxon's test). The chi-squared test was used to analyze the dependence or independence between demographic and baseline characteristics and evaluation parameters. Significance level chosen was 0.05. Stratified analyses according to investigation site were also done. Categorical variables were given as frequencies and percentages.

RESULTS

One-hundred thirty-one patients were enrolled from November 2012 to October 2014; then follow-up continued up to January 2015. Eighty-one patients received Calprost® and 50 terazosin. Fifty patients (25 per treatment group) were included both "Luis Díaz Soto" and "Iván Portuondo" hospitals. In the "Joaquín Albarrán" Hospital 31 patients received Calprost® formulation. A total of 15 patients (11.5%) withdrew voluntarily the trial; nine of them were receiving treatment with terazosin. These withdrawals occurred mostly during the second month of treatment.

Characteristics at entry of the included patients are shown in Table 1. Groups were homogeneous regarding each demographic characteristic. Mean age was around 65 years for both groups and white skin color prevailed (>70%). The prostate size in the Calprost® group was mostly grade I, being predominantly grade II in terazosin group.

Global IPSS median values at the end of the study were significantly reduced in both treatment groups. However, differences between groups were no detected in both evaluation times (Table 2). According to IPSS data, before treatment most of the patients in both groups showed moderate symptoms, which changed to mild at the end, which was 74% in Calprost® group and 54% in the terazosin group, as observed in Fig. 2. Only one patient, this case from the control group, remained with severe symptoms at the end of the study.

In order to obtain a better clinical comparison between groups, IPSS initial and final mean values for each urinary symptom were plotting (Fig. 3). In the case of obstructive symptoms, although all scores decreased, final values reached around or below value 1 (less than 1 in 5 times) only in the Calprost® group. Similar behavior was obtained with the irritative symptoms (except nocturia) in the same group. In contrast, in the control group, the reduction in the intermittency was almost negligible and a slight increase in the urgency was observed.

The residual bladder volume was significantly lower at the end of the study in those patients treated with Calprost® in comparison with terazosin-treated patients. The magnitude of this reduction (10 mL) was also significant into the study group. However, in the terazosin group a not significant increment of 3 mL occurred. Meanwhile, both initial and final median prostate volumes were significantly lower in the Calprost® group, where

initial-final reduction was significant. For this variable, once more an increment was evidenced in the control group, but this change was not significant (Table 2).

Table 1. Demographic and baseline characteristics of the patients involved in the clinical trial with Calprost® (140 mg/d) and terazosin (2 mg/d) during three months.

Characteristic		Calprost® group n=81	Terazosin group n=50
Skin color	White	63 (77.8%)	34 (68.0%)
	Non-white	18 (22.2%)	16 (32.0%)
Age (years)		67 ± 8 (50 – 80)	66 ± 8 (50 – 80)
Weight (kg)		72.6 ± 10.0 (53.0 – 94.0)	74.1 ± 11.2 (52.5 – 93.0)
Height (cm)		168 ± 7 (150 – 190)	166 ± 6 (155 – 178)
BMI (kg/m²)		25.6 ± 3.4 (18.3 – 32.5)	26.8 ± 3.7 (20.3 – 34.4)
Prostate size	Grade I	45 (55.6%)	13 (26.0%)
	Grade II	32 (39.5%)	26 (52.0%)
	Grade IIII	4 (4.9%)	11 (22.0%)

Data are reported as number of patients (%) or mean ± standard deviation (range).
Prostate size was determined by rectal tact examination; <5mm: Grade I; >5mm to 10mm: Grade II; >10mm: Grade III.
BMI: Body Mass Index

Table 2. Overall symptomatology and imagenological results before and after treatment with Calprost® (140 mg/d) and terazosin (2 mg/d) during three months.

Variable		Calprost® group	Terazosin group	p (Mann-Whitney's U test)
IPSS	Initial	11 ± 12 (2 – 33)	14 ± 11 (2 – 31)	0.056
	Final	4 ± 5 (0 – 16)	4 ± 6 (0 – 22)	0.828
	p (Wilcoxon's test)	<0.0001	<0.0001	–
Residual urine volume (mL)	Initial	55 ± 72 (0 – 400)	59 ± 45 (4 – 227)	0.675
	Final	45 ± 53 (0 – 240)	62 ± 50 (0 – 275)	0.029
	p (Wilcoxon's test)	0.048	0.163	–
Prostate volume (cm³)	Initial	38 ± 27 (8 – 143)	57 ± 40 (20 – 142)	<0.0001
	Final	36 ± 26 (3 – 206)	61 ± 41 (14 – 142)	<0.0001
	p (Wilcoxon's test)	0.002	0.438	–

Data are reported as median ± interquartile range (range).
IPSS: International Prostate Symptoms Score

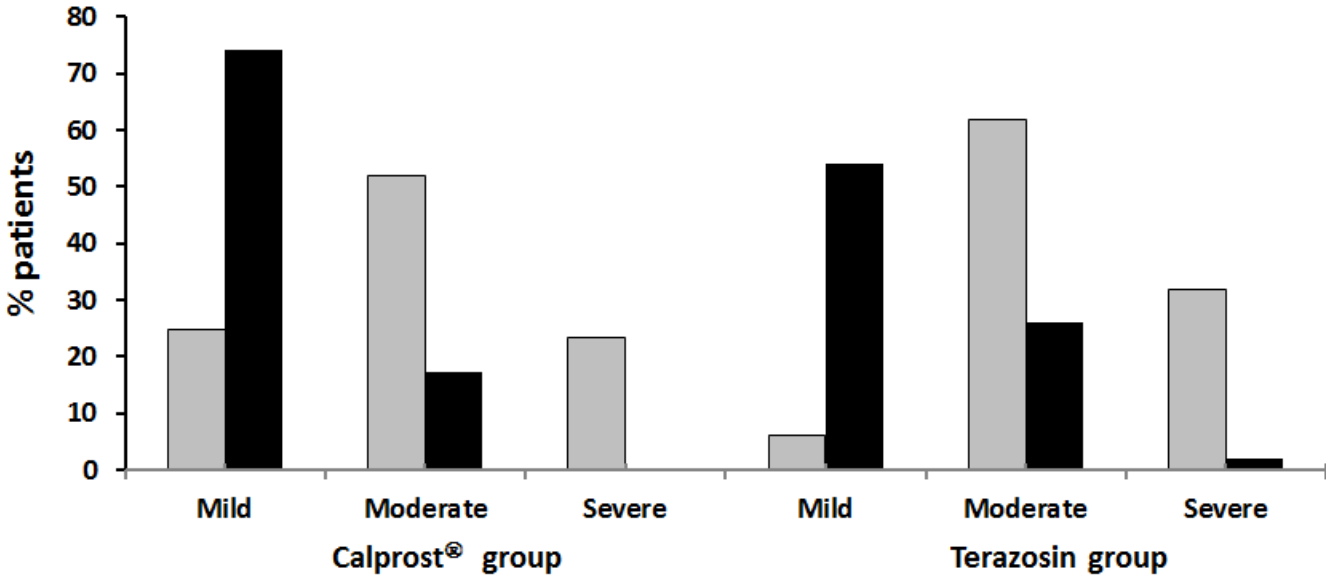

Figure 2. Severity of lower urinary tract symptoms during three months of treatment with Calprost® (140 mg/d) or terazosin (2 mg/d).

Data correspond to the percentage distribution of patients with BPH according total IPSS before (gray bars, n=131) and after treatment (black bars, n=116) in each group. Withdrawals were not included in post-treatment data.

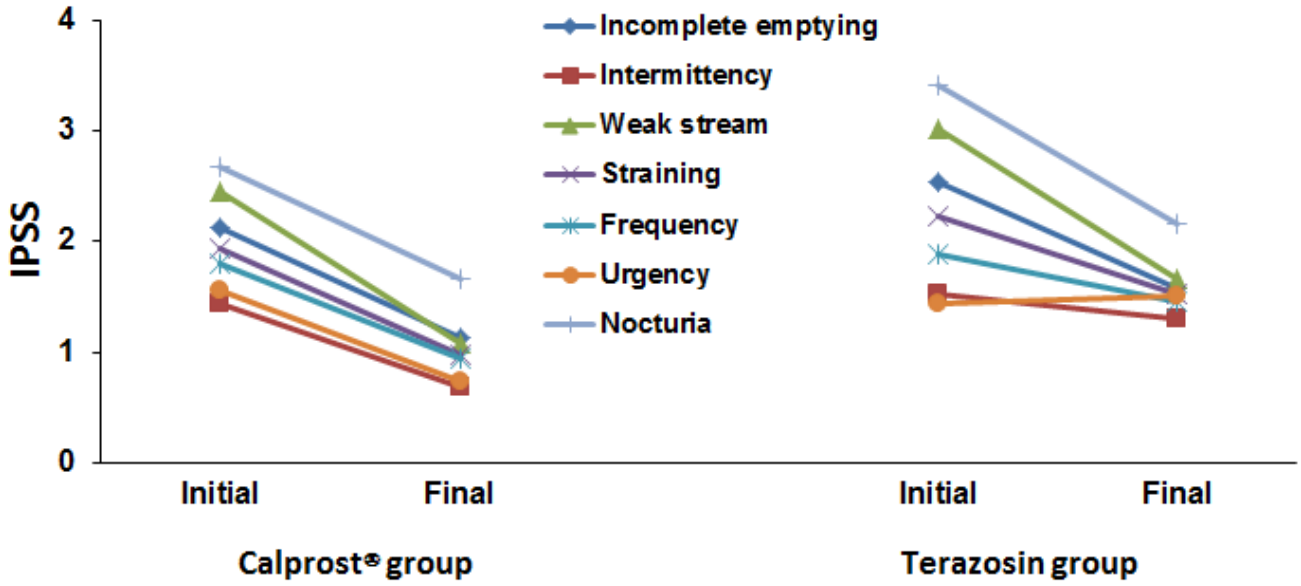

Figure 3. Specific urinary symptoms before and after treatment with Calprost® (140 mg/d) and terazosin (2 mg/d) during three months.

Legend: Each point corresponds to the median score value for each symptom, using IPSS scale, in each group of treated patients. Deviations are not shown for the sake of simplicity of the illustration. IPSS: International Prostate Symptoms Score.
All variations initial vs. final were significant ($p<0.05$, Wilcoxon's test) except for Intermittency, frequency and urgency in the terazosin group.

Quality of life improved in both groups (Table 3). After treatment, approximately half of the patients included in the study group felt as “pleased”. At the same time most of the patients in control group were “mostly satisfied”. The five patients who felt terribly wrong at entry improved after Calprost® treatment, one of them to “pleased” status. No influence of prostate size or other baseline characteristic on outcome variables was detected (data not shown).

The percentage of patients with overall satisfactory response was markedly superior in those patients treated with Calprost® (69% vs. 31%). This evaluation was done under the intention-to-treat principle, where all withdrawals are considered as failures (Table 4). The largest number of responders treated with Calprost® (22 patients) was obtained in the "Iván Portuondo" Hospital.

Fourteen adverse events were presented during the treatment (Table 5). At least one event occurred in 6% of the patients in the Calprost® group and 24% in the terazosin group. Postural hypotension was the most relevant event, only recorded in the control group. Other constitutional symptoms (headache, blurry vision, dizziness) prevailed in the same group. On the other hand, soft stools occurred only in three patients treated with Calprost®.

Table 3. Quality of life of the patients involved in the clinical trial with Calprost® (140 mg/d) and terazosin (2 mg/d) during three months.

Category		**Calprost® group n=81**	**Terazosin group n=50**
Before treatment	Delighted	3 (3.7%)	--
	Pleased	4 (4.9%)	--
	Mostly satisfied	23 (28.4%)	12 (24.0%)
	Mixed	22 (27.2%)	16 (32.0%)
	Mostly dissatisfied	23 (28.4%)	22 (44.0%)
	Unhappy	1 (1.2%)	--
	Terribly wrong	5 (6.2%)	--
After treatment	Delighted	6 (7.4%)	3 (6.0%)
	Pleased	39 (48.1%)	19 (38.0%)
	Mostly satisfied	24 (29.6%)	28 (56.0%)
	Mixed	7 (6.4%)	--
	Mostly dissatisfied	4 (4.9%)	--
	Unhappy	1 (1.2%)	--
	Terribly wrong	--	--

Data are reported as number of patients (%).

Table 4. Overall response in patients involved in the clinical trial with Calprost® (140 mg/d) and terazosin (2 mg/d) during three months.

Response	Calprost® group n=81	Terazosin group n=50
Successful	56 (69.1%)	10 (20.0%)
Failures	25 (30.9%)	40 (80.0%)

Data are reported as number of patients (%).

Table 5. Adverse events during treatment with Calprost® (140 mg/d) and terazosin (2 mg/d) during three months.

Adverse event	Calprost® group n=81	Terazosin group n=50
Any adverse event	5 (6.2%)	12 (24.0%)
Postural hypotension	–	7 (14.0%)
Headache	1 (1.2%)	3 (6.0%)
Asthenia	1 (1.2%)	2 (4.0%)
Sickness	1 (1.2%)	2 (4.0%)
Blurry vision	–	3 (6.0%)
Soft stools	3 (3.7%)	–
Dizziness	–	3 (6.0%)
Dry mouth	–	2 (4.0%)
Abdominal pain	–	1 (2.0%)
Anorexia	–	1 (2.0%)
Arterial hypotension	–	1 (2.0%)
Fatigue	–	1 (2.0%)
Insomnia	–	1 (2.0%)
Itching scalp	1 (1.2%)	–

Data are reported as number of patients (%).

Most of the events were classified as mild in both groups, percentage slightly higher in the Calprost® group (71.4% vs. 59.3%). None event was classified as severe. Regarding intensity, four grade 3 adverse events, two of them postural hypotension, were reported in patients treated with terazosin, being well controlled with or without pharmacological intervention (e.g. fludrocortisone). Headache events were resolved with dipyrone treatment. Five events in the control group were definitively caused by the treatment whereas probable or possible events prevailed in the study group. Urinary symptoms, closely related to the disease, were not accounted as adverse reactions. Significant differences or variations in clinical laboratory tests were not detected and mean values kept within normal ranges.

DISCUSSION

The efficacy of the natural product Calprost® in patients with HPB could be considered at least at the same level of a well-established therapy as terazosin. In this study, urinary symptoms decreased with both treatments according with global

IPSS scale but some obstructive and irritative symptoms were reduced more notably in the Calprost® group. These observations were confirmed by imagenological studies, since patients treated with this natural product reduced significantly residual bladder volume (below 50 mL) in comparison with those treated with terazosin. Additionally, reduction in prostate volume was only evidenced in the study group.

The above-commented results together with the adherence to treatment influenced the clear differences in the overall comparative assessment of response to treatment, where the percentage of responders was clearly superior in the Calprost® group. This could be explained that terazosin only acts reducing smooth muscle tone and reducing hypertonia or dynamic obstruction of the urinary tract produced by the prostate gland. In contrast, Calprost® action involves several mechanism of action that could potentiate their efficacy (Pérez-Guerra et al., 2011).

Cucurbita pepo L. seed oil has a demonstrated biological activity as 5-alpha reductase inhibitor and antiandrogenic. Additionally, anti-inflammatory, antioxidant, antiproliferative and diuretic activities have been observed with this product (Calabaza, 2014; Gossell-Williams et al., 2006). These effects could be produced by the action of the main components of pumpkin seed, polyunsaturated fatty acids, mostly linoleic, oleic, palmitic and stearic acids (Menéndez-Castillo et al., 2006). The potential alpha adrenergic antagonist effect of microencapsulated seed oil of *Cucurbita pepo* was proven in animal models. In this study the urinary output flow in rats was improved, given by the relaxation of smooth muscle and the reduction of the symptomatology caused by urinary retention (Tillán-Capó et al., 2009). A dose higher than 200 mg/kg of the extract inhibited testosterone-induced prostatic growth in an experimental murine model of BPH (Bellma-Menéndez et al., 2006). Experimental pharmacology studies conducted in different biomodels of inflammation demonstrated anti-inflammatory effect of the extract inhibiting induction of cyclooxygenase. Different *in vitro* tests performed in mouse peritoneal macrophages justified from the molecular point of view this anti-inflammatory effect (Núñez-Figueredo, unpublished observations).

This extract did not show acute toxicity after oral administration of 2000 mg/kg in rats. The administration of 1000 mg/kg/day for 90 days did not cause toxic symptoms and mortality in the treated animals. Only slight variations in hemoglobin, leukocytes, glucose and transaminases that not exceed normal values were reported after treatment. No histopathological changes in any of the organs tested (liver, kidneys, adrenals, testes, epididymides, ovaries, thymus, spleen, brain, heart) were observed. The micronucleus induction test in mouse bone marrow showed that the extract, administered orally at different dose levels is not cytotoxic nor genotoxic (Piloto J, unpublished observations).

In the clinics, the administration of 90 mg of a mixture containing delta7 sterols isolated from *Cucurbita pepo* to patients suffering BPH, four and three days before prostatectomy, decreased significantly dihydrotestosterone levels in prostatic tissue as well as serum acid phosphatase (Colectivo de Autores, 2009).

Our results are consistent with findings in a double-blind trial where *Curcurbita pepo* L. was better than placebo after three months of treatment, since symptoms improved significantly; particularly nocturia, without the presence of adverse reactions (Carbin et al., 1990). In other double-blind, placebo-controlled study, significant effects preventing and reducing nocturia and other urinary symptoms were achieved (Nishimura et al., 2014). This natural product seems to be especially effective in the early stages of the disease (Pagano et al., 2014).

Regarding the use of other natural products, no differences in IPSS scale improvement were obtained between *Serenoa repens* 320 mg/day and tamsulosin 0.4 mg/day in 811 patients with moderate to severe BPH, followed during 12 months (Debruyne et al., 2002). In contrast, saw palmetto treatment (160 mg twice a day) showed no significant differences regarding placebo in the symptoms score, changes in prostate size, residual urine volume, quality of life and development of adverse reactions (Bent et al., 2006). The concomitant use of *Cucurbita pepo* and saw palmetto (each 320 mg/day) by other authors (Hong et al., 2009) produced a serum prostate specific antigen reduction after three months of treatment, but no changes were

observed in prostate volume and quality of life score was improved only after six months.

Patients treated with Calprost® had fewer adverse events and consequently less voluntary abandonments than terazosin group. Several authors report a high incidence of orthostatic hypotension, dizziness, malaise, low blood pressure, weakness, headache, nausea, sexual affectations, among others, in patients treated with terazosin (Roehrborn et al., 1996; Millán-Rodríguez, 2005). As a result, many patients are not satisfied with this medication and they not conclude the treatment period. In the current study, more intense events were very probably caused by terazosin treatment. In the literature, adverse reactions to natural products derived from pumpkin seed oil are nausea, insomnia, dizziness and abdominal pain (Calabaza, 2014). Some of them were no registered in the Calprost® group.

Currently, there are several drugs used in the treatment of BPH/LUTS, which differ in efficacy and safety. However, the search for new, increasingly effective and safe agents remains in force until the present; hence a boom in the use of phytotherapeutic alternatives to treat BPH is perceived in recent years. The combination of these drugs with established treatments could be a feasible strategy to reduce urinary symptoms and improve quality of life of the affected patients.

CONCLUSIONS

The results obtained may justify the rationality to use Calprost®, an effective and safe natural product for the treatment of BPH patients, non-responder or intolerant to conventional treatments. Further, more extensive, controlled clinical trials are encouraged to confirm this assessment.

APPENDIX

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CONFLICT OF INTEREST

Authors DJR, TFC, RDH and IGG are employees of the Center for Drug Research and Development (CIDEM), Havana, Cuba, where Calprost® formulation is produced. The rest of the authors have no competing interests at all. The Ministry of Public Health of Cuba supported the clinical trial (hospital facilities and general medical care of the patients).

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Concepts or Ideas	X	X		X							X		
Design		X	X										
Definition of intellectual content	X			X	X	X	X	X	X				
Literature search	X	X	X									X	
Clinical studies	X	X	X	X	X	X	X	X	X		X	X	X
Data acquisition	X	X	X	X	X	X	X	X	X				X
Data analysis	X	X	X									X	X
Statistical analysis										X			
Manuscript preparation		X										X	
Manuscript editing	X											X	
Manuscript review			X	X	X								

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