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EVALUATING THE EFFICIENCY OF A COMBINATION OF PYGEUM AFRICANUM AND STINGING NETTLE (URTICA DIOICA) EXTRACTS IN TREATING BENIGN PROSTATIC HYPERPLASIA (BPH): DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED TRIAL

ÉZER A. MELO, EDUARDO B. BERTERO, LUIZ A. S. RIOS, DEMERVAL MATTOS JR.

Division of Urology, Hospital do Servidor Público Estadual de São Paulo, SP, Brazil

ABSTRACT

Objectives: In spite of its historical use, published data about phytotherapic products is characterized by the absence of well conducted studies, leading to conflictive and indefinite results about efficiency and safety of theses drugs. In that sense, we have analyzed the results of a combination of *Pygeum africanum* and stinging nettle (Urtica dioica) extracts in patients with benign prostatic hyperplasia (BPH), based in a double-blind, randomized, placebo-controlled protocol.

Materials and Methods: We have selected, according to inclusion and exclusion criteria, only patients with ≥50 years, presenting urinary symptoms assessed by the International Prostatic Symptoms Score (IPSS), with minimum score of 12, and Quality of Life (QoL) index of at least 3 points, rectal examination consistent with BPH, and maximum urinary flow rate (Q_{max}) between 5 and 15 mL/s. Phytotherapic and placebo groups were formed by 27 and 22 patients, respectively. The major variables analyzed during the study were IPSS variation, Q_{max}, and side effects. Reduction of ≥30% and ≥50% in IPSS were the parameters used to define a clinically significant response (CSR). We have also analyzed ≥30% and ≥50% Q_{max} increases.

Results: After six months of treatment we did not observe significant differences in clinical improvement potential between the phytotherapic combination and placebo groups. Percent IPSS drop of 21.6% in the phytotherapic group was similar to 19.7% obtained in the placebo group (p=0.928). Neither we observed any difference (p=0.530) for QoL improvement between phytotherapic (9.26%) and placebo (5.98%) groups. The alterations of Q_{max} followed the trend line observed in clinical data, with no significant difference (p=0.463) in Q_{max} increasing percent between phytotherapic (17.2%) and placebo (13.3%) groups. The CSR evaluation of clinical and urodynamic data was also similar between the groups.

Conclusion: The combination of 25mg *Pygeum africanum* and 300mg stinging nettle extracts produced clinical and urodynamic effects similar to placebo in a group of HBP patients.

Key words: prostate; prostatic hyperplasia; phytotherapy; *Pygeum africanum*
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INTRODUCTION

The use of phytotherapic drugs for the treatment of benign prostatic hyperplasia (BPH) patients has a long history, especially in European countries. Nevertheless, there is still a considerable degree of skepticism from the urologic community about the efficiency and safety of these products. This is mainly due to the absence of an established mechanism of action for phytotherapics.

Phytotherapics used in this clinical trial consisted in a combination of plant extracts with 25mg *Pygeum africanum* and 300mg stinging nettle. Stinging nettle presents a complex mixture of water and alcohol soluble compounds in its composition (1). Its presumed mechanism of action, tested in experimental animals, is related to the inhibition of growing factors, suppression of metabolism and growing of prostatic cell, and modulation of globulin binding to sexual hormone receptor in cell membrane (2-4).

Pygeum africanum extract is taken from the bark of the african plum tree. *In vitro* studies indicate that the effect of *Pygeum africanum* would be exerted by the inhibition of growing factors, anti-inflammatory and anti-estrogenic action (5). Recently, Levin et al., in experimental studies, suggested that *P. africanum* extract could revert or protect bladder dysfunctions secondary to prostatic obstructive process (6). However, to obtain these functional effects, we used up to 100mg/kg doses (7). Recommended dose for clinical use is 100 mg/day.

The objective of this study is to assess efficiency and safety of 25mg *Pygeum africanum* and 300mg stinging nettle extracts in the treatment of BPH patients. To our knowledge, this is the first clinical trial with this combination of plant extracts where evaluation criteria recommended by international consensus on BPH according to MEDLINE and LILACS were used.

MATERIALS AND METHODS

Inclusion and exclusion criteria used in patients' selection were already published previously (8). Were included only the patients ≥50 years, with urinary symptoms assessed by IPSS with minimal score=12, Quality of Life (QoL) index of at least 3 points, rectal examination consistent with BPH, and maximum urinary flow rate (Q_{max}) between 5 and 15 mL/s. The study protocol was approved by the Committee of Ethics and Research of our hospital, and each patient signed an informed consent.

The study protocol had 6 months. After initial visits for selection, each patient was oriented to return in 6 periods of 4 weeks, totaling 6 return visits, to answer IPSS and assess side effects. Q_{max} was measured in the initial visit and after 6 months of treatment. Prostatic volume and urinary residual post-voiding were determined only during the initial visit for selection.

Patients were divided in 2 groups according to a prospective, randomized, and double-blind protocol: phytotherapy group (PhyG) with 27 patients, and placebo group (PlaG) with 22 patients. The randomization process was done by the laboratory, where pills bottles were identified by numbers. At the end of the study the keys indicating which patients received phytotherapics or placebo were opened. Each group received 1 PO bid *Pygeum africanum* 25mg + stinging nettle 300 mg or placebo pill during 6 months.

Major variables analyzed were IPSS observed variation, Q_{max}, and side effects during the study. We have defined 2 levels of clinically significative response (CSR): ≥30% and ≥50% IPSS drop. We have also analyzed ≥30% and ≥50% Q_{max} increases.

STATISTICS

Presence of association among qualitative variables was evaluated through Chi-square (χ^2) test or Fisher's exact test, and comparison between both groups regarding quantitative variables was made by Student's t-Test and Mann-Whitney non-parametric test (U-test). Comparisons between initial and after 6 months of treatment measures, within each group, were made by Wilcoxon's paired signed rank test (z).

RESULTS

Table-1 show major demographics, clinical, and laboratorial characteristics of patients selected in each group. Patients mean age was 65 years in both groups (p=0.899). Length of urinary symptoms was also similar between the groups (p=0.919).

After 6 months of treatment, we did not observe significant differences between patients receiving *Pygeum africanum* + stinging nettle combination and placebo, regarding clinical improvement (Tables-2 and 3). Although there was a significative drop in IPSS between the groups, we did not observe differ-

Table 1 - *Patients demographics in phytotherapy and placebo groups.*

	Phytotherapy group		Placebo group		p value
Age (years)	65.3	(52 - 86)	65	(50-79)	0.899
Length of symptoms (months)	44.6 months	(12 - 142)	39.4		0.919
High blood pressure (N)	11		11		0.517
Diabetes mellitus (N)	5		4		1.000
Creatinine (mg/dl)	1.10	(0.7 - 1.7)	1.13		0.391
PSA (ng/mL)	2.56	(0.2 - 13.2)	3.44	(0.7 - 9.6)	0.200
Prostatic volume (g)	42.4	(21 - 86)	54.6	(21 - 121)	0.239
Postvoid residual (mL)	60.4	(0 - 238)	76.6	(17 - 191)	0.370

N o.= number of patients

ences in the percent variation between the groups at the end of the treatment (p=0.928). The reduction percent in QoL in PhyG (mean 9.26%) and in PlaG (mean 5.98%) was not significative either after 6 months of treatment (p=0.530).

In Q_{max} a difference marginally significative was observed between the groups at the initial evaluation (p=0.066), i.e., there was a trend towards PhyG patients presenting Q_{max} greater than PlaG patients (Table-4). However, even though this trend was veri-

Table 2 - *Alterations in International Prostatic Symptoms Score (IPSS) after 6 months of treatment in phytotherapy and placebo groups.*

	Initial	After 6 Months	Δ%	
Group	Mean ± SD Median Min/Max	Mean ± SD Median Min/Max	Mean ± SD Median Min/Max	Comparison
Phytotherapy group	19.3 ± 5.2 19 12/34	14.6 ± 7.3 14.0 2/34	- 21.60 ± 37.04 - 23.08 - 91.30/50.00	z = 2.69 p = 0.007 *
Placebo group	20.0 ± 5.9 19.5 12/34	15.6±7.9 14.5 3/33	- 19.72 ± 42.57 - 20.53 - 80.00/92.31	z = 2.68 p = 0.007 *
Comparison	U = 285.0 p = 0.809	U = 275.0 p = 0.658	U = 292.5 p = 0.928	

*SD = standard deviation; * p<0.05 (statistically significative); Δ% = percent variation of the quantitative variable; U = Mann-Whitney U-test; Z = Wilcoxon's paired signed rank test*

Table 3 - *Initial and final Quality of Life Index (QoL) in phytotherapy and placebo groups.*

	Initial	**After 6 Months**	**Δ%**	
Group	Mean ± SD Median Min/Max	Mean ± SD Median Min/Max	Mean±SD Median Min/Max	Comparison
Phytotherapy group	3.81 ± 0.83 4 3/6	3.33 ± 1.27 3 0/6	- 9.26 ± 34.92 0.00 - 100.00/100.00	z = 1.90 p = 0.058
Placebo group	3.95 ± 1.09 4 3/6	3.73 ± 1.52 3.5 0/6	- 5.98 ± 31.19 0.00 - 100.00/50.00	z = 0.89 p = 0.371
Comparison	U = 288.5 p = 0.855	U = 250.0 p = 0.315	U = 267.5 p = 0.530	

fied in PhyG, we did not observe differences in percent increase between the groups (p=0.463).

Evaluating IPSS and QoL percent variation among patients studied, we did not find statistically significant differences between the 2 groups regarding =30% (p=0.407 and p=0.440) and =50% (p=0.683 and p=1.000) drop after completion of the clinical trial. Regarding Q_{max}, no significant differences between the groups for =30% (p=0.354) e =50% (p=0.269) increases at treatment completion were observed either (Table-5).

Table 4 - *Urodynamic effects according to alterations on maximum urinary flow (Q_{max}) after 6 months of treatment in phytotherapy and placebo groups.*

	Initial	**After 6 Months**	**Δ%**	
Group	Mean ± SD Median Min/max	Mean ± SD Median Min/Max	Mean ± SD Median Min/Max	Comparison
Phytotherapy group	11.4 ± 3.1 12 5/15	12.5 ± 6.1 11 5/27	17.23 ± 66.72 0.00 - 46.67/228.57	z = 0.27 p = 0.787
Placebo group	10.2 ± 2.4 10 5/14	11.4 ± 3.8 11 5/18	13.36±32.52 23.61 - 53.85/80.00	z = 1.73 p = 0.084
Comparison	U = 206.5 p = 0.066	U = 282.5 p = 0.770	U = 260.5 p = 0.463	

Table 5 *- Clinically significative response after the treatment in phytotherapy and placebo groups.*

Δ% drop	Phytotherapy Group		Placebo Group		
IPSS	**No.**	**%**	**No.**	**%**	**Comparison**
≥ 30%	13	48.1	8	36.4	p = 0.407
≥ 50%	6	22.2	6	27.3	p = 0.683
Δ% drop	**Phytotherapy Group**		**Placebo Group**		
QoL	**No.**	**%**	**No.**	**%**	**Comparison**
≥ 30%	3	11.1	5	22.7	p = 0.440
≥ 50%	2	7.4	1	4.5	p = 1.000
Δ% increase	**Phytotherapy Group**		**Placebo Group**		
Q_{max}	**No.**	**%**	**No.**	**%**	**Comparison**
≥ 30%	8	29.6	4	18.2	p = 0.354
≥ 50%	6	22.2	2	9.1	p = 0.269

The percent of adverse events verified during the study was similar between patients receiving phytotherapics and placebo (Table-6). There was no predominance of any type of adverse event over other, suggesting that phytotherapics do not cause any specific adverse event.

DISCUSSION

The use of phytotherapic agents in clinical management of BPH patients, largely employed in Europe, has gained popularity in USA in the 90's, when there was a rapid increase in clinical use of these drugs (1). According to Astin (9), reasons contributing to the increase of phytotherapics use were determined by changes in values, beliefs and orientation of individuals concerning health and well-being. In addition, these drugs are understood as more natural, safe, and healthy.

In order to evaluate phytotherapics potential as alternative for clinical management of BPH, we studied a group of patients using a combination of 25mg *Pygeum africanum* and 300mg stinging nettle extract and compared it to placebo, according to a prospective, randomized, double-blind protocol, during 6 months. After this period of treatment we did not find

Table 6 *- Adverse events during the treatment in phytotherapy and placebo groups.*

Phytotherapy Group			Placebo Group		Total	
Side Effect	**No.**	**%**	**No.**	**%**	**No.**	**%**
Headache	1	3.7	1	4.5	2	4.1
Chest pain			1	4.5	1	2.0
Epigastric pain	4	14.8			4	8.2
Drowsiness	1	3.7	1	4.5	2	4.1
Vertigo			1	4.5	1	2.0

significative differences in clinical improvement potential between combination of phytotherapics and placebo. Evaluation of CSR was also similar between the groups, for both clinical and urodynamic data.

A multicentric and randomized study, published by Barlet et al. (10) analyzing 263 patients using *Pygeum africanum* 50 mg bid or placebo during 60 days, showed "voiding improvement" to 66% in PhyG and 31% in PlaG, and 17.2% and 4.3% increases in Q_{max} in PhyG and PlaG, respectively. In this study, the authors demonstrated a clear improvement of Q_{max} in PhyG compared to PlaG. However, our data indicate that the placebo effect may determine increasing of Q_{max} in up to 13%. Thus, urodynamic effects of a particular type of clinical treatment for BPH may be considered significative only if they act in a more consistent manner over the obstructive prostatic process, what would be demonstrated by a more expressive increase in Q_{max}. On the other hand, evaluation of clinical efficiency in that study was compromised, both for the absence of a validated score system and for the short period of treatment. In other multicentric study, Breza et al. (11) reported 40% improvement in IPSS and 18% increase in Q_{max} for 85 patients treated with 100mg *Pygeum africanum* during 2 months. In this study, the absence of a control group limits interpretation of the results obtained. In addition, 2 months cannot be considered a conclusive period of treatment. Recently, Chaterlain et al. (12) reported the results of a study involving 174 patients using *Pygeum africanum* (50mg bid and 100mg qd) during 12 months. Initially the patients entered into a comparative phase, double-blind, during 2 months, where they received *Pygeum africanum* 50mg bid or *Pygeum africanum* 100mg in one dose. During this initial period, both treatments presented comparable efficiency. Then the patients started to receive *Pygeum africanum* 100mg/day in one dose during 10 months. After 12 months of treatment, there was a 46% drop in IPSS e 15% increase in Q_{max}. Here, again, the percent increase of Q_{max} shows that results obtained in our study are consistent with that obtained in the literature. The use of an adequate methodology is crucial for any clinical trial about BPH, because variations induced by placebo effect may produce clinical improvement in up to 40% (13). Thus, the absence of a control group limits significantly IPSS improvement obtained in Chatelain et al. report. Alternatively, difference in IPSS improvement *pro*file, compared to our clinical trial may be related to *Pygeum africanum* extract dose, suggesting that improving *Pygeum africanum* dose from 25mg to 100mg may occasionally be translated by an improvement in clinical efficacy.

The single recent study about stinging nettle, performed in Germany, involving 41 patients treated during 3 months with a liquid presentation of the product, showed IPSS improvement superior to placebo (14). However, the preparation has been removed from the market, because its unacceptable taste was rejected by patients.

Analysis of these reports show that most published studies about phytotherapics present important methodological defects. To better illustrate this scenario, Andro & Riffaud (15) published a review of 25 years of experience with *Pygeum africanum*, where they found 2.262 patients treated with this extract. *Pygeum africanum* dose ranged from 50mg to 200mg, and no study lasted more than 12 weeks. Only twelve of these studies involved a double-blind, placebo controlled protocol, and just seven presented Q_{max} analysis. Results showed wide variations, from absence of urodynamic effect, to 91% increase of Q_{max} in patients receiving the drug. As the majority of the studies reported in this review were done before the 90's, none has used a validated scoring system. Thus, none is according to the norms established by international consensus on BPH (16), what makes comparison with our data rather difficult. Actually, our study seems to be the first to use a combination of *Pygeum africanum* and stinging nettle, 25mg and 300mg, respectively, for clinical treatment of BPH patients, using the methodology recommended by the international consensus of BPH.

Adverse events occurring during the clinical trial were similarly distributed between PhyG and PlaG, supporting the belief that, if they are not beneficial in controlled studies, they don't cause important adverse effects.

Current research lines adopted identify only 2 mechanisms scientifically proven through which it

is possible to relieve clinically the symptoms from prostatic obstructive process: decreasing of prostatic smooth muscle tonus, through blockade of α-1adrenergic receptors, and reduction of prostatic volume mediated by the inhibition of 5-α reductase (17). Phytotherapic drugs do not act upon none of these 2 mechanisms and, thus, from the scientific point of view, should not be considered first line drugs in BPH clinical management. However, it is worth emphasizing that the use of phytotherapic agents in BPH clinical approach is widespread. Thus, it is crucial that we establish a process of patterning to theses drugs, determining the composition, pharmacokinetics, and mechanism of action involved. Finally, only through multicentric, prospective, randomized, placebo controlled, long term studies, involving an adequate number of patients, will we be able to offer the necessary support for the definition of phytotherapics' role in BPH.

CONCLUSION

Combination of 25mg *Pygeum africanum* and 300mg stinging nettle extract produced clinical and urodynamic effects similar to placebo in a group of BPH patients.

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Correspondence address:
Dr. Ézer Amoras Melo
Av. Ricardo Jafet, 148
São Paulo, SP, 04260-020, Brazil
Fax: + 55 21 272-0966
E-mail: ezeramelo@uol.com.br