Clinical Complementary Medicine and Pharmacology 2 (2022) 100043

Contents lists available at ScienceDirect

Clinical Complementary Medicine and Pharmacology

journal homepage: www.elsevier.com/locate/ccmp

A Prospective, Observational Study of Use Combination Silodosin 8 mg Plus Serenoa Repens, Urtica Dioica, Cucurbita Pepo (Rotaprost) Compared With Silodosin 8 mg Alone in Treatment Patients with Benign Prostate Hyperplasia

Denis V. Krakhotkin[a,*], Volodymyr A. Chernylovskyi[b], Ruslan A. Bugaev[a], Dmitry N. Pikhovkin[c]

[a] Central District Hospital, Outpatient Clinic, Kamenolomni 346480, Rostov Region, Russia
[b] Department of Urology, City Clinical Hospital No. 4, Dnipro 49102, Ukraine
[c] Central District Hospital, Department of Surgery, Aksay 346720, Rostov Region, Russia

ARTICLE INFO

Keywords:
BPH
Silodosin
Serenoa repens
Urtica dioica
Cucurbita pepo
Lower urinary tract symptoms

ABSTRACT

Background: Benign prostatic hyperplasia (BPH) is one of the most common causes of lower urinary tract symptoms (LUTS) in older men. Nowadays, there are several plant extracts used for the treatment of LUTS due to BPH.

Objective: The aim of this study is to compare the effect of combining silodosin 8 mg with *Serenoa repens, Urtica dioica, Cucurbita pepo* (Rotaprost 530 mg) compared to silodosin 8 mg and Rotaprost 530 mg alone in patients with LUTS/BPH.

Methods: Four hundred five men with symptomatic BPH were recruited for the study from June 2020 to January 2021. Three hundred eighty-nine patients were followed up for 6 months. All participants provided written informed consent. This prospective study included analysis of three treatment groups: Group I patients (n = 130) received a combination of silodosin 8 mg and Rotaprost 530 mg (containing a dry extract of *Serenoa repens* 80 mg, a dry extract of *Urtica dioica* 150 mg, a dry extract of *Cucurbita pepo* seeds 200 mg, zinc (in the form of zinc picolinate) 0.105 mg, and selenium (as sodium selenite) 22.5 μg); the group II (n = 129) received silodosin 8 mg alone, and the group III (n = 130) received Rotaprost 530 mg alone. Outcomes were measured by changes from baseline in International Prostate Symptom Score (IPPS) total score, PSA value, prostate volume, residual urine after urination, and maximum flow rate. Statistical significance was set at $P < 0.05$.

Results: In group I, IPSS, prostate volume, and maximum urinary flow rate (Qmax) improved significantly ($P < 0.05$) compared with groups II and III during follow-up. Prostate volume in group I showed a significant decrease only during 6 months of therapy ($P < 0.05$). No serious adverse effects were registered in the three groups.

Conclusion: Combination therapy with silodosin 8 mg significantly reduced LUTS/BPH, Qmax, and prostate volume compared with silodosin 8 mg alone. Rotaprost 530 mg can also reduce PSA by at least 20.6–25.7% after 6-months of treatment.

1. Introduction

Benign prostatic hyperplasia (BPH) is one of the most common causes of lower urinary tract symptoms (LUTS) in older men. The prevalence of BPH in men older than 50 years ranges from 50% to 80% (Lokeshwar et al., 2019). The exact etiologic factors and molecular mechanisms underlying the development and progression of LUTS/BPH are not yet fully understood. Nowadays, chronic inflammation is considered one of the crucial pathogenetic mechanisms of BPH, in which high expression of pro-inflammatory cytokines and growth factors promotes the excessive development of fibromuscular tissue of prostate (De Nunzio et al., 2016; De Nunzio et al., 2020). Drug therapy with α1 blockers and 5α-reductase inhibitors (5-ARI) is the first treatment option for LUTS/BPH. The benefits of combination therapy have been demonstrated in several clinical trials (Boeri et al., 2017; Hailot et al., 2011; Morgia et al., 2014).

In the MTOPS (Medical Therapy of Prostatic Symptoms) trial, Kaplan et al. showed that treatment with finasteride, either alone or in combination with doxazosin, resulted in a significant reduction in prostate volume compared with placebo in patients with LUTS/BPH

* Corresponding author.
E-mail address: den_surgeon@mail.ru (D.V. Krakhotkin).

https://doi.org/10.1016/j.ccmp.2022.100043
Received 6 January 2022; Received in revised form 27 April 2022; Accepted 27 April 2022

(Kaplan et al., 2008). In the 4-year CombAT trial, Roehrborn et al. showed that combination therapy was statistically better than tamsulosin in reducing the risk of acute urinary retention or BPH-related surgery in patients with a prostate volume > 42 cm^3 (Roehrborn et al., 2011). However, despite the improvement in lower urinary tract symptoms, side effects (ejaculatory dysfunction, erectile dysfunction, and loss of libido) can significantly limit treatment adherence. For these reasons, some phytotherapeutic agents such as lipidosterol extracts from *Serenoa repens* and *Urtica dioica* are currently administered to improve symptoms and avoid potential side effects.

In a meta-analysis, Vela-Navarrete et al. showed that hexane extract of Serenoa repens (Permixon) reduced nocturia and improved Qmax compared with placebo and had similar efficacy to tamsulosin and short-acting 5-ARIs (5α-reductase inhibitors) in alleviating LUTS (Vela-Navarrete et al., 2018). There are data in the literature on equivalent efficacy of the combination of *Serenoa repens* plus *Urtica dioica* and finasteride in improving IPSS score. At the same time, the combination therapy with *Serenoa repens* and *Urtica dioica* was better tolerated than finasteride. In the literature, there is a single study describing a significant improvement in IPPS scores after the combination of silodosin and Serenoa repens (Boeri et al., 2017).

The Silodosin is uroselective α-adrenoceptor antagonist with high selectivity for α(1A)- relative to α(1B)- adrenoceptors, which is actively used in urological practice for treatment of BPH/LUTS (Villa et al., 2019). There are no studies in the literature that have investigated the combination of *Serenoa repens*, *Urtica dioica*, *Cucurbita pepo*, and silodosin 8 mg in the treatment of BPH/LUTS.

This prospective, open-label study was designed to evaluate and compare the effects of the combination of silodosin 8 mg plus Rotaprost 530 mg and silodosin 8 mg alone and monotherapy with Rotaprost 530 mg in men with LUTS/BPH over 6 months.

2. Materials and Methods

2.1. Chemicals and reagents

Rotaprost is a complex of three dry plant extracts provided by *Kendy Ltd.*, Bozhurishte, Bulgaria (seeds of Cucurbita pepo, batch no. P20210722, roots of *Urtica dioica*, batch no. N20210713, and fruits of Serenoa repens, batch no. S20210725). The raw materials from the seeds of *Cucurbita pepo*, the roots of *Urtica dioica*, and the fruits of *Serenoa repens* were extracted, dried, crushed, and sieved, and the final material obtained was mixed at a constant ratio. The result is a total extract consisting of three separate pharmacologically active fractions encapsulated in capsule form with a hard gelatin shell. The composition of one capsule of Rotaprost contains dry extracts of *Cucurbita pepo* 200 mg; *Urtica dioica* 150 mg; *Serenoa repens* 80 mg; selenium (as sodium selenite) 22.5 μg and zinc (in the form of zinc picolinate) 0.105 mg. The content of β-sitosterol ($C_{29}H_{50}O$), scopoletin ($C_{10}H_8O_4$), and total amino acids in 1 g of *Urtica dioica* powder was determined by a thin-layer chromatographic identification test. The content of fatty acid methyl esters (Table 1), long-chain alcohols, and sterols (campesterol, stigmasterol, β-sitosterol) in the extract of *Serenoa repens* was determined by gas chromatography. In pumpkin seed extracts (*Cucurbita Pepo*), the content of β-carotenoids (lutein, β-carotene; violaxanthin, lactucaxanthin, β-cryptoxanthin) and palmitic acid (C 16:0), palmitoleic acid (C 16:1), stearic acid (C 18:0), oleic acid (C 18:1), linoleic acid (C 18:2), linolenic acid (C 18:3) and gadoleic acid (C 20:1) were determined by high performance liquid chromatography.

2.2. Patient selection

This open-label, prospective, observational study included 405 patients with symptomatic BPH who were studied from June 2020 to January 2021. All participants provided written informed consent (IRB approval number 29-0458-S39). Inclusion criteria included a prostate volume > 25 cm^3, an International Prostate Symptom Score (IPSS) ≥ 10, a maximum flow rate of 5–15 mL/s, a postvoid residual volume (PVR) ≥ 50 mL, and a serum PSA level of ≤ 4 ng/mL. Patients with a history of urethral strictures, pelvic irradiation, prostate cancer, recurrent urinary tract infections, carcinoma in situ of the urinary bladder, urinary incontinence, incidental urinary tract infections at the time of the study were excluded, previous prostate surgery (transurethral resection of the prostate (TURP), open adenomectomy), chronic pelvic pain syndrome, and use of 5α-reductase inhibitors within the past 6 months. Patients were assigned to one of the studied groups on the basis of the initial visits, at which all patients were evaluated by completion of the IPSS questionnaire, measurement of PSA level, ultrasonography of the prostate (abdominal and transrectal US examination for measurement of volume after defecation and prostate volume, respectively), urine culture and microscopy of urine sediment to exclude urinary tract infection (UTI), and uroflowmetry during the enrollment period. During the recruitment period, none of the patients received α1 blockers, which could have an impact on the parameters evaluated. This study involved the comparative analysis of three groups: Group I: patients received a combination of silodosin 8 mg and Rotaprost 530 mg; Group II: silodosin 8 mg alone; Group III: Rotaprost 530 mg alone. This study did not include a placebo control. Safety assessment included vital signs (blood pressure and heart rate), laboratory tests, electrocardiograms, and physical examination. Adverse events (AEs) were classified by the investigators according to their severity and relationship to the study.

The study conformed to the principles of the 1964 Declaration of Helsinki and was approved by the independent ethics committees of the participating centers and countries.

Table 1
Methyl esters of fatty acid extracted with hexane solvent and its concentration in extract *Serenoa repens*.

Methyl Ester	Concentration (mg/mL)
Methyl laurate	5
Methyl oleate	5
Methyl myristate	2
Methyl palmitate	2
Methyl linoleate	1
Methyl caproate	0.4
Methyl caprylate	0.4
Methyl caprate	0.4
Methyl palmitoleate	0.4
Methyl stearate	0.4
Methyl linolenate	0.4

2.3. Study design

Over a 6-month period, a prospective, observational, open-label, controlled, nonrandomized clinical trial of men with LUTS/BPH was designed as follows. Patients who met inclusion criteria at baseline were assigned to one of the following three groups:

- Group I: silodosin 8 mg + Rotaprost 530 mg.
- Group II: silodosin 8 mg alone.
- Group III: Rotaprost 530 mg alone.

In group I, silodosin 8 mg was selected for its uroselectivity for α1A-adrenoreceptors with minimal cardiovascular side effects, and Rotaprost 530 mg was selected for its known constituents with moderate antiproliferative and anti-inflammatory effects. Follow-up assessments were performed at baseline and at 3 and 6 months. The IPSS total score and its subscores for storage, bladder emptying and quality of life (QoL), Qmax, and PVR were determined at baseline and after 3 and 6 months. Prostate volume and serum PSA levels were measured at baseline and after 3 and 6 months.

Table 2
The demographic and clinical baseline parameters of the patients with LUTS/BPH.

	Group I (Silodosin 8 mg+ Rotaprost 530 mg)	**Group II** (Silodosin 8 mg)	**Group III** (Rotaprost 530 mg)	***P-value***
Number of Patients, n (%)	130 (33.4%)	129 (33.2%)	130 (33.4%)	
Age (years), mean ± SD	61.3 ± 2.7	63.8 ± 4.2	62.0 ± 3.4	0.089*
BMI (kg/m^2), mean ± SD	25.4 ± 3.7	24.7 ± 4.1	25.9 ± 3.8	0.123**
Total IPSS, mean ± SD	15.5 ± 1.7	15.2 ± 1.6	15.9 ± 1.4	0.145*
Storage subscore, mean ± SD	8.4 ± 0.6	8.3 ± 0.5	8.5 ± 0.7	0.078*
Voiding subscore, mean ± SD	7.1 ± 1.1	6.9 ± 0.8	7.0 ± 1.2	0.069**
IPSS-QoL, mean ± SD	4.6 ± 1.4	4.3 ± 1.7	4.4 ± 1.5	0.138*
Prostate volume (cm^3), mean ± SD	57.4 ± 0.8	57.8 ± 0.6	56.5 ± 0.7	0.169*
Qmax (mL/s), mean ± SD	9.5 ± 0.4	9.6 ± 0.6	9.7 ± 0.5	0.075**
PVR (mL), mean ± SD	67.9 ± 4.7	68.2 ± 4.3	67.4 ± 4.1	0.102*
PSA (ng/mL), mean ± SD	3.5 ± 0.3	3.3 ± 0.5	3.4 ± 0.7	0.092**

SD, Standard deviation; BMI, Body mass index; IPSS, International Prostate Symptom Score; QoL, quality of life; Qmax, maximal urinary flow rate; PVR, post-void residual volume; PSA, prostate-specific antigen.*P-*value* by Kruskal-Wallis H test, **P-*value* by one-way analysis of variance ($P < 0.05$ is considered statistically significant).

2.4. Endpoints

The main endpoint was improvement in IPSS. IPSS subscores for storage, voiding, and quality of life were also assessed. The secondary endpoints were changes in Qmax, total PSA, PVR, and prostate volume. Prostate volume was determined by transrectal ultrasonography and PVR by abdominal ultrasonography.

2.5. Statistical analysis

Data are presented as means ± SD. Continuous variables were compared using the unpaired Student's t test. Normality of the distribution of variables was tested with the Kolmogorov-Smirnov test. Categorical variables were tested with the χ^2 test. The Kruskal-Wallis H test and the one-way test ANOVA were used to compare changes in assessed parameters among the three study groups. Statistical analyses were performed using *SPSS 20.0* (SPSS, Chicago IL, USA). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Demographics and patient disposition

Four hundred five men with symptomatic BPH were recruited for the study from June 2020 to January 2021. During the enrollment period, 16 patients were not included in the study because they had previously received a 5α-reductase inhibitor ($n = 4$), pelvic radiotherapy ($n = 2$), prostate cancer ($n = 7$), and recurrent urinary tract infection ($n = 3$). A total of 389 men with a mean age of 62.5 ± 5.7 years (range, 45–82 years) were followed up for 6 months. After 3 months, three men in group I and two men in group II refused to participate in the study because of significant nasal congestion. After 6 months, no men had dropped out of the study (Fig. 1). Baseline demographic and clinical parameters of the patients are shown in Table 2. There was no statistically significant difference between the two treatment groups in terms of baseline demographic and clinical parameters.

3.2. Primary endpoint

Statistically significant ($P < 0.05$) improvements from baseline in IPSS total scores, quality of life, bladder emptying, and storage capacity were observed after month 6 only in the combination treatment group (silodosin 8 mg + Rotaprost 530 mg) compared with monotherapy with silodosin 8 mg or Rotaprost 530 mg (Tables 3 and 4). The mean changes in IPSS total scores from baseline to month 6 were −12.4 ± 0.33, −9.3 ± 0.14, and −3.0 ± 0.14 for the combination group, silodosin 8 mg, and Rotaprost 530 mg, respectively. The dynamic changes in the mean of the IPSS score and its subscores are shown in Fig. 2. The adjusted mean difference between the combination treatment, silodosin 8 mg, and Rotaprost 530 mg was −4.87 points after month 6.

3.3. Secondary endpoints

3.3.1. PSA level

After 6 months, the PSA level had decreased by 25.7% in group I and by 20.6% in group III. However, there were no statistically significant differences between the three comparison groups (Table 3).

3.3.2. Maximum flow rate of urine (Qmax)

At month 6, men in group I had a statistically significant improvement in maximum flow rate Qmax (mL/s) compared with patients in groups II and III, who received monotherapy with silodosin 8 mg and Rotaprost 530 mg, respectively (Table 3).

3.3.3. Prostate volume

Patients in groups I and III had a statistically significant reduction in prostate volume after 6 months of treatment. At the same time, the prostate volume of patients in the II group was at baseline levels (Table 3).

3.3.4. Post-void residual volume (PVR)

Changes in postvoid residual volume (PVR) were statistically significant in group I and II after 6 months of treatment. The average changes in PVR from baseline to month 6 were −46.5 mL and −45.1 mL for combination treatment and monotherapy with silodosin 8 mg, respectively. At the same time, patients in the III group experienced a slight decrease in PVR to −4.7 mL at month 6 of treatment.

3.3.5. Safety assessment

During the 6-month treatment period, 49 (37.9%) patients treated with silodosin 8 mg alone, 42 (32.3%) men treated with Rotaprost 530 mg + silodosin 8 mg, and 9 (6.9%) patients receiving Rotaprost 530 mg alone experienced various drug-related adverse effects such as orthostatic hypotension, nasal congestion, nausea, rash, pruritus (itchy skin), ejaculatory dysfunction (emission reduction), dry mouth (xerostomia), abdominal discomfort, and diarrhea (Table 5). However, these adverse events were not a reason to discontinue the study. No serious adverse effects were noted.

4. Discussion

This prospective observational study was conducted to evaluate the effects of combination therapy (silodosin 8 mg + Rotaprost 530 mg) and monotherapy with either silodosin 8 mg or Rotaprost 530 mg for

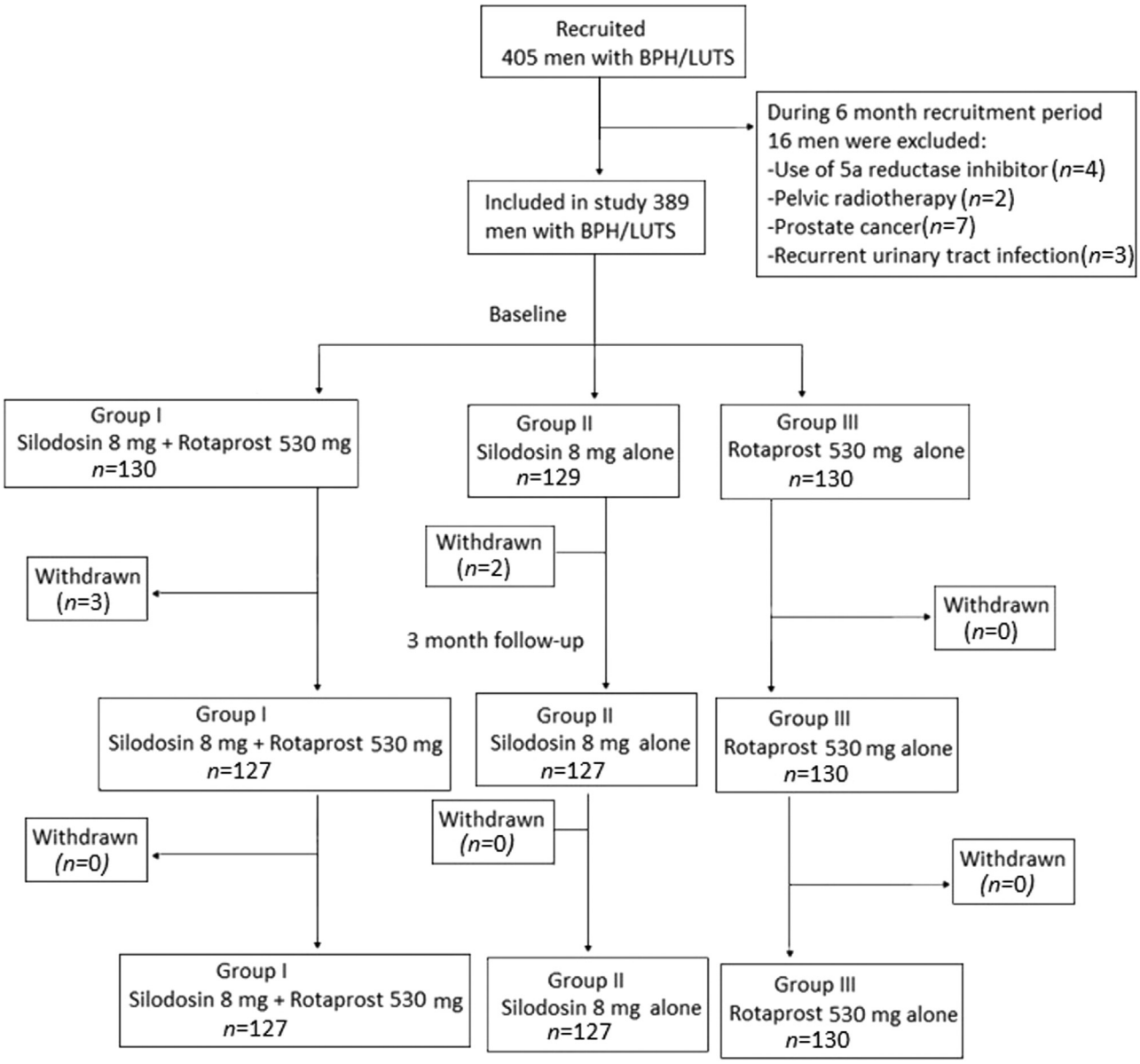

Fig. 1. The flow chart of the study.

6 months in patients with LUTS/BPH. In current EAU guidelines, phytotherapeutics have weak recommendation strength due to numerous methodological flaws in many clinical trials (Gratzke et al., 2015).

Nowadays, lipidosterolic extract of *Serenoa repens* is one of the most widely used phytotherapeutics for the treatment of LUTS/BPH. A large meta-analysis of 30 randomized controlled trials (RCTs) with 5,222 men and a follow-up period of 4 to 60 weeks showed that treatment with *Serenoa repens* was not better than placebo, finasteride or tamsulosin in terms of improvement of IPSS, Qmax and reduction of prostate size. In another meta-analysis of RCTs and observational studies, Novara et al. showed that hexane extract of *Serenoa repens* (Permixon) reduced nocturia and improved Qmax compared with placebo and had similar efficacy to tamsulosin and short-term 5-ARI in relieving LUTS (Novara et al., 2016).

There are some reports of other phytotherapeutic agents that may improve the lower urinary tract in patients with BPH. In a study RCT, Safarinejad M.R. showed that patients in the *Urtica dioica* group had greater improvement in IPSS and Q max compared to placebo (Safarinejad, 2005). Patients in the *Urtica dioica* group had a statistically significant reduction in PVR and a modest reduction in prostate size, as measured by transrectal ultrasound examination (TRUS), from 40.1 to 36.3 cm^3 ($P < 0.001$). Similarly, Akbar Karami et al. demonstrated that an extract of *Urtica dioica* improved IPSS and had an intermediate effect on superoxide dismutase (SOD) without side effects (Akbar Karami et al., 2020).

In our study, we found that both groups had statistically significant improvement in Qmax, prostate volume, and IPSS quality of life score only 6 months after therapy. The rate of adverse events was similar in both groups. Previously, Boeri et al. reported that patients receiving a combination of *Serenoa repens* and silodosin had significant improvement in IPSS score at follow-up compared with men treated with silodosin alone, with a comparable rate of side effects (Boeri et al., 2017).

The pharmacological uroselectivity of silodosin provides good urodynamic efficacy and minimizes the propensity for cardiovascular side effects caused by blockade of α1B-adrenoreceptors (Califano et al., 2020; Fusco et al., 2016). In a pooled analysis of phase 3 and phase 4 trials, Creta et al. showed that silodosin monotherapy produced statisti-

Table 3
Comparison of the treatment outcomes at the follow-up assessment and mean changes in values from baseline to 3 months (A) and 6 months (B) in three groups of patients.

(A)	Group I (Silodosin 8 mg+ Rotaprost 530 mg)	Group II (Silodosin 8 mg)	Group III (Rotaprost 530 mg)	*P-value*
Total IPSS	10.8 ± 0.38	10.4 ± 0.52	14.0 ± 1.40	0.0006
Storage subscore	7.3 ± 0.15	7.5 ± 0.35	7.1 ± 0.80	0.5945
Voiding subscore	3.5 ± 0.23	3.3 ± 0.17	6.9 ± 0.90	0.0011
IPSS-QoL	2.1 ± 0.20	3.1 ± 0.50	4.1 ± 0.70	0.0021
Qmax, mL/s	12.4 ± 0.72	12.3 ± 0.55	11.8 ± 0.90	0.0625
Prostate volume, cm^3	53.4 ± 1.80	57.5 ± 1.90	53.9 ± 1.44	0.0081
PVR change, mL	39.3 ± 1.90	39.2 ± 1.40	65.9 ± 3.90	0.0091
PSA change, ng/mL	3.2 ± 0.24	3.3 ± 0.50	3.2 ± 0.41	0.3689
(B)	**Group I (Silodosin 8 mg + Rotaprost 530 mg)**	**Group II (Silodosin 8 mg)**	**Group III (Rotaprost 530 mg)**	***P-value***
Total IPSS	3.1 ± 1.37	5.9 ± 1.46	12.9 ± 1.26	0.0005
Storage subscore	2.9 ± 0.48	4.8 ± 0.68	6.7 ± 0.73	0.0012
Voiding subscore	0.2 ± 0.19	1.1 ± 0.78	6.2 ± 0.53	0.0019
IPSS-QoL	0.4 ± 0.38	2.8 ± 0.43	3.4 ± 0.71	0.0064
Qmax, mL/s	16.4 ± 0.22	12.3 ± 0.15	11.2 ± 0.91	0.0018
PVR change, mL	21.4 ± 1.98	23.1 ± 1.54	62.7 ± 4.30	0.0021
Prostate volume, cm^3	50.5 ± 1.60	57.3 ± 1.40	50.1 ± 1.80	0.0098
PSA change, ng/mL	2.6 ± 0.15	3.3 ± 0.50	2.7 ± 0.25	0.0732

IPSS, International Prostate Symptom Score; QoL, quality of life; Qmax, maximal urinary flow rate; PVR, post-void residual volume; PSA, prostate-specific antigen. *P-value* by Kruskal-Wallis H test ($P < 0.05$ is considered statistically significant).

Table 4
The changes values of total IPSS, quality of life(QoL), storage and voiding subscores after 3 and 6 months from start of treatment in each study group.

Group I (A) (Silodosin 8 mg ± Rotapost 530 mg)				
After 3 months of treatment		**After 6 months of treatment**		***P-value***
Total IPSS	10.8 ± 0.38	Total IPSS	3.1 ± 1.37	0.011
Voiding subscore	3.5 ± 0.23	Voiding subscore	0.2 ± 0.19	0.029
Storage subscore	7.3 ± 0.15	Storage subscore	2.9 ± 0.48	0.036
QoL	2.1 ± 0.21	QoL	0.4 ± 0.38	0.025
Group II (B) (Silodosin 8 mg alone)				
After 3 months of treatment		**After 6 months of treatment**		***P-value***
Total IPSS	10.4 ± 0.52	Total IPSS	5.9 ± 1.46	0.049
Voiding subscore	3.3 ± 0.17	Voiding subscore	1.1 ± 0.78	0.032
Storage subscore	7.5 ± 0.35	Storage subscore	4.8 ± 0.68	0.025
QoL	3.1 ± 0.5	QoL	1.8 ± 0.43	0.019
Group III (C) (Rotapost 530 mg alone)				
After 3 months of treatment		**After 6 months of treatment**		***P-value***
Total IPSS	14.0 ± 1.4	Total IPSS	12.9 ± 1.26	0.203
Voiding subscore	6.9 ± 0.9	Voiding subscore	6.2 ± 0.53	0.383
Storage subscore	7.1 ± 0.8	Storage subscore	6.7 ± 0.73	0.124
QoL	4.1 ± 0.7	QoL	3.4 ± 0.71	0.494

QoL-quality of life; IPSS-International prostate symptom score.
Data are presented as mean ± standard deviation (SD).
P value by χ^2 test ($P < 0.05$ is statistically significant).

cally significant improvements in the subgroup of patients with severe LUTS/BPO (Creta et al., 2021).

Our results show statistically significant differences in improvement in IPSS subscores and PVR during 6-month follow-up. Similarly, Melo et al. showed that the decline in IPSS scores and their subscores was similar in the phytotherapy group (*Urtica dioica* + *Pygeum africanum*) and the placebo group (Melo et al., 2002). The study by Soekeland showed that Qmax increased in both the *Serenoa repens* + *Urtica dioica* group and the finasteride group during follow-up, with no statistically significant difference between them.

The combination of *Urtica dioica* + *Serenoa repens* was better tolerated than finasteride treatment (Soekeland, 2000). In the German research activities on natural urogicals (GRANU) study, Vahlensieck et al. showed that 12 months of treatment with Cucurbita pepo resulted in a clinically relevant reduction in IPSS in men with BPH compared to placebo (Vahlensieck et al., 2015). In a pilot study, Leibbrand et al. demonstrated that an oil-free hydroethanolic pumpkin seed extract significantly reduced postvoid residual volume (PVR) and improved overall IPSS after 12 weeks of treatment (Leibbrand et al., 2019). Our study showed a similar reduction in PVR after 6 months of therapy, with no statistically significant differences between the two groups.

The observed effects of Rotaprost can be explained by the moderate antiandrogenic action and anti-inflammatory properties of its con-

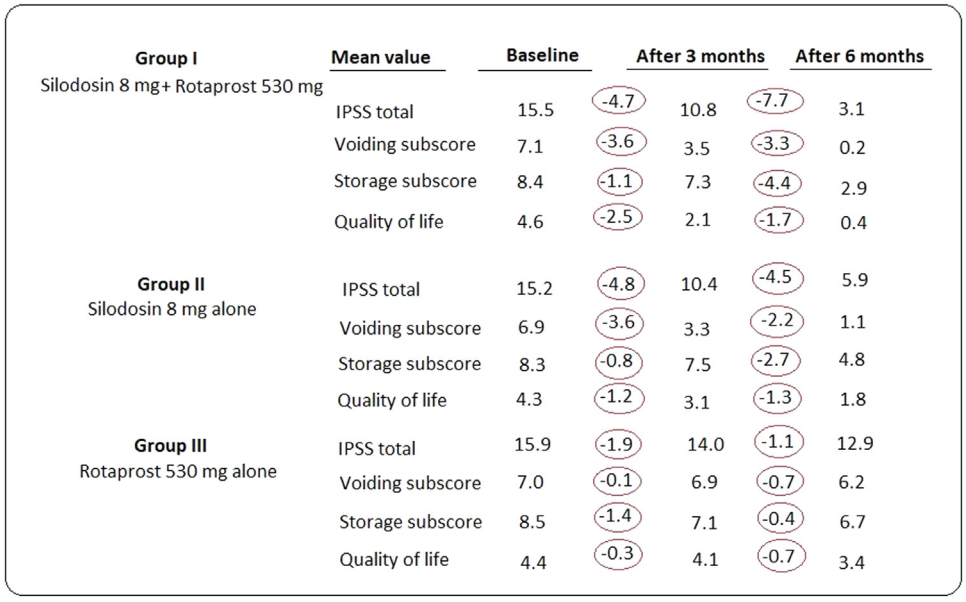

Fig. 2. Dynamic of changes IPSS and its subscores during 6 months therapy in three treatment arms.

Table 5
Summary of drug-related adverse effects.

	Group I (Silodosin 8 mg + Rotaprost 530 mg)	**Group II** (Silodosin 8 mg)	**Group III** (Rotaprost 530 mg)
Total	42 (32.3%)	49 (37.9%)	11 (8.4%)
Ejaculation disorder	18 (42.8%)	23 (46.9%)	0 (0%)
Orthostatic hypotension	5 (11.9%)	6 (12.5%)	0 (0%)
Nasal congestion	6 (14.3%)	7 (14.2%)	0 (0%)
Dry mouth (xerostomia)	3 (7.1%)	2 (4.1%)	0 (0%)
Nausea	2 (4.8 %)	3 (6.1%)	2 (18.1%)
Abdominal discomfort	1 (2.4%)	2 (4.1%)	5 (45.4%)
Diarrhoea	2 (4.8%)	3 (6.1%)	0 (0%)
Skin rash	2 (4.8%)	2 (4.0%)	2 (18.1%)
Pruritus (itchy skin)	3 (7.1%)	1 (2.0%)	2 (18.1%)

stituents. *Urtica dioica* has the ability to block the conversion of androgens to estrogens, interact with sex hormone binding globulin (SHBG) and reduce the amount of dehydrotestosterone (DHT) (Nahata and Dixit, 2012; Hryb et al., 1995).

Cucurbita pepo extract contains Δ7 -sterols (avenasterol and spinasterol) that significantly reduce elevated DHT levels in men with LUTS/BPH and produce a tonic effect and relaxation of the sphincter at the bladder neck (Cicero et al., 2019; Leibbrand et al., 2019; Pagano et al., 2014).

The pharmacological properties of *Serenoa repens* extract include anti-inflammatory, antiandrogenic and antiproliferative effects. *Serenoa repens* extract is able to inhibit prolactin-induced prostate growth and downregulate the pro-inflammatory cytokine profile in prostate tissue (Ooi and Pak, 2017; Bernichtein et al., 2015; Tacklind et al., 2012). Vela-Navarrete et al. found that the BAX/BCL2 ratio in transurethral prostate tissue of men with symptomatic BPH was increased after 3 months of therapy with an extract of *Serenoa repens* compared with untreated controls (Vela-Navarrete et al., 2005). The antiandrogenic effect of *Serenoa repens* on BPH tissues occurs via free fatty acids (lauric acid) that inhibit 5α-reductase activity (Kwon, 2019). In a randomized international study of 1,098 patients with BPH, Carraro et al. showed that *Serenoa repens* extract did not alter PSA levels compared with finasteride (Carraro et al., 1996).

In contrast, our data show that group I patients receiving Rotaprost had a statistically significant reduction in PSA levels only after 6 months of treatment.

In our study, we demonstrated that Rotaprost can reduce PSA levels by 20.6–25.7% from baseline. In the QUALIPROST study, Alcaraz et al. demonstrated that the combination of tamsulosin and hexane extract of *Serenoa repens* resulted in more effective relief of clinical symptoms and greater improvement in quality of life than either treatment alone, with acceptable tolerability (Alcaraz et al., 2020).

Our study also showed significant improvement in clinical parameters after 6 months of treatment, but there were some limitations. First, the study was not randomized. Second, the study did not include a placebo arm, and the follow-up period of 6 months was relatively short.

The beneficial effect of combined therapy can be explained by its influence on different links of the pathogenesis of LUTS/BPH. The significant improvement of clinical symptoms is due to the effect of silodosin 8 mg on α1-adrenergic receptors (AR), which are located in the tissues of the urethra and prostate and cause smooth muscle relaxation, as well as to the free fatty acids (lauric acid), which cause inhibition of 5α-reductase, and phytosterol (β-sitosterol) with anti-inflammatory effect of *Serenoa repens, Urtica dioica* and *Cucurbita pepo* (Rotaprost). It should also be noted that Selenium and Zinc were used in our study in order to maintain their tissue homeostasis, since with aging, especially in men with BPH, their content decreases.

However, the role of the interaction of these two microelements with each other in relation to the prostate tissue is controversial according to the literature, which requires additional studies both *in vivo* and *in vitro* (Daragó et al., 2016; Karunasinghe et al., 2019; Sapota et al., 2009).

Therefore, large prospective randomized trials with longer follow-up periods are needed to more clearly determine the benefit of a combined treatment approach with Rotaprost in patients with LUTS/BPH.

5. Conclusion

The combination of silodosin 8 mg with Rotaprost 530 mg results in a significant reduction in LUTS/BPH, Qmax, and prostate volume compared with silodosin 8 mg and Rotaprost 530 mg each taken alone. Rotaprost 530 can also reduce PSA levels to at least 20.6–25.7% after 6 months of treatment. The significant effect of combined therapy may be due to influence on different links of pathogenesis of LUTS/BPH.

Ethical Approval

This research has approved by the independent ethics committees of the participating centers and countries (Approval No. 29-0458-S39).

Data Availability

Nil.

Funding

Nil.

Declaration of Competing Interest

"Rotaprost" is manufactured by *Kendy Ltd* in Bulgaria. On the territory of the Russian Federation, the marketing of the food supplement is carried out by *Asfarma International Pharma Marketing*. This research is not sponsored by any of the above companies.

CRediT authorship contribution statement

Denis V. Krakhotkin: Investigation, Methodology, Writing – original draft. **Volodymyr A. Chernylovskyi:** Writing – review & editing, Investigation. **Ruslan A. Bugaev:** Formal analysis. **Dmitry N. Pikhovkin:** Methodology, Supervision.

Acknowledgement

We thank all included patients with LUTS/BPH for taking part in this trial.

ORCID

Krakhotkin Denis, https://orcid.org/0000-0003-1540-6647.

Supplementary Materials

Nil.

References

Akbar Karami, A, Sheikhsoleimani, M, Reza Memarzadeh, M, et al., 2020. Urtica dioica root extract on clinical and biochemical parameters in patients with benign prostatic hyperplasia, randomized controlled trial [J]. Pak. J. Biol. Sci. 23 (10), 1338–1344.

Alcaraz, A, Rodríguez-Antolín, A, Carballido-Rodríguez, J, et al., 2020. Clinical benefit of tamsulosin and the hexanic extract of Serenoa repens, in combination or as monotherapy, in patients with moderate/severe LUTS-BPH: A subset analysis of the QUALIPROST study [J]. J Clin Med 9 (9).

Bernichtein, S, Pigat, N, Camparo, P, et al., 2015. Anti-inflammatory properties of Lipidosterolic extract of Serenoa repens (Permixon®) in a mouse model of prostate hyperplasia [J]. Prostate 75 (7), 706–722.

Boeri, L, Capogrosso, P, Ventimiglia, E, et al., 2017. Clinically meaningful improvements in LUTS/BPH severity in men treated with silodosin plus hexanic extract of Serenoa repens or silodosin alone[J]. Sci. Rep. 7 (1), 15179.

Califano, G, Collà Ruvolo, C, Creta, M, et al., 2020. Focus on silodosin: pros and cons of uroselectivity [J]. Res Rep Urol 12, 669–672.

Carraro, J C, Raynaud, J P, Koch, G, et al., 1996. Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1,098 patients [J]. Prostate 29 (4), 231–240.

Cicero, A, Allkanjari, O, Busetto, G M, et al., 2019. Nutraceutical treatment and prevention of benign prostatic hyperplasia and prostate cancer [J]. Arch. Ital. Urol. Androl. 91 (3).

Creta, M, Cornu, J N, Roehrborn, C G, et al., 2021. Clinical efficacy of silodosin in patients with severe lower urinary tract symptoms related to benign prostatic obstruction: a pooled analysis of phase 3 and 4 trials [J]. Eur Urol Focus 7 (2), 440–443.

Daragó, A, Sapota, A, Nasiadek, M, et al., 2016. The Effect of Zinc and Selenium Supplementation Mode on Their Bioavailability in the Rat Prostate. Should Administration Be Joint or Separate? [J]. Nutrients 8 (10), 601.

De Nunzio, C, Presicce, F, Tubaro, A, 2016. Inflammatory mediators in the development and progression of benign prostatic hyperplasia [J]. Nat Rev Urol 13 (10), 613–626.

De Nunzio, C, Salonia, A, Gacci, M, et al., 2020. Inflammation is a target of medical treatment for lower urinary tract symptoms associated with benign prostatic hyperplasia [J]. World J. Urol. 38 (11), 2771–2779.

Fusco, F, Palmieri, A, Ficarra, V, et al., 2016. α1-blockers improve benign prostatic obstruction in men with lower urinary tract symptoms: a systematic review and meta–analysis of urodynamic studies [J]. Eur. Urol. 69 (6), 1091–1101.

Gratzke, C, Bachmann, A, Descazeaud, A, et al., 2015. EAU guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction [J]. Eur. Urol. 67 (6), 1099–1109.

Haillot, O, Fraga, A, Maciukiewicz, P, et al., 2011. The effects of combination therapy with dutasteride plus tamsulosin on clinical outcomes in men with symptomatic BPH: 4-year post hoc analysis of European men in the CombAT study [J]. Prostate Cancer Prostatic Dis. 14 (4), 302–306.

Hryb, D J, Khan, M S, Romas, N A, et al., 1995. The effect of extracts of the roots of the stinging nettle (Urtica dioica) on the interaction of SHBG with its receptor on human prostatic membranes [J]. Planta Med. 61 (1), 31–32.

Kaplan, S.A, Roehrborn, C G, McConnell, J D, et al., 2008. Long-term treatment with finasteride results in a clinically significant reduction in total prostate volume compared to placebo over the full range of baseline prostate sizes in men enrolled in the MTOPS trial [J]. J. Urol. 180 (3), 1030–1032.

Karunasinghe, N, Ng, L, Wang, A, et al., 2019. Selenium Supplementation and Prostate Health in a New Zealand Cohort [J]. Nutrients 12 (1), 2.

Kwon, Y., 2019. Use of saw palmetto (Serenoa repens) extract for benign prostatic hyperplasia [J]. Food Sci. Biotechnol. 28 (6), 1599–1606.

Leibbrand, M, Siefer, S, Schön, C, et al., 2019. Effects of an oil-free hydroethanolic pumpkin seed extract on symptom frequency and severity in men with benign prostatic hyperplasia: a pilot study in humans [J]. J. Med. Food 22 (6), 551–559.

Lokeshwar, S D, Harper, B T, Webb, E, et al., 2019. Epidemiology and treatment modalities for the management of benign prostatic hyperplasia [J]. Transl Androl Urol 8 (5), 529–539.

Melo, EA., Bertero, EB, Rios, L A, et al., 2002. 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 [J]. Int. Braz J. Urol. 28 (5), 418–425.

Morgia, G, Russo, G I, Voce, S, et al., 2014. Serenoa repens, lycopene and selenium versus tamsulosin for the treatment of LUTS/BPH. An Italian multicenter double-blinded randomized study between single or combination therapy (PROCOMB trial) [J]. Prostate 74 (15), 1471–1480.

Nahata, A, Dixit, VK., 2012. Ameliorative effects of stinging nettle (Urtica dioica) on testosterone-induced prostatic hyperplasia in rats [J]. Andrologia 44 (1), 396–409.

Novara, G, Giannarini, G, Alcaraz, A, et al., 2016. Efficacy and safety of hexanic lipidosterolic extract of Serenoa repens (Permixon) in the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia: systematic review and meta-analysis of randomized controlled trials [J]. Eur Urol Focus 2 (5), 553–561.

Ooi, S L, Pak, S C, 2017. Serenoa repens for lower urinary tract symptoms/benign prostatic hyperplasia: current evidence and its clinical implications in naturopathic medicine [J]. J. Altern. Complement. Med. 23 (8), 599–606.

Pagano, E, Laudato, M, Griffo, M, et al., 2014. Phytotherapy of benign prostatic hyperplasia. A minireview [J]. Phytother. Res. 28 (7), 949–955.

Roehrborn, C G, Barkin, J, Siami, P, et al., 2011. Clinical outcomes after combined therapy with dutasteride plus tamsulosin or either monotherapy in men with benign prostatic hyperplasia (BPH) by baseline characteristics: 4-year results from the randomized, double-blind combination of avodart and tamsulosin (CombAT) trial [J]. BJU Int. 107 (6), 946–954.

Safarinejad, MR., 2005. Urtica dioica for treatment of benign prostatic hyperplasia: a prospective, randomized, double-blind, placebo-controlled, crossover study [J]. J. Herb. Pharmacother. 5 (4), 1–11.

Sapota, A, Darago, A, Taczalski, J, et al., 2009. Disturbed homeostasis of zinc and other essential elements in the prostate gland dependent on the character of pathological lesions [J]. Biometals 22 (6), 1041–1049.

Sökeland, J., 2000. Combined sabal and urtica extract compared with finasteride in men with benign prostatic hyperplasia: analysis of prostate volume and therapeutic outcome [J]. BJU Int. 86 (4), 439–442.

Tacklind, J, Macdonald, R, Rutks, I, et al., 2012. Serenoa repens for benign prostatic hyperplasia [J]. Cochrane Database Syst. Rev. 12, CD001423.

Vahlensieck, W, Theurer, C, Pfitzer, E, et al., 2015. Effects of pumpkin seed in men with lower urinary tract symptoms due to benign prostatic hyperplasia in the one-year, randomized, placebo-controlled GRANU study [J]. Urol. Int. 94 (3), 286–295.

Vela-Navarrete, R, Alcaraz, A, Rodríguez-Antolín, A, et al., 2018. Efficacy and safety of a hexanic extract of Serenoa repens (Permixon®) for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH): systematic review and meta-analysis of randomised controlled trials and observational studies [J]. BJU Int. 122 (6), 1049–1065.

Vela-Navarrete, R, Escribano-Burgos, M, Farré, A L, et al., 2005. Serenoa repens treatment modifies bax/bcl-2 index expression and caspase-3 activity in prostatic tissue from patients with benign prostatic hyperplasia [J]. J. Urol. 173 (2), 507–510.

Villa, L, Capogrosso, P, Capitanio, U, et al., 2019. Silodosin: An Update on Efficacy, Safety and Clinical Indications in Urology [J]. Adv. Ther. 36 (1), 1–18.