RESEARCH

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Effects of Protoves-M1® and IPB-tre® on the prevention and the treatment of irritative symptoms after REZUM therapy of benign prostatic hyperplasia (BPH)

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Abstract

Background: To analyze the role of Protopine and Nuciferine (Protoves-M1®) and IPB-tre® in the prevention and treatment of irritative symptoms after REZUM.
Materials and Methods: Fifty consecutive patients underwent REZUM between September 2020 and November 2022. All patients received a combined therapy with Protoves-M1® (Protopine and Nuciferine) syrup, 10 mL, once a day, and IPB-tre® 1 tablet/day two weeks before REZUM and for a period of 3 months, postoperatively and they were on medical therapy with alpha-blockers which were continued for 30 days after the procedure. Postoperative pain rating was assessed by visual analogue scale and efficacy and tolerability of therapy were evaluated by using Treatment Satisfaction Questionnaire for Medication (TSQM 1.4).
Results: Median age was 64.1 years old (interquartile range IQR 46–79) with a median prostate volume of 68.6 mL (IQR 40–160). The median operative time was 11.44 (IQR 7–16) minutes and patients received a median of 7.2 (IQR 4–14) PEEK vapor needle injections. After the interruption of anti-inflammatory therapy, we assisted in a significant decrease of VAS on the 10th postoperative day, with a median value of 1.6 (1-3). Median TSQM scores on effectiveness, side effect, convenience, and satisfaction were 75.2, 100.0, 82.5, and 85.9, respectively. Any grade of toxicity was reported.
Conclusion: A combined therapy with Protoves-M1® and IPB-tre® could be safe and efficient in reducing irritative symptoms after REZUM, even after the interruption of traditional anti-inflammatory therapy. Moreover, all patients reported a high level of satisfaction with the therapy in absence of side effects.
Keywords: Benign prostate hyperplasia, lower urinary symptoms, water vapor therapy, phytotherapy, outcomes

Introduction

Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) represent one of the most widespread diseases that affect men over 50 years of age, strongly influencing health-related quality of life [1, 2]. There is a correlation between symptoms related to BPH and patient age, leading, in some cases, to unfavorable outcomes such as acute urinary retention (AUR) or the need for surgery [3, 4]. Pharmacological therapy showed very limited adherence rates due to the collateral effects that these therapies could have on sexual life, with relevant implications on clinical outcomes [5]. Several surgical options exist for BPH management with a significant range of invasiveness, efficacy, and cost, including resection of the prostate, enucleation and vaporization of the prostate, open and minimal invasive simple prostatectomy [6]. Unfortunately, all these techniques are often associated with the retrograde ejaculation and increased morbidity for the patient.

The choice of a surgical approach is based on the severity of symptoms, patients' wish to preserve ejaculation, and anatomical characteristics of the prostate such as length and volume (PV), prostatic urethral angle (PUA), median lobe (ML), elevated central zone (ECZ), intravesical prostatic protrusion (IPP), and risk to bleeding [6-8]. In the last years, the clinical interest and application of

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minimally invasive surgical treatments (MISTs) for BPH, including water vapor thermal therapy (Rezūm System, Boston Scientific, Marlborough, MA, USA), has further increased, and actually MISTs represent a valid alternative to any pharmacotherapy or traditional endoscopic surgery [9-17]. One of the most relevant clinical and economic advantages of Rezūm treatment is represented by the possibility of performing this treatment under local anesthesia in an office setting. Steam is injected into the hyperplastic prostatic tissue through a dedicated cystoscope for a short amount of time (9 seconds for each injection), thus releasing thermal energy (540 calories/mL H_2O) and leading to cell membrane disruption [15-17]. Starting from the 4th postoperative week, the prostatic tissue shrinks up to 40%, with an improvement in urinary symptoms and quality of life and with a low risk (4–10%) for retrograde ejaculation [15]. Unfortunately, in the early postoperative phase, patients can claim irritative symptoms which can impact their quality of life.

Phytotherapy has been recently proposed as a valid alternative to medical drugs in the therapy of prostatic inflammation and BPH and its efficacy has been also suggested by a recent study [18]. This study aimed to analyze the efficacy of Protopine and Nuciferine (Protoves-M1®) and IPB-tre® in the prevention and treatment of irritative symptoms (urgency and dysuria) associated with water vapor thermal therapy.

Materials and methods

This was an observational study including 50 consecutive patients who underwent REZUM therapy for BPH from September 2020 to November 2022. All patients received combined therapy with Protoves-M1® (Protopine 4,8 mg and Nuciferine 500 mg) syrup, 10 mL once a day, and IPB-tre® (pinaster 5 mg, Serenoa repens 320 mg) 1 tablet/day: the therapy was administered two weeks before REZUM and continued for a period of 3 months, postoperatively. All included patients were on medical therapy with alpha-blockers (AB) which was continued for 30 days after the procedure. Anti-inflammatory therapy with oral ibuprofen 600 mg and antibiotic therapy with cephalosporins twice daily was maintained for the 3 postoperative days.

We included in the study patients affected by symptomatic BH after failure of the medical therapy but we excluded patients with severe systemic diseases (ASA III or IV), post-void residual urine ≥ 300 mL, increased risk for intra- and postoperative bleeding, chronic pelvic pain, urinary tract infection, neurological disease, overactive bladder, bladder lithiasis, chronic renal insufficiency, tachycardia, and heart failure. Postoperative pain rating was assessed on the 1st postoperative day, at 10 postoperative days (at catheter removal), and 1 month after the procedure by visual analog scale (VAS).

The efficacy and tolerability of the therapy were evaluated by using a self-report Treatment Satisfaction Questionnaire for Medication (TSQM 1.4), which consisted of 14 items in four scales: effectiveness, side effect, convenience, and satisfaction. Scores ranged from 0 (extremely dissatisfied) to 100 (extremely satisfied) and were separated into 4 groups: 0-25 (not satisfied), 26-50 (not satisfied or dissatisfied), 51-75 (satisfied), 76-100 (very satisfied) [19] (Table 1). Furthermore, patients were assessed at 1-, 3- and 6- months follow-ups for symptom relief (IPSS: International Prostatic Symptoms Score), peak urinary flow rate (Qmax), postvoid residual volume (PVR), voided volume, prostate serum antigen (PSA).

Continuous parametric variables were reported as the median and interquartile range (IQR). Categorical variables were reported as frequencies and proportions. The Student's paired t-tests were used to compare two dependent factors. Statistical significance was set as $p < 0.05$. All tests were two-sided. Analyses were performed using STATA v.14.1 (StataCorp LP, College Station, TX, USA), and graphics using Microsoft® Excel Professional Plus 2016.

Results

The median age was 64.1 years old (interquartile range IQR 46–79) with a median ASA of 2 (IQR 1–3) and a median PSA of 3.79 (IQR 0.41–23). Median prostate volume was 68.6 mL (IQR 40–160) and a middle lobe was pre-

Table 1. Final items for the treatment satisfaction questionnaire for medication (TSQM).

Item	TSQM Item
1	How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
2	How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
3	How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?
4	As a result of taking this medication, do you currently experience any side effects at all?
5	How bothersome are the side effects of the medication you take to treat your condition?
6	To what extent do the side effects interfere with your physical health and ability to function (*i.e.*, strength, energy levels, *etc.*)?
7	To what extent do the side effects interfere with your mental function (*i.e.*, ability to think clearly, stay awake, *etc.*)?
8	To what degree have medication side effects affected your overall satisfaction with the medication?
9	How easy or difficult is it to use the medication in its current form?
10	How easy or difficult is it to plan when you will use the medication each time?
11	How convenient or inconvenient is it to take the medication as instructed?
12	Overall, how confident are you that taking this medication is a good thing for you?
13	How certain are you that the good things about your medication outweigh the bad things?
14	Taking all things into account, how satisfied or dissatisfied are you with this medication?

sented in 70% of the patients.
Before the treatment, all patients received treatment with alpha-blockers (AB) for a period of a minimum of 1 year and 5 patients (10%) received combination therapy with 5-alpha reductase inhibitors (5-ARI), but without a clinical benefit (median IPSS 27.1; IQR 14–35). Nevertheless, no patients referred pain at baseline.
At preoperative uroflowmetry, the preoperative median Q_{max} was 10.1 (IQR 3.5–16.4) with a median PVR of 101.3 mL (IQR 33–250). Two patients (4%) had acute urinary retention (AUR) and an indwelling catheter was preoperatively inserted (Table 2).

Table 2. Pre-operative characteristics of the patients.

Variable	Patients (n = 50)
Median age (years)	64.1 (IQR 46–79)
Median ASA score	2 (IQR 1–3)
Median PSA (ng/mL)	3.79 (IQR 0.41–23)
Prior prostate biopsy (n, %)	4 (8%)
Median prostate size (mL)	68.6 (IQR 40–160)
Middle lobe rate (n, %)	35 (70%)
AB therapy (n)	50
5-ARI therapy (n)	5
Preoperative median IPSS	27.1 (IQR 14–35)
Preoperative median Q_{max} (mL/s)	10.1 (IQR 3.5–16.4)
Preoperative median postvoid residual (mL)	101.3 (IQR 33–250)

The median operative time from the instrument transurethral insertion to patient catheterization was 11.44 (IQR 7–16) minutes. Patients received a median of 7.2 (IQR 4–14) PEEK vapor needle injections and the median time for dismissal was 1.5 hours after the procedure (IQR 1–2). The indwelling urinary catheter was removed after a median of 11.7 (IQR 10–30) days.
Patients reported a significant decrease of IPSS from baseline at first [27.1 (IQR 14–35) *vs* 16.8 (IQR 7–32), $p = 0.03$], third [27.1 *vs* 9.6 (IQR 2–22), $p < 0.02$] and sixth [27.1 *vs* 5.3 (IQR 0–12), $p < 0.0001$] month after surgery. Nevertheless, at a 3-month follow-up, 4 patients (8%) maintained a pharmacological therapy with AB.
The median VAS on 1st postoperative day was 2.9 (IQR 2–4). After the interruption of anti-inflammatory therapy with ibuprofen, we assisted in a significant decrease of VAS on the 10th postoperative day, with a median value of 1.6 (1–3). At 1 postoperative month, only 3 patients (6%) referred a VAS of 1.
Median TSQM scores on effectiveness, side effects, convenience, and satisfaction were 75.2, 100.0, 82.5, and 85.9, respectively. Any grade of toxicity was reported (Table 3).

Discussion

In the last decade, novel MISTs-like Rezum System have represented an effective and safe procedure in the treatment of BPH. McVary *et al.* [7] reported a double-blind Rezum RCT, suggesting a significant and long-term mean IPSS score improvement. Mean IPSS improvement from baseline remained significant from the early response at 3 months (49.9%) to 1 year (52.2%), 2 years (50.7%), 3 years (49.7%), and 4 years (46.7%), $p < 0.0001$. Moreover, IPSS quality of life (QoL) (42.9%, $p < 0.0001$) and Q_{max} (49.5%, $p < 0.0001$) improved significantly at a 4-year follow-up. An improvement of urinary outcomes [median Q_{max} of + 8.9 mL/s (IQR 5–13), median IPSS of –12 ($p < 0.01$), and a median PVR of –65.6 cc ($p < 0.001$)] was also reported in another recent study [20].
The physical principle of REZUM is based on the convective properties of water, releasing large amounts of stored thermal energy (540 calories/mL H_2O) as the vapor contacts prostate tissue and condenses back to the water. In this way, the vapor disrupts prostatic hyperplasic cells and shrinks the obstructive treated tissue. No thermal effects occur outside the targeted treatment zone [7]. Nevertheless, the high temperature of the water vapor at 103°C and its injection by a needle can determine an inflammation of the treated prostatic tissue, which is responsible for postoperative irritative urinary symptoms such as urgency and dysuria [17].
In the last years, the role of phytotherapy in the treatment of prostatic inflammation and BPH has increased, and it has been well-defined [18]. *In vitro*, plant extracts can have anti-inflammatory, anti-androgenic, and estrogenic effects; they can decrease sexual hormone binding globulin, inhibit several enzymatic activities (aromatase, lipoxygenase, 5 α-reductase), growth factor-stimulated proliferation of prostatic cells, α-adrenoceptors, muscarinic cholinoceptors, dihydropyridine receptors, vanilloid receptors and neutralize free radicals [21]. A small trial by Shoskes *et al*. investigated the clinical efficiency of quercetin, a bioflavonoid with antioxidative properties. The daily use of Quercetin (500 mg 2 times per day) over a period of 4 weeks was associated with a significant improvement of urinary symptoms compared with placebo [22, 23]. Another clinical trial analyzed the therapeutic benefit of cernilton, a standardized pollen extract [24]. Even in this clinical experience, a 3-month therapy of cernilton (two capsules every 8 h) determined a significant improvement in the symptoms compared with a placebo. With only very few side effects, phytotherapeutic agents can be recommended as primary therapy or a combination in multimodal treatment regimens in the management of chronic prostatitis and chronic pelvic pain syndrome [22].
A recent Italian study evaluated the role of Protopine associated with Nuciferine in controlling adverse events during hyperthermic intravesical chemotherapy instillations, suggesting that Protopine and Nuciferine syrup can be an interesting alternative to anti-inflammatory and antimuscarinic agents to treat irritative and pain related symptoms of intravesical chemo/immunotherapy [25].
Several studies have suggested an anticholinergic and GABAergic action of Protopine and its capacity to positively influence some neurological systems responsible for bladder functions [25-29]. Moreover, its anti-acetylcholinesterase action gives it an anti-amnesic effect that al-

Table 3. Postoperative outcomes.

Variable	Patients (n = 50)
Median operative time (minutes)	11.44 (IQR 7–16)
median PEEK vapor needle injection	7.2 (IQR 4–14)
the median time for dismissal after the procedure (hours)	1.5 (IQR 1–2)
Median indwelling urinary catheter time (days)	11.7 (IQR 10–30)
Postoperative median IPSS	
1-month	616.8 (IQR 7–32)
3-month	9.6 (IQR 2–22)
6-month	5.3 (IQR 0–12)
VAS	
1st postoperative day	2.9 (IQR 2–4)
10th postoperative day	1.6 (IQR 1–3)
30th postoperative day	0.06 (IQR 0–1)
TSQM	
Effectiveness	75.2 (IQR 50–100)
side effect	100.0 (IQR 100–100)
convenience	82.5 (IQR50–100)
satisfaction	85.9 (IQR50–100)

leviates certain memory deficiencies reported in dementia [30]. Protopine increases the p53-mediated transcriptional activity, resulting in the stabilization of the p53 protein. It exerts an antiproliferative activity and it is supposed to have a potential effect as a chemo-preventive agent for colon cancer [31]. Nuciferin is a partial antagonist of D2-like receptor and has a demonstrated regulatory action on the dopaminergic system affecting the bladder muscles and nerves [32]. Moreover, Nuciferin can reduce states of tension and anxiety with a pharmacologic profile similar to Chlorpromazine [33, 34]. Nuciferine also significantly inhibited the lipopolysaccharide (LPS)-induced inflammatory cytokine IL-6 and TNF-α production in RAW 264.7 cells having potential anti-inflammatory activities [35]. Its use significantly decreases the expression of TLR4 in a dose-dependent manner and potently improves LPS-induced mastitis by inhibition of the TLR4-NF-κB signaling pathway [36]. Finally, Nuciferine reduces fructose-induced inflammation by blocking TLR4/PI3K/NF-κB signaling and NLRP3 inflammasome activation in rat renal cortex and HK-2 cells, which may contribute to the improvement of renal injury [37].

In our experience, Protopine associated with Nuciferine was adopted in combination of Serenoa repens, Pinus pinaster, and β-sitosterol, which are present in IPB-tre®. Serenoa repens has a well-known anti-inflammatory, anti-hemogenic and anti-androgenic activity [38]. Pinus pinaster is a bark extract rich in Oligomeric proanthocyanidins (OPC) with strong anti-inflammatory and antioxidant properties [39]. β-sitosterol is an antagonist of DHT for the receptor located on the cellular membrane of prostate cells, thus lowering the hyperproliferation and stimulation by DHT that leads to BPH. Moreover, β-sitosterol does not interfere with 5-α-reductase, thus avoiding reports of sexual dysfunction [40]. All patients underwent combined therapy with Protoves-M1® and IPB-tre® for a period including two weeks before REZUM and 3 months post-operatively. Interestingly, after interruption of anti-inflammatory therapy with ibuprofen and maintaining therapy with Protoves-M1® and IPB-tre®, we assisted in a significant decrease of VAS at the 10th postoperative day, with a median value of 1.6 (1–3). At 1 postoperative month, only 3 patients (6%) referred a VAS of 1.

TSQM 1.4 is a validated questionnaire that evaluates global satisfaction with the performance of a medication. The combined therapy did not reveal significant side-effect (median TSQM scores on side effects was 100%). All patients were satisfied concerning the effectiveness of the combined therapy (median TSQM scores of 75.2) but they were very satisfied with the convenience and results of the therapy (median TSQM scores on convenience and satisfaction were 82.5 and 85.9, respectively). Finally, any grade of toxicity was reported during the period of the combined therapy with Protoves-M1® and IPB-tre®. Nevertheless, the positive effect of Protoves-M1® and IPB-tre® on irritative symptoms in the early postoperative period was strengthened by the association with AB therapy.

Conclusions

Combined therapy with Protoves-M1® and IPB-tre® could be safe and efficient in reducing irritative symptoms after REZUM, even after the interruption of traditional anti-inflammatory therapy. Moreover, all patients reported a high level of satisfaction with the therapy in the absence of side effects. Nevertheless, we suggest maintaining an AB therapy for the early 30 postoperative days to strengthen the positive effect of Protoves-M1® and IPB-tre®. More observational studies with a greater cohort of patients and longer follow-up should investigate the possibility of replacing traditional anti-inflammatory therapy with combined phytotherapy for the treatment of irritative symptoms which can be reported after surgical therapy of BPH.

Declarations

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Conflicts of interest: Francesco Greco is a member of the editorial board of *Uro-Technology Journal*. The authors declare that they have no conflicts and were not involved in the journal's review or decision regarding this manuscript.

Ethical statement: This study was approved by the Institute Research Medical Ethics Committee of Centro Salute Uomo. All patients were informed of the procedures and provided written informed consent.

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