European Review for Medical and Pharmacological Sciences 2020; 24: 9116-9120

Postoperative treatment with phytotheraphy Graminex G63 (CERNILEN-Flogo®) after greenlight laser XPS (180W) photovaporization of the prostate (PVP), can affect patient's quality of life?

A.B. DI PASQUALE[1], A. CASSANI[1,2], S. MASCIOVECCHIO[1], G. ZASA[1,2], G. RANIERI[1], G. ROMANO[1], L. DI CLEMENTE[1]

[1]Department of Urology, "S. Salvatore" Hospital, Urology Unit, L'Aquila, Italy; ASL Abruzzo 1 ,L'Aquila, Italy
[2]Università degli Studi dell'Aquila, Italy; ASL Abruzzo 1, Dipartimento Medicina Clinica, Sanità Pubblica, Scienze della Vita e dell'Ambiente, Urology, L'Aquila, Italy

Abstract. – OBJECTIVE: Phytotherapic treatment as Cernilen-flogo® is commonly used to treat chronic pelvic pain, chronic prostatitis, and BPE (benign prostatic enlargement). In our study, for the first time, we aim to evaluate postoperatively Cernilen-flogo® therapy in patients with BPE/LUTS (lower urinary tract symptoms) previously treated with Greenlight laser XPS (180W) photovaporization of prostate (PVP) to improve surgical outcomes.

MATERIALS AND METHODS: We collected data from patients treated with PVP for BPE/LUTS international prostate symptom score (IPSS) >20 unresponding to conventional treatment. Two groups of patients were analyzed: Group A including 15 patients (50%) treated postoperatively with Cernilen-flogo® *vs*. no treatment Group B. One expert surgeon performed all the procedures.

RESULTS: 30 patients included with BPE/LUTs previously treated with PVP. There was no difference between patients' demographic, median age, prostate volume and PSA (prostate specific antigen) level. All patients had a postoperative evaluation after 30-45 days. Patients with postoperative complications (acute urinary retention, postoperative hematuria) were excluded from our study. All patients had a preoperative and postoperative evaluation of IPSS, bother score (BS) and pelvic discomfort (visual analogic scale VAS). Preoperatively there was no significative difference in IPSS, BS and VAS. IPSS Group A was postoperatively 7.13 (SD 1.64) and Group B was 7.33 (SD 1.58) (*p*=0.67); BS Group A was postoperatively 1.33 (SD 0.81), Group B was 1.73 (SD 1.09) (*p*=0.30), and VAS Group A was 2.73 (SD 1.9) and Group B was 4.33 (SD 1.58) (*p*=0.004) showing a statistically significative difference between the two groups in pelvic discomfort with a better outcome in patients treated with Cernilen-flogo®.

CONCLUSIONS: Our study showed that Cernilen-flogo® treatment after PVP is effective and minimize patient's pelvic discomfort showed by lower VAS level resulting in better postoperatively patient's quality of life (QOL).

Key Words:
Benign prostatic hyperplasia, Cernilen-flogo®, Prostatitis, Photovaporization of prostate PVP, Lower urinary tract symptoms LUTS, Cernitin pollen extract, Phytotherapy, Prostatic hyperplasia, Histological prostatitis, Integrative medicine, Complementary and alternative medicine.

Introduction

Benign Prostatic Enlargement (BPE) is a common condition that affects 50-75 % of 50 years old men and 80% of 70 years old men and older[1]. There are a lot of possible therapies for this condition, including medical and surgical treatments[2,3]. Laser vaporization of the prostate (PVP) is one of the possible treatments, commonly used in patients with low prostate volume and comorbidity that indicate a more secure surgical technique[4]. There is a lack in the literature regarding postoperative medical treatment after this surgical procedure to reduce irritative LUTS (lower urinary tract symptoms) caused by the procedure. Cernilen-flogo® is a Phytotherapic treatment commonly used in chronic prostatitis and chronic pelvic pain com-

Corresponding Author: Alessandra Cassani, MD; e-mail: alessandra.cassani73@gmail.com

posed by: Graminex G63 a pollen extract with anti-androgenic and anti-inflammatory effects influencing alpha1-adrenoblockers located in the zone of the detrusor and urethra[5], Quercetin a bioflavonoid anti-inflammatory drug[6], Bromelain anti-inflammatory anti-edematous proprieties[7], Valerian anti-stress and decongestant proprieties and Mallow anti spasmolytic and analgesic agent. We aim to report the efficacy of Cernilen-flogo® therapy after surgical treatment in reducing pelvic discomfort and postoperatively pain level.

Patients and Methods

Patients and Study Population

We retrospectively collected data about patients treated with laser Photo vaporization of the prostate (PVP) with greenlight laser XPS (180W) for BPE/LUTS with international prostate symptom score (IPSS) >20 and prostate volume between 45 to 65 ml unresponding to pharmacological therapy (alpha-blockers). A total of 30 patients were included in our study. All patients underwent classical surgical PVP treatment performed by the same expert surgeon. After surgery, patients were randomly divided in two groups. 15 patients in Group A (50%) were treated postoperatively with Cernilen-flogo® (1-2 tablet/day for 45 days); the other 15 patients in Group B (50%) had not additional therapy after the surgical treatment. All patients had a postoperative evaluation after 30-45 days.

Our analyses included data about patients' demographic age measured in years Group A 65.2 (SD 8.3), Group B 69.4 (SD 6.23) (p=0.11); prostate volume Group A 58 ml (SD 9.59), Group B 62 ml (SD 12.07) (p=0.35) and PSA (prostate specific antigen) level Group A 3.04 ng/ml (SD 0.75), Group B 2.75 ng/ml (SD 0.73) (p=0.25). All patients had a preoperative and postoperative evaluation of IPSS; Bother score (BS) and pelvic discomfort analyzed by Visual analogic scale (VAS) with 0 as no pain and 10 high level of pain and pelvic discomfort. Were excluded from our study patients that showed postoperative complication (acute urinary retention RAU, postoperative hematuria who required a second surgical treatment).

Statistical Analysis

Descriptive analyses were employed. Quantitative variables were reported as absolute and relative frequencies (%). Quantitative variables were reported as median and Standard deviation (SD). T student test for paired data tested the hypothesis that the median IPSS, BS and VAS were different before the treatment than after, and between the two groups. A level of statistical significance was set at p-value $p< 0.05$.

Results

There was no statistically significant difference between the patients' demographic between the two groups. Median age of Group A was 65.2 years (SD 8.3) *vs.* Group B 69.4 years (SD 6.23) (p=0.11); prostate volume of Group A was 58 ml (SD 9.59) *vs.* Group B 62 ml (SD 12.07) (p=0.35) and PSA level of Group A was 3.04 ng/ml (SD 0.75) *vs.* Group B 2.75 ng/ml (SD 0.73) (p=0.25).

Group A Median IPSS was preoperatively 22.6 (SD 2.5) and postoperatively 7.13 (SD 1.64) (p=0.001); median BS was preoperatively 5.06 (SD 1.48) and postoperatively 1.33 (SD 0.81) (p=0.001) and median VAS was preoperatively 1.8 (SD 0.86) and postoperatively 2.73 (SD 1.9) (p=0.14).

Group B Median IPSS was 21.27 (SD 2.25) preoperatively and 7.33 (SD 1.58) (p=0.001) postoperatively; median BS was preoperatively 5.13 (SD 1.12) and postoperatively 1.73 (SD 1.09) (p=0.001) and median VAS was preoperatively 1.66 (SD 0.89) and postoperatively4.33 (SD 1.58) (p=0.001).

According to the literature[3,8-9], these analyses show the efficacy of the surgical PVP treatment with a statistically significant improvement in all the variables analyzed (Table I).

After this analysis, we compared the two groups' results to highlight the improvement defined by the assumption of Cernilen-flogo®. Comparing the two groups Group A *vs.* Group B preoperatively IPSS (p=0.22); BS (p=0.86) and VAS (p=0.16), there were no statistically significant differences between the two groups.

Postoperative values of IPSS (p=0.67); Bother score (p=0.30) and VAS (p=0.004) were compared between group A and Group B, showing a statistically significant difference between the two groups when analyzing the pelvic discomfort with an improvement in the Group A treated with Cernilen-flogo®.

Discussion

Phytotherapy is a commonly used treatment for pelvic conditions. Cernilen-flogo® is commonly used to treat pelvic discomfort caused by chronic

Table I. Variables analyzed preoperatively and postoperatively.

	Group A (Cernilen 1/day)	Group B (no therapy)	*p*-value
IPSS preoperatively	22.6 (SD 2.5)	21.27 (SD 2.25)	$p = 0.22$
IPSS postoperatively	7.13 (SD 1.64)	7.33 (SD 1.58)	$p = 0.67$
BS preoperatively	5.06 (SD 1.48)	5.13 (SD 1.12)	$p = 0.86$
BS postoperatively	1.33 (SD 0.81)	1.73 (SD1.09)	$p = 0.30$
VAS preoperatively	1.8 (SD 0.86)	1.66 (SD 0.89)	$p = 0.16$
VAS postoperatively	2.73 (SD 1.9)	4.33 (SD 1.58)	$p = 0.004$

IPSS: International Prostate Symptom Score; BS: Bother Score; VAS: Visual Analogical Scale; SD: Standard Deviation.

non-bacterial prostatitis, chronic pelvic pain and BPE/LUTS of low-moderate grade in association with conventional therapy. The European association of urology guidelines recommends the use of cernitin pollen extract for patients with inflammatory prostate pain syndrome.

For the first time, we analyzed in a small cohort, the efficacy of phytotherapy treatment after surgical treatment with PVP with the aim to decrease the pelvic discomfort commonly relied to the PVP surgical treatment.

Literature shows the benefit of this surgical procedure highlighting the safety and efficacy of PVP even in a critical patient that can't tolerate the same procedure with bipolar or monopolar system TURP (transurethral resection of the prostate)[3,8,9].

Literature shows the benefit of phytotherapy treatment for urological condition as UTIs (urinary tract infection) as prevention for recurrence, Ledda et al[10-12] showed the benefit of Cranberry extract supplementation in patients with UTI with a lower recurrence rate in the group treated with phytotherapy. Berretta et al[13,14] analyzed in their studies the use of Complementary and Alternative Medicine (CAM) in chronic disorders, including cancer and the knowledge and attitude of the physician in prescribing CAM therapies. In a study, they interviewed 468 patients under treatment for cancer and showed that 48.9% of patients were CAM users (67.7% self-prescribed, 11.4 % prescribed by doctors) highlighting the importance of physicians' knowledge of alternative medicine to educate patients about beneficial effects and toxicity, potential adverse events and to guide treatment modalities and dosage (85% of patients were not aware of potential risk, side effects and interaction of CAM). They showed how CAM therapies should be better studied by health care professional, because of its large use, to establish integrated individualized therapeutic regimens to improve the potential beneficial role of CAM and minimize the potential toxicity.

In their *in vitro* study, Dizeyiet al[15] highlights the mechanism of action of pollen extract to explain its clinical effect. They demonstrate that pollen extract regulates cytokines level in both prostatic cell lines and is associated with decreased androgen receptor and prostate specific antigen levels, resulting in anti-inflammatory and anti-androgenic proprieties.

In a study, Togo et al[16] and to develop an ideal protocol to avoid an unnecessary biopsy procedure.\nMethods: A total of 61 patients were administrated cernitin pollen extract tablets (two tablets t.i.d. analyzed the efficacy of cernitin pollen extract in preventing unnecessary biopsy procedures in patients with high PSA levels. The study demonstrated the anti-inflammatory proprieties of pollen extract by showing a decrease of PSA serum level in 72.1% of patients with a mean change in serum PSA level from the baseline -0.6 ± 1.4 ng/mL ($p = 0.0003$), with a more relevant change in PSA level in patients with negative biopsy results and negative MRI (Magnetic resonance imaging) findings before biopsy.

Wagenlehner et al[5] reported the effect of 12-week administration of cernitin pollen extract in chronic prostatitis/chronic pelvic pain syndrome patients with a statistically significant decrease of NIH-CPSI total and pain domain scores when compared with placebo (-8.72 *vs.* -4.77, $p = 0.0003$; and -4.93 *vs.* -2.79, $p=0.0009$; respectively) with an improvement in patients' quality of life.

Qian et al[17] in their study analyzed the efficacy of cernitin pollen extract (Cernilton®) in patients with histological prostatitis after TURP in decreasing LUTS and sexual dysfunction related to the procedure. They divided the patients in three groups according to the grade of histo-

logical prostatitis in A low grade, B moderate, C high grade and randomized the patients' in Cernilton® therapy *vs.* placebo. Their study showed a statistically significative improvement in LUTS (QOL Cernilton® *vs.* control 2.6 ± 0.3 *vs.* 3.7 ± 0.6 $p<0.05$ Storage symptoms 2.3 ± 0.5 *vs.* 3.4 ± 0.7 $p<0.05$) and sexual dysfunction (IIEF5 Cernilton® *vs.* control group 10.7 ± 0.4 *vs.* 5.2 ± 0.3 $p<0.05$) in the high grade group, only in sexual dysfunction in moderate group (IIEF5 Cernilton® *vs.* control group 11.2 ± 1.8 *vs.* 6.2 ± 0.8 $p<0.05$) and no difference in the low grade group. With this study, they demonstrate that in patients with histological prostatitis after TURP, Cernilton® can improve the lower urinary tract symptoms and sexual dysfunction depending on the grade of prostatitis.

In our study, according to literature, we highlight the efficacy of pollen extract as an anti-inflammatory drug as demonstrate by the improvement in patients' quality of life.

The main limitation of our study is the small sample size and the follow-up was only 30-45 days. More studies, larger sample size and longer duration of follow-up are required to confirm the therapeutic efficacy.

Conclusions

Our study showed that, in patients previously treated with PVP, postoperative treatment with Cernilen-flogo® is an effective therapy when analyzing the patient's pelvic discomfort. Our statement is supported by the improvement in the VAS level achieving lower pelvic discomfort and resulting in a better quality of life in the postoperative time.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

We would like to thank all the urologists that performed the procedures and followed the patients during the follow-up.

References

1) Egan KB. The epidemiology of benign prostatic hyperplasia associated with lower urinary tract symptoms. Urol Clin North Am 2016; 43: 289-297.
2) Lokeshwar SD, Harper BT, Webb E, Jordan A, Dykes TA, Neal DE Jr, Terris MK, Klaassen Z. Epidemiology and treatment modalities for the management of benign prostatic hyperplasia. Transl Androl Urol 2019; 8: 529-539.
3) Cornu J-N. Bipolar, monopolar, photovaporization of the prostate, or holmium laser enucleation of the prostate. Urol Clin North Am 2016; 43: 377-384.
4) Barco-Castillo C, Plata M, Zuluaga L, Santander J, Trujillo CG, Caicedo JI, Serrano A, Fernández N, Azuero J. Functional outcomes and safety of Green Light photovaporization of the prostate in the high-risk patient with lower urinary tract symptoms due to benign prostatic enlargement. Neurourol Urodyn 2020; 39: 303-309.
5) Wagenlehner FME, Schneider H, Ludwig M, Schnitker J, Brähler E, Weidner W. A pollen extract (Cernilton) in patients with inflammatory chronic prostatitis-chronic pelvic pain syndrome: a multicentre, randomised, prospective, double-blind, placebo-controlled phase 3 study. Eur Urol 2009; 56: 544-551.
6) Lu Y, Jia YP. Quercetin upregulates ABCA1 expression through liver X receptor alpha signaling pathway in THP-1 macrophages. Eur Rev Med Pharmacol Sci 2016; 20: 3945-3952.
7) Inchingolo F, Tatullo M, Marrelli M, Inchingolo AM, Picciariello V, Inchingolo AD, Dipalma G, Vermesan D, Cagiano R. Clinical trial with bromelain in third molar exodontia. Eur Rev Med Pharmacol Sci 2010; 14: 771-774.
8) Akhtar OS, Raina S. A study of the role of 180W XPS lithium triborate laser in the treatment of patients with lower urinary tracts symptoms due to benign prostatic hyperplasia. J Lasers Med Sci 2018; 9: 261-267.
9) Bachmann A, Muir GH, Collins EJ, Choi BB, Tabatabaei S, Reich OM, Gómez-Sancha F, Woo HH. 180-W XPS greenlight laser therapy for benign prostate hyperplasia: early safety, efficacy, and perioperative outcome after 201 procedures. Eur Urol 2012; 61: 600-607.
10. Ledda A, Bottari A, Luzzi R, Belcaro G, Hu S, Dugall M, Hosoi M, Ippolito E, Corsi M, Gizzi G, Morazzoni P, Riva A, Giacomelli L, Togni S. Cranberry supplementation in the prevention of non-severe lower urinary tract infections: a pilot study. Eur Rev Med Pharmacol Sci 2015; 19: 77-80.
11) Ledda A, Belcaro G, Dugall M, Riva A, Togni S, Eggenhoffner R, Giacomelli L. Highly standardized cranberry extract supplementation (Anthocran®) as prophylaxis in young healthy subjects with recurrent urinary tract infections. Eur Rev Med Pharmacol Sci 2017; 21: 389-393.
12) Ledda A, Belcaro G, Dugall M, Feragalli B, Riva A, Togni S, Giacomelli L. Supplementation with high titer cranberry extract (Anthocran®) for the prevention of recurrent urinary tract infections in elderly men suffering from moderate prostatic hyperplasia: a pilot study. Eur Rev Med Pharmacol Sci 2016; 20: 5205-5209.
13) Berretta M, Della Pepa C, Tralongo P, Fulvi A, Martellotta F, Lleshi A, Nasti G, Fisichella R, Romano C, De Divitiis C, Taibi R, Fiorica F, Di Francia R, Di

Mari A, Del Pup L, Crispo A, De Paoli P, Santorelli A, Quagliariello V, Iaffaioli RV, Tirelli U, Facchini G. Use of complementary and alternative medicine (CAM) in cancer patients: an Italian multicenter survey. Oncotarget 2017; 8: 24401-24414.

14. Berretta M, Di Francia R, Cazzavillan S, Rossi P, Scorba A, Sciacca PG, Santagà D. Integrative Medicine in Oncology, Milan October 19th, 2019. WCRJ 2019; 6: e1400.

15) Dizeyi N, Mattisson IY, Ramnemark L, Grabe M, Abrahamsson PA. The effects of Cernitin® on inflammatory parameters and benign prostatic hyperplasia: an in vitro study. Phytother Res 2019; 33: 2457-2464.

16) Togo Y, Ichioka D, Miyazaki J, Maeda Y, Kameyama K, Yasuda M, Hiyama Y, Takahashi S, Nagae H, Hirota S, Yamamoto S; Japanese Research Group for Urinary Tract Infection (JRGU). Oral administration of cernitin pollen extract (Cernilton ®) for 30 days might be useful to avoid unnecessary biopsy in prostate biopsy candidates: a preliminary study. Int J Urol 2018; 25: 479-485.

17) Qian X, Kong X, Qian Y, Xu D, Liu H, Zhu Y, Guan W, Zheng J, Wang Z, Qi J. Therapeutic efficacy of Cernilton in benign prostatic hyperplasia patients with histological prostatitis after transurethral resection of the prostate. Int J Clin Exp Med 2015; 8: 11268-11275.