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Original Article

Therapeutic efficacy of Cernilton in benign prostatic hyperplasia patients with histological prostatitis after transurethral resection of the prostate

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Abstract: Objective: This study was to prospectively evaluate the therapeutic efficacy of Cernilton in benign prostatic hyperplasia (BPH) patients with histological prostatitis after transurethral resection of the prostate (TURP). Materials and methods: One hundred patients with histological prostatitis were recruited from January 2007 to January 2013. All patients were divided into groups A (mild), B (moderate), and C (severe) based on symptom severity, and then randomly subgrouped into Cernilton group and control group. Patients in Cernilton group were treated with Cernilton for 3 months after TURP, while patients in control group received placebo. A series of patient indicators were evaluated before, perioperatively (peri), and after TURP. Results: The assessed indicators remained unchanged peri-TURP as compared to those before surgery. 6 months after TURP, indicators remained stable in group A, and significant differences were observed in the International Index of Erectile Function-5 (IIEF-5) in group B and in the storage symptom score (Ss), quality of life (QoL) and IEFF-5 in group C. In addition, there were significant differences in Ss, QoL and IEFF-5 between Cernilton group and control group. Conclusion: In BPH patients with histological prostatitis after TURP, Cernilton can improve the lower urinary tract symptoms and sexual dysfunction depending on the grade of prostatitis.

Keywords: Prostatic hyperplasia, histological prostatitis, cernilton, transurethral resection of prostate

Introduction

Benign prostatic hyperplasia (BPH) is a common urological disease with a prevalence of approximately 40% for men in their fifties that increase to 90% for men in their nineties [1, 2]. Prostatitis is one of risk factors of BPH. Nearly 20% of patients with BPH-related lower urinary tract symptoms (LUTS) may have concomitant symptoms of prostatitis [3]. It has been found that 70% of men with urinary retention have acute and/or chronic intraprostatic inflammation, 45% of whom also experience LUTS [4, 5]. However, even after the transurethral resection of prostate (TURP), about 10%-30% of men with BPH may still suffer from LUTS [6, 7]. Thus, it is important to administer pharmacotherapy in these patients to relieve LUTS symptoms after TURP.

Cernilton is commonly used to treat patients with prostatitis and has been reported to reduce LUTS [8]. While Cernilton clearly improves symptoms of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and delays BPH progression before an operation, the clinical benefits of sustained Cernilton therapy in patients with histological prostatitis after TURP have not been well studied. Thus, a prospective, randomized, and controlled study was conducted from January 2007 to January 2013 and the therapeutic efficacy of Cernilton was

Table 1. Classification criteria of prostatic inflammatory infiltrates

Feature	Details
Anatomical location	Histological pattern
Glandular and/or lumens	Inflammatory infiltrates located within duct/gland epithelium and/or lumens
Periglandular	Inflammatory infiltrates located within the stroma, centered around ducts/glands, and within 50 mm of ducts/glands
Stromal	Inflammatory cells located within prostatic stroma but not centered on prostatic glands/ducts and ≥ 50 mm from ducts/glands
Extent	Percent tissue area with inflammatory cell infiltrates
Focal	< 10%
Multifocal	10 ± 50%
Diffuse	> 50%
Grade	Morphological description (typical inflammatory cell density; cells/mm^2)
1 (mild)	Individual inflammatory cells, most of which are separated by distinct intervening spaces (< 100)
2 (moderate)	Confluent sheets of inflammatory cells with no tissue destruction or lymphoid nodule/follicle formation (100 ± 500)
3 (severe)	Confluent sheets of inflammatory cells with tissue destruction and/or nodule/follicle formation (> 500)

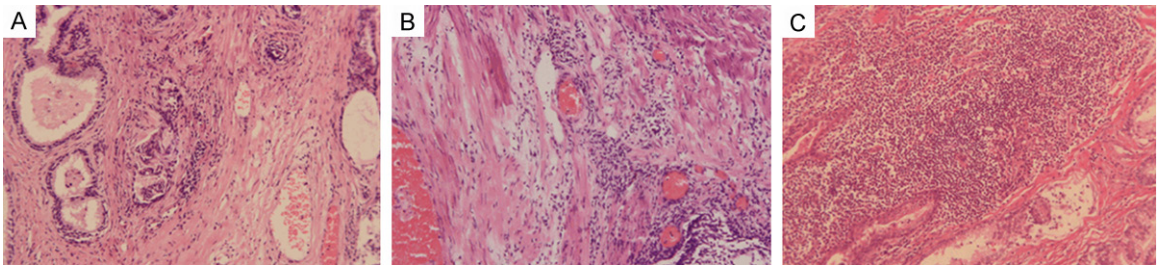

Figure 1. A. Representative image of mild histological prostatitis in group A (HE × 100); B. Representative image of moderate histological prostatitis in group B (HE × 100); C. Representative image of severe histological prostatitis in group C (HE × 100).

Table 2. Baseline characteristics of patients in both groups before TURP

	Cernilton Group (n = 50)	Control Group (n = 50)	P
Age (y)	67.1 ± 6.4	68.3 ± 7.3	0.38
PV (ml)	75.1 ± 17.6	74.2 ± 16.9	0.79
PSA (ng/ml)	4.8 ± 0.4	4.9 ± 1.1	0.54
PVR (ml)	242.1 ± 25.3	242.7 ± 27.7	0.91
Qm (ml/s)	5.7 ± 2.0	6.1 ± 1.1	0.22
PdetQm (cmH_2O)	77.6 ± 31.1	78.1 ± 32.2	0.94
IPSS	21.2 ± 4.7	21.8 ± 5.7	0.57
Vs	10.2 ± 2.3	10.8 ± 1.7	0.14
Ss	8.1 ± 1.5	8.4 ± 0.9	0.23
QoL	4.8 ± 1.1	5.0 ± 0.5	0.24
AUR history	36 (72%)	37 (74%)	0.82
HU history	17 (34%)	14 (28%)	0.52
UTIhistory	9 (18%)	8 (16%)	0.79
IEFF-5	8.8 ± 1.0	8.5 ± 0.8	0.10

Note: PV: prostate volume, PSA: prostate specific antigen, PVR: post void residual volume, Qm: maximum urine flow rate, PdetQmax: pressure of detrusor at Qmax, IPSS: International Prostate Symptom Score, Vs: voiding symptom score, Ss: storage symptom score, QoL: quality of life, AUR: acute urinary retention, HU: hematuria, UTI: urinary tract infection, IEFF-5: International Index of Erectile Function-5.

investigated in BPH patients with histological prostatitis after TURP.

Patients and methods

Sample collection

This study was performed in three clinical centers: the Department of Urology at the Affiliated Xinhua Hospital of School of Medicine, Shanghai Jiaotong University; the Department of Urology at the Affiliated Ninth People's Hospital of School of Medicine, Shanghai Jiaotong University; and the Department of Urology at the Affiliated Tenth People's Hospital of School of Medicine, Tongji University. The study was approved by the Ethics Committee of the Chinese Clinical Trial Register. The written informed consent was obtained from each patient before study.

Patients

A total of 142 patients were recruited from January 2007 to January 2013. The mean age was 68.2 ± 6.7 years (range, 62-77 years). At the end of six-month follow-up, 100 patients completed this randomized clinical trial (RCT). In Cernilton group, there were 50 patients treated with Cernilton; in control group, there were 50 patients treated with placebo.

Prostate volume (PV; PV = 0.52 × transverse × antero-posterior × cephalocaudal diameter) was measured by trans-rectal ultrasound. Post-void residual volume (PVR) was measured by trans-abdominal ultrasound. The maximum urine flow rate (Qm) and pressure of detrusor at Qm (PdetQm) were measured by urodynamic examination. Voiding symptoms and quality of life (QoL) were graded on the basis of the International Prostate Symptom Score (IPSS), voiding symptom score (Vs), storage symptom score (Ss), and QoL assessment index. In addition, the prostate-specific antigen (PSA), acute urinary retention (AUR), hematuria (HU), bladder stone, and urinary tract infection (UTI) history were also determined.

The inclusion criteria were as follows: 1) PV > 30 mL; 2) IPSS ≥ 13, QoL ≥ 3; 3) PVR ≥ 200 mL;

Table 3. Comparisons of perioperative parameters in both groups

	Cernilton Group (n = 50)	Control Group (n = 50)	P
OM (min)	48.1 ± 13.4	46.0 ± 12.1	0.41
RR (%)	43.1 ± 3.2	42.3 ± 4.7	0.32
IHAO (h)	47.0 ± 5.6	48.2 ± 5.2	0.48
CDAO (days)	3.1 ± 1.0	3.2 ± 1.2	0.65
HDAO (days)	4.5 ± 1.0	4.7 ± 1.3	0.86

Note: OM: operation minutes, RR: resection ratio, IHAO: irrigation hours after operation, CDAO: catheterization days after operation, HDAO: hospitalized days after operation.

4) Qm < 15 mL/s; 5) age ≥ 60 years; 6) absence of Cernilton therapy before TURP; 7) no prostatitis symptoms before TURP; 8) presence of histological prostatitis in pathology after TURP.

The exclusion criteria were as follows: 1) prostate cancer or bladder cancer, 2) urethral stenosis, 3) neurogenic bladder, 4) refractory diabetes, 5) urological system tuberculosis, 6) no histological prostatitis in pathology after TURP, 7) no erectile function before TURP, 8) patients with symptoms of urinary tract infection or prostatitis before TURP, and 9) patients with mental diseases.

Therapies

A total of 100 patients were randomized into Cernilton group and control group and received monopolar TURP by a urologist with an experience of over 100 cases. All the operations were performed under general or spinal anesthesia using a standard technique (ACMI of America *or* Storz of Germany) and the electro-surgical instrument system. During TURP, continuous irrigation was performed using a 5% mannitol solution, and the removed prostate tissues were weighed. After TURP, all the patients were indwelled by using an F24 catheter, and received routine irrigation with normal saline. After 2-5 days, the catheter was removed and patients were discharged. After discharge, patients in Cernilton group were administered Cernilton (70 mg, bid) for 3 months at least; patients in control group were administered a placebo. All of the patients were followed up at 6 months after discharge.

Pathological examination

The chronic prostatic inflammation was pathologically evaluated with a histopathological classification system [9] as shown in **Table 1**. For each patient, the prostatic inflammatory infiltrates in a specific location were categorized by the extent and the grade of inflammation. If more than one grade of inflammation was present for a given anatomical location, the dominant grade or the higher grade was used, e.g. multifocal mild glandular inflammation, focal mild periglandular inflammation, diffuse mild stromal inflammation and focal severe stromal inflammation. According to the pathology, patients were divided into group A (mild), B (moderate), and C (severe). The representative images of histopathological prostatitis are shown in **Figure 1**.

Observations

Before TURP, following information was collected: age, PV, PVR, PSA, IPSS, Vs, Ss, QoL, Qm, PdetQm, AUR history, HU history, UTI history, and IEFF-5 score. In the peri-TURP period, following information was collected: operation time in minutes (OM), resection ratio [RR; calculated as RR = weight of resected prostate tissue/(1.05 × PV)], duration of catheterization after operation in days (CDAO), and hospital stays after operation (HDAO). At 6 months after surgery, the PVR, PSA, IPSS, Vs, Ss, QoL, Qm, and IEFF-5 score were determined.

Statistical analysis

Statistical analysis was carried out with SPSS® version 18.0.1 (SPSS, Amonk, NY, USA) for Windows®. Differences between two groups were compared using the Student's t-test, and the incidence of adverse events was analyzed using Pearson's χ^2-test or Fisher exact test. A value of $P < 0.05$ was considered statistically significant.

Results

A total of 142 patients with BPH were recruited into present study, and approximately 30% of patients were lost to follow-up. Thus, after 6-month follow-up, only 100 patients completed this RCT. Fifty patients remained in Cernilton group and control groups, respectively. The characteristics at baseline are shown in **Table 2**. There were no significant differences be-

Table 4. Comparison between two groups and among three subgroups at 6 months after TURP

	Group A (n = 20)		Group B (n = 23)		Group C (n = 57)	
	Cernilton (n = 11)	Control (n = 9)	Cernilton (n = 13)	Control (n = 10)	Cernilton (n = 31)	Control (n = 26)
PSA (ng/ml)	2.9 ± 0.5	3.0 ± 0.3	3.4 ± 0.7	3.6 ± 0.4	3.7 ± 0.3	3.8 ± 0.8
Qm (ml/s)	19.3 ± 4.1	19.8 ± 4.7	17.6 ± 3.2	17.8 ± 3.7	18.3 ± 5.1	18.7 ± 4.9
IPSS	7.5 ± 2.7	7.8 ± 3.8	8.5 ± 2.7	8.7 ± 1.7	8.8 ± 2.3	9.5 ± 3.4
Vs	5.2 ± 2.0	5.4 ± 1.7	5.2 ± 1.1	5.7 ± 2.2	6.2 ± 1.4	6.3 ± 3.1
Ss	2.5 ± 0.8	2.7 ± 0.8	3.1 ± 0.9	3.2 ± 0.7	2.3 ± 0.5*	3.4 ± 0.7*
QoL	2.8 ± 0.6	2.6 ± 0.6	2.9 ± 0.3	2.7 ± 0.4	2.6 ± 0.3*	3.7 ± 0.6*
PVR (ml)	12.7 ± 4.2	12.4 ± 4.1	13.7 ± 3.9	13.5 ± 3.5	11.3 ± 1.9	11.7 ± 3.9
IEFF-5	15.7 ± 0.7	15.5 ± 0.5	11.2 ± 1.8*	6.2 ± 0.8*	10.7 ± 0.4*	5.2 ± 0.3*

Note: PSA: prostate specific antigen, Qm: maximum urine flow rate, IPSS: the International Prostate Symptom Score, Vs: voiding symptom score, Ss: storage symptom score, QoL: quality of life, PVR: post void residual volume, IEFF-5: International Index of Erectile Function-5. *P < 0.05.

Table 5. Comparisons of parameters between two groups at 6 months after TURP

	Cernilton Group (n = 50)	Control Group (n = 50)	P
PSA (ng/ml)	3.5 ± 0.7	3.9 ± 0.5	0.41
Qm (ml/s)	17.3 ± 4.5	17.4 ± 3.2	0.90
IPSS	9.0 ± 3.7	9.5 ± 2.9	0.45
Vs	5.2 ± 2.1	5.8 ± 1.2	0.08
Ss	3.1 ± 0.8	2.5 ± 0.2	< 0.001
QoL	2.7 ± 0.6	3.6 ± 0.8	< 0.001
PVR (ml)	12.7 ± 4.9	14.2 ± 5.6	0.16
IEFF-5	12.2 ± 0.8	10.4 ± 0.9	< 0.001

Note: PSA: prostate specific antigen, Qm: maximum urine flow rate, IPSS: the International Prostate Symptom Score, Vs: voiding symptom score, Ss: storage symptom score, QoL: quality of life, PVR: post void residual volume, IEFF-5: International Index of Erectile Function-5.

tween Cernilton group and control group in the parameters assessed at baseline (P > 0.05). According to the symptom severity, 20, 23, and 57 patients were included in groups A, B, and C, respectively. The baseline characteristics of all patients in both groups are shown in **Table 2**. The mean age was 67.1 ± 6.4 years and 68.3 ± 7.3 years, respectively. PV was 75.1 ± 17.6 ml and 74.2 ± 16.9 ml, respectively. PSA was 4.8 ± 0.4 ng/ml and 4.9 ± 1.1ng/ml, respectively. PVR was 242.1 ± 25.3 ml and 242.7 ± 27.7 ml, respectively. Qm was 5.7 ± 2.0 ml/s and 6.1 ± 1.1 ml/s, respectively. PdetQm was 77.6 ± 31.1 cm and 78.1 ± 32.2 cm$H_2$0, respectively. IPSS was 21.2 ± 4.7 and 21.8 ± 5.7, respectively. Vs was 10.2 ± 2.3 and 10.8 ± 1.7, respectively. Ss was 8.1 ± 1.5 and 8.4 ± 0.9, respectively. QoL was 4.8 ± 1.1 and 5.0 ± 0.5, respectively. IEFF-5 was 8.8 ± 1.0 and 8.5 ± 0.8, in Cernilton group and control group, respectively. The rates of AUR, hematuria, and UTI history before TURP were 72%, 34% and 18% in Cernilton group, respectively, and 74%, 28%, and 16% in control group, respectively.

All the patients successfully underwent TURP and none died. Parameters collected in the peri-TURP period in both groups are presented in **Table 3**. The OM was 48.1 ± 13.4 min and 46.0 ± 12.1 min, respectively. The RR was 43.1 ± 3.2% and 42.3 ± 4.7%, respectively. Th IHAO was 47.0 ± 5.6 h and 48.2 ± 5.2 h, respectively. The DCAO was 3.1 ± 1.0 days and 3.2 ± 1.2 days, respectively. The HDAO was 4.5 ± 1.0 days and 4.7 ± 1.3 days, in Cernilton group and control group, respectively. There were no significant differences in these parameters between Cernilton group and control group (P > 0.05).

Comparisons of parameters collected at 6 months after TURP in two groups and in three subgroups (A, B and C) are presented in **Table 4**. In group A, there were no significant differences between Cernilton group and control group (P > 0.05) for all these parameters. In group B, significant difference was observed in only IEFF-5 (11.2 ± 1.8 and 6.2 ± 0.8, respectively, P < 0.05) between Cernilton group and control group. In group C, Ss (2.3 ± 0.5 vs 3.4 ± 0.7), QoL (2.6 ± 0.3 vs 3.7 ± 0.6) and IEFF-5 (10.7 ± 0.4 vs 5.2 ± 0.3) were significantly different (P < 0.05) between Cernilton group and control group.

Table 5 displays the comparisons of parameters measured at 6 months after TURP for all the patients in both groups. PSA was 3.5 ± 0.7 ng/ml and 3.9 ± 0.5 ng/ml, respectively. Qm was 17.3 ± 4.5 ml/s and 17.4 ± 3.2 ml/s, respectively. IPSS was 9.0 ± 3.7 and 9.5 ± 2.9, respectively. Vs was 5.2 ± 2.1 and 5.8 ± 1.2,

respectively. Ss was 3.1 ± 0.8 and 2.5 ± 0.2, respectively. QoL was 2.7 ± 0.6 and 3.6 ± 0.8, respectively. PVR was 12.7 ± 4.9 ml and 14.2 ± 5.6 ml, respectively. IEFF-5 after operation was 12.2 ± 0.8 and 10.4 ± 0.9, respectively. There were significant differences in Ss (3.1 ± 0.8 vs 2.5 ± 0.2), QoL (2.7 ± 0.6 vs 3.6 ± 0.8), and IEFF-5 (12.2 ± 0.8 vs 10.4 ± 0.9) between Cernilton group and control group ($P < 0.001$). There were no adverse reactions observed in the follow up period.

Discussion

Histological prostatitis has been reported as one of important risk factors affecting the clinical progression of BPH [4, 10, 11]. The Medical Treatment of Prostate Symptoms (MTOPS) study showed that 544 of 1197 patients with BPH had histological prostate inflammatory changes and that patients with histological inflammation were more likely to develop advanced progression of BPH as compared to those without inflammation [12]. The chronic prostatic inflammation leads to tissue damage and continuous wound healing, contributing to the prostatic enlargement. Indeed, patients with chronic prostatic inflammation and BPH have been shown to also have a larger PV, more severe LUTS, and a higher probability for acute urinary retention than their counterparts without inflammation. Wei [13] reported that, among 112 surgical specimens collected from patients with BPH, 81 (72.3%) had histological prostatitis, and there was a positive correlation between prostatitis and BPH clinical progression, suggesting an important role of inflammation in the BPH progression. Histological prostatitis, in addition to LUTS and age, is reported to be a potential contributor to sexual dysfunction [14, 15]. El-Nashaar and Shamloul [16] indicated that prostatitis was closely associated with sexual dysfunction and, more significantly, that prostatitis was one of the most important factors leading to the development of sexual dysfunction.

The pollen extract Cernilton contains 63 mg of the defined pollen extract fractions cernitin T60 (water soluble fraction) and cernitin GBX (fat soluble fraction). These extracts contain carbohydrates, fat, amino acids, vitamins and minerals, and have been used for the treatment of BPH and prostatitis. The therapeutic efficacy of Cernilton has been confirmed in BPH and prostatitis [17-19].

Although some clinicians propose that pharmacotherapy for BPH is unnecessary after TURP, the incidence of LUTS after TURP is as high as 10%-30% [6, 7], which suggests that post-TURP therapy is necessary for those with histological prostatitis. Prostatic inflammation detected on TURP pathology has been reported as an independent variable affecting the development of urethral stricture or bladder neck contracture after TURP [20]. Based on these findings, Cernilton therapy may help relieve post-TURP prostatic inflammation. Thus, from January 2007 to January 2013, we conducted a prospective, randomized, and controlled study focusing on prostatic histological inflammation.

The baseline characteristics were similar between Cernilton group and control group. In the peri-operative period, the parameters were also comparable between Cernilton group and control group. However, at 3 months and 6 months after surgery, Cernilton treatment significantly improved the postoperative QoL, Ss, and sexual function as compared to control group ($P < 0.001$). For BPH patients with histological prostatitis after TURP, Cernilton therapy helped improve LUTS and sexual dysfunction. Cernilton was also well tolerated over the entire study period. There is evidence showing that, for BPH patients, histological prostatitis may serve as a major risk factor for sexual dysfunction while having little effect on LUTS [12]. This finding may be a result of different effects depending on the grade of histological prostatitis. In our study, Cernilton therapy did not improve LUTS and sexual dysfunction in group A. However, while the grade of histological prostatitis was moderate in group B, Cernilton only improved the sexual dysfunction but not LUTS. Patients in group C (severe histological prostatitis) achieved the greatest benefit from Cernilton therapy, characterized by improvements in both sexual dysfunction and LUTS. Thus, Cernilton therapy is beneficial for BPH patients with histological prostatitis after TURP, and may significantly improve the sexual dysfunction and LUTS without adverse reactions.

However, this study had a small sample size (N = 100), follow-up was conducted for only 6 months, and it was not a double blind trial. Thus, our results might not be generalized to BPH patients after TURP. More studies larger sample size and longer duration of follow-up are required to confirm the therapeutic efficacy

of Cernilton in BPH patients with histological prostatitis after TURP.

Conclusion

For BPH patients with histological prostatitis after TURP, Cernilton therapy may not benefit those with mild prostatitis, but may improve the LUTS in those with moderate prostatitis, and improves both LUTS and sexual dysfunction in those with severe prostatitis. Overall, Cernilton therapy is able to improve the LUTS and sexual dysfunction in BPH patients with histological prostatitis after TURP.

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Disclosure of conflict of interest

None.

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