Long-term outcomes after treatment with Optilume BPH

Four-year results from the EVEREST study

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Cite as: Kaplan SA, Pichardo M, Rijo E, et al. Long-term outcomes after treatment with Optilume BPH: Four-year results from the EVEREST study. *Can Urol Assoc J* 2024;18(11):E319-25. http://dx.doi.org/10.5489/cuaj.8737

Published online June 17, 2024

ABSTRACT

INTRODUCTION: The purpose of this study was to gather initial safety and efficacy data with the Optilume® BPH Catheter System for the treatment of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH).

METHODS: A total of 80 men with moderate-to-severe LUTS secondary to BPH were enrolled and treated with the Optilume BPH Catheter System. Symptoms were evaluated using the International Prostate Symptom Score (IPSS) and Benign Prostatic Hyperplasia-Impact Index (BPH-II). Improvement in urinary flow and relief of obstruction was evaluated by way of peak urinary flow rate (Qmax) and postvoid residual urine volume (PVR). Subjects were prospectively queried for adverse events at each study visit, and relatedness to the study device was evaluated by the investigators, as well as centrally adjudicated by the study principal investigator.

RESULTS: Previous reports of symptom improvement in this cohort were maintained through four-year followup, with a significant reduction in IPSS and IPSS quality of life maintained through four years (-12.1, -2.8, respectively). Clinically meaningful improvement in Qmax was maintained in the majority of subjects, with an average improvement from baseline of +5.6 mL/sec. No treatment-related adverse events were reported in the long-term followup period.

CONCLUSIONS: Long-term followup through four years for subjects treated with the Optilume BPH Catheter System indicates durable outcomes in symptom improvement and functional improvement in flow rate. These results indicate the unique mechanism of action for Optilume BPH successfully achieves an immediate mechanical effect that is maintained long-term through incorporation of paclitaxel to maintain patency.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a prevalent condition in the aging male characterized by a non-malignant enlargement of the prostate gland. Prostatic enlargement is typically accompanied by lower urinary tract symptoms (LUTS) that increase in frequency and severity with age.[1] These LUTS represent a significant burden to patient quality of life (QoL) as they increase in severity.

Generally, LUTS can be divided into those symptoms that are associated with storage of urine, such as urgency and frequency, and those associated with voiding/emptying, such as weak stream and incomplete emptying. Identifying the primary cause of LUTS and the optimal treatment algorithm can be a complex undertaking whereby storage symptoms may be secondary to bladder outlet obstruction (BOO) or may be due to underlying instability/dysfunction of the detrusor and overactive bladder (OAB) or other factors.

The basic management of LUTS necessitates an initial evaluation to identify contributing factors and rule out differential diagnoses (e.g., urinary tract infection [UTI]). For patients with mixed storage and voiding symptoms, pressure/flow urodynamic studies may be helpful in differentiating between predominantly obstructive or predominantly irritative etiologies and inform the appropriate treatment pathway.

For patients with confirmed BOO, typical management is characterized initially by lifestyle modifications, with step-up therapy to medical management where necessary.

KEY MESSAGES

- Symptomatic and functional improvements were maintained through four years in men with LUTS secondary to BPH treated with Optilume BPH.
- Improvement was seen in both storage and voiding symptoms.
- We saw no late-onset device complications or impact on sexual function.

Although medical management has been a mainstay of therapy for decades, increasing attention is being paid to the high rate of patient discontinuation due to side effects and potential for long-term complications from lifelong use.[2] Patients with symptoms refractory to medical management have historically been managed by the gold-standard surgical therapy of transurethral resection of the prostate (TURP).[3]

TURP has been shown to consistently deliver significant improvement in symptoms and urinary flow rate post-procedure; however, dissatisfaction with the invasiveness and morbidity associated with the procedure have led to the development of a plethora of minimally invasive surgical therapies (MISTs).[4,5] These MIST devices have been shown to improve symptoms, and to a lesser extent flow rate, while delivering a more tolerable procedure in an ambulatory setting and without side effects such as retrograde ejaculation typically associated with TURP.[6-9]

The Optilume® BPH Catheter System (Urotronic, Inc., Plymouth, MN, U.S.) is a minimally invasive, drug-coated balloon dilation system that allows for mechanical dilation and achievement of an anterior commissurotomy with concurrent circumferential delivery of paclitaxel drug to the dilated area. A randomized, sham-controlled trial has recently been reported that showed significant and sustained improvements in symptoms and flow rate compared to a sham procedure through one year.[10] The EVEREST study is a first-in-human study evaluating outcomes after treatment with Optilume BPH in a cohort of 80 men with moderate-to-severe LUTS secondary to BPH. Initial experience with Optilume BPH has been reported for this cohort through two years.[11,12] This report includes results through four years of post-procedural followup.

METHODS

Study design and participants

The EVEREST study (NCT03423979) is a prospective, single-arm, open-label, multicenter clinical study conducted at six centers in the Dominican Republic and Panama. The ethics committee for each center provided review and approval of the study prior to study initiation, and all subjects provided written informed consent prior to participation in the study.

Inclusion criteria included men 50 years of age or older, an International Prostate Symptom Score (IPSS) ≥13, peak urinary flow rate (Qmax) 5–15 mL/sec with minimum voided volume of ≥125 mL, postvoid residual (PVR) urine volume ≤250 mL, prostate volume 20–80 g, and prostatic urethra length 35–55 mm. Patients with prior minimally invasive or surgical interventions, intravesical protrusion >1 cm, and confounding urologic conditions were excluded. Medication washouts prior to treatment included six months for 5-alpha reductase inhibitors (ARIs) and three weeks for alpha-blockers. Transrectal ultrasound (TRUS) was performed to determine prostate dimensions.

The Optilume BPH Catheter System has been described in previous publications.[10-12] Briefly, Optilume BPH is a novel MIST that combines mechanical dilation with the delivery of paclitaxel to treat LUTS secondary to BPH. Mechanical dilation with Optilume BPH achieves an anterior commissurotomy, separating the lateral lobes of the prostate, while paclitaxel delivery is intended to maintain luminal patency during healing. A Foley catheter is placed for at least two days post-procedure.

After the procedure, followup assessments were conducted at one month, three months, six months, one year, and annually through four years. Assessments included self-administered questionnaires, including IPSS, the BPH Impact Index (BPH-II), the International Index of Erectile Function (IIEF), and the Men's Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD). PVR urine volume and uroflowmetry were measured at each visit, with a minimum voided volume of ≥125 mL needed for a valid reading.

Study endpoints and statistical methodology

The prespecified hypothesis-tested primary and secondary endpoints for this study were planned at three months followup and reported previously.[11] Sample size for the study was based on the primary endpoint analysis at three months. Primary endpoints for long-term

followup included functional assessments and symptomology. Continuous outcomes were summarized using descriptive statistics and categorical variables summarized with frequencies and proportions. Changes from baseline were evaluated using a two-sided Student's paired t-test, with $p<0.05$ indicating statistical significance. Primary data is reported from the intent-to-treat population, with no imputation for missing data. A sensitivity analysis was conducted using the last observation carried forward (LOCF) methodology for missing data.

Symptomatic responders to treatment were defined as those experiencing a ≥30% improvement in IPSS from baseline to the four-year followup. Symptom scores were further broken into storage (frequency, urgency, nocturia) and voiding (straining, weak stream, intermittency, incomplete emptying) domains. Due to the imbalanced contribution of these domains to the total IPSS score based on the number of questions included in each subdomain, a mean storage and voiding subscore was calculated on a scale of 0 (no symptoms) to 5 (greatest symptoms), as described by Barry et al.[13]

Safety was assessed by the type and rate of adverse events (AEs), which were adjudicated by the study principal investigator. Sexual function was evaluated using the MSHQ-EjD and the IIEF.

RESULTS

Of the 80 men enrolled between December 2017 and February 2019, 59 were evaluable at four years. Baseline characteristics ae listed in Table 1. Reasons for missing data included 10 subjects with a missed visit and 11 early exits. The 11 early study exits included four deaths due to non-study-related causes (bowel obstruction, COVID-19, cerebrovascular accident), three subjects lost to followup, one subject withdrawing consent, one subject who received a prostatectomy due to refractory hematuria with an onset at 18 months, one subject with prostate cancer, and one subject who withdrew due to an AE.

Functional and symptomatic response

Symptoms improved significantly post-treatment, and that improvement was maintained through four years of followup (Table 2). Improvement was seen in both storage and voiding subscores, however, the improvement was greatest in the voiding domain, with approximately two-thirds of the overall improvement seen here (Figure 1). Maximal improvement in the voiding domain was achieved immediately post-procedure, while maximal improvement in the storage domain was achieved approximately six months post-procedure. No differences were noted in IPSS improvement from baseline to four years when comparing the *as observed* to the LOCF methodology for missing data (12.1 vs. 12.6).

Table 1. Subject demographics and baseline characteristics

Characteristic	Mean (SD, range) N=80
Age, years	65.8 (7.82, 52–87)
Race/ethnicity, n/N (%)	
Black or African origin	10/80 (12.5%)
Caucasian	2/80 (2.5%)
Hispanic or Latino	68/80 (85.0%)
History of incontinence, n/N (%)	2/80 (2.5%)
Genitourinary history, n/N (%)	
Erectile dysfunction	6/80 (7.5%)
Kidney stone	1/80 (1.3%)
Urinary tract infection	2/80 (2.5%)
Prostate volume, g	35.9 (13.2, 20.9–77.0)
Intravesical prostatic protrusion, n/N (%)	10/80 (12.5%)
PSA, ng/mL	3.01 (2.98, 0.24–14.39)
IPSS	22.3 (4.9, 14–35)
Moderate (IPSS ≤18), n/N (%)	20/80 (25%)
Severe (IPSS ≥19), n/N (%)	60/80 (75%)
IPSS QoL	4.6 (0.86, 1–6)
Qmax, mL/sec	10.9 (2.9, 5–15)
PVR, mL	63.1 (55.0, 0–225)

IPSS: International Prostate Symptom Score; PSA: prostate-specific antigen; PVR: postvoid residual; Qmax: peak flow rate; QoL: quality of life; SD: standard deviation.

Forty-six of the 59 evaluable subjects at four years were symptomatic responders (78.0%, 95% confidence interval [CI] 65.3–87.7%). Non-responders showed a much smaller improvement in storage symptoms immediately post-procedure as compared to responders (Figure 2). There was no difference in average prostate size or baseline symptom scores (total or subscores) for non-responders. Three subjects underwent additional treatment; two subjects re-initiated BPH medications and one aforementioned subject underwent a prostatectomy procedure. Conservatively treating the prostatectomy for refractory hematuria as a surgical retreatment, the overall surgical retreatment rate through four years remained low at 1.3%. Statistically significant improvements were observed in both QoL measures. The mean IPSS Q0L improved from 4.6 at baseline to 1.3 at one year and 1.8 at four years ($p<0.001$). The BPH-II improved from 6.9 at baseline to

Table 2. Summary of symptom and flow improvement after treatment with Optilume BPH

Measure	Baseline	3-month	6-month	1-year	2-year	3-year	4-year
IPSS n Mean ± SD Change % change	80 22.3±4.9	79 8.1±6.1 -14.2±7.0 63.0	77 8.0±7.2 -14.4±7.7 64.0	75 7.9±7.6 -14.4±7.8 64.9	68 8.2±7.3[a] -14.4±6.4 65.3	63 9.8±8.0[a] -12.7±7.9 56.8	59 10.3±8.0[a] -12.1±8.5 54.5
IPSS QoL n Mean ± SD Change	80 4.6±0.9	79 1.5±1.3 -3.1±1.6	77 1.6±1.6 -3.0±1.9	75 1.3±1.4 -3.3±1.5	68 1.6±1.6[a] -3.0±1.7	63 1.8±1.7[a] -2.7±1.9	59 1.7±1.8[a] -2.8±1.0
BPH Impact Index n Mean ± SD Change	80 6.9±3.0	79 3.4±3.4[a] -3.5±4.5	77 2.6±3.3[a] -4.3±4.5	75 2.0±3.1[a] -5.1±4.3	68 2.3±3.5[a] -4.7±4.4	63 2.7±3.6[a] -4.2±4.4	58 2.9±3.9[a] -4.1±4.8
Qmax (mL/sec) n Mean ± SD Change	80 10.9±2.9	77 20.5±9.5 +9.6±9.45	74 19.6±8.7 +8.8±8.5	74 18.4±8.2 +7.4±8.2	56 17.2±9.0[a] +6.2±8.9	58 16.7±10.7[a] +5.3±10.6	53 17.2±9.7[a] +5.6±9.7
PVR (mL) n Mean ± SD Change	80 63.1±55.0	77 34.3±33.1 -30.0±58.9	74 28.8±29.5 -35.0±51.6	74 34.4±32.3 -30.1±51.6	56 45.0±50.9 -12.9±66.8	58 49.1±79.3 -5.6±80.9	53 49.0±81.1 -5.2±84.0

BPH: benign prostatic hyperplasia; IIEF: International Index of Erectile Function; MSHQ-EjD: Male Sexual Health Questionnaire - Ejaculatory Dysfunction; SD: standard deviation.

2.0 at one year and 2.9 at four years (p<0.001).Qmax increased significantly from an average of 10.9 mL/sec at baseline to 17.2 mL/sec at four years (p<0.001). The majority of patients experienced a clinically meaningful increase in Qmax of at least +2 mL/sec. The paired change in Qmax values from three to four years was minimal (average paired change +1.2 mL/sec), indicating stability in Qmax values during long-term followup. PVR was reduced from 63.1 mL at baseline to 49.0 mL at four years (p=0.656).

Safety

A total of 136 AEs were reported in 56 subjects through four years. The majority of events (64%, 86/135) occurred within three months of the treatment procedure, with only 17 events occurring between 24 and 48 months, none of which were treatment-related. Serious adverse events (SAE) occurring between 24 and 48 months included four non-study-related SAEs, including cerebrovascular accident, COVID-19, heart failure, and larynx cancer. None of these SAEs were deemed to be related to the Optilume BPH Catheter System.

Sexual function, as measured by the IIEF and MSHQ-EjD, was preserved at four years, as there was no statistically significant change in any measure (Table 3). There were no device- or procedure-related AEs related to erectile dysfunction.

DISCUSSION

Early experience with this cohort of patients treated with the Optilume BPH Catheter System has been promising, showing excellent increases in flow rate and symptom improvement.[11,12] This experience was corroborated with outcomes from a randomized, sham-controlled trial reporting significant increases in flow rate and durable symptom improvement through one year post-treatment when compared to a sham procedure.[10] This report represents the first long-term followup for patients treated with Optilume BPH, with followup through four years.

The ultimate goal of a MIST is to provide functional and symptomatic improvement to a similar degree and durability as more invasive surgical options, while concurrently reducing the risk profile and increasing tolerability and speed of recovery. Optilume BPH appears to address these goals, providing functional flow improvements that approach that of TURP with a simple, outpatient procedure that appears to be well-tolerated.[10,14] The current report supports that the significant improvements in flow and symptomology

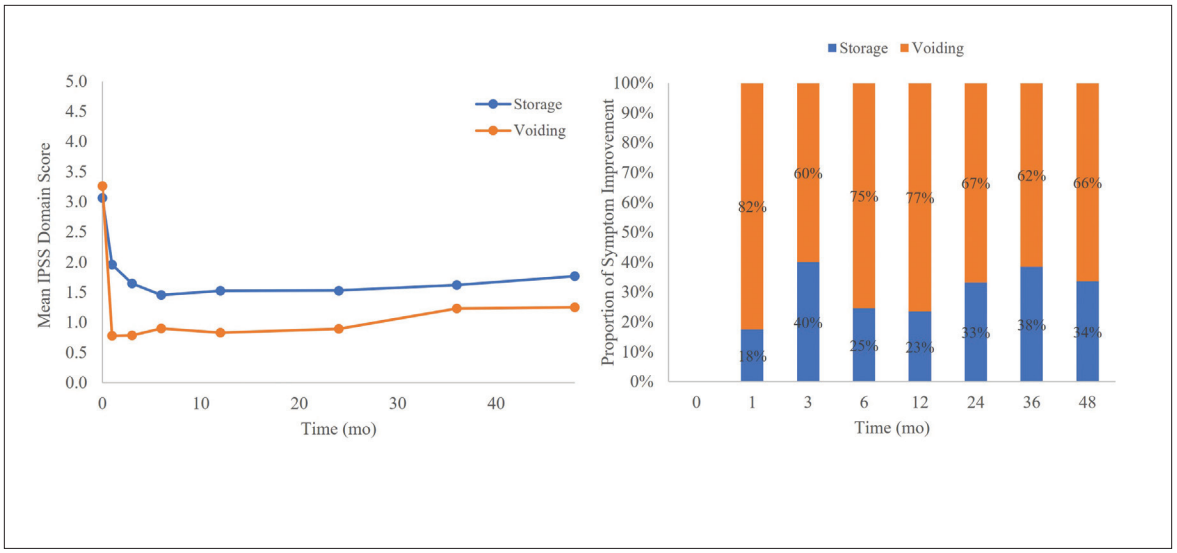

Figure 1. Mean International Prostate Symptom Score (IPSS) domain scores over time and proportion of symptom improvement. Storage and voiding domain scores are presented separately.

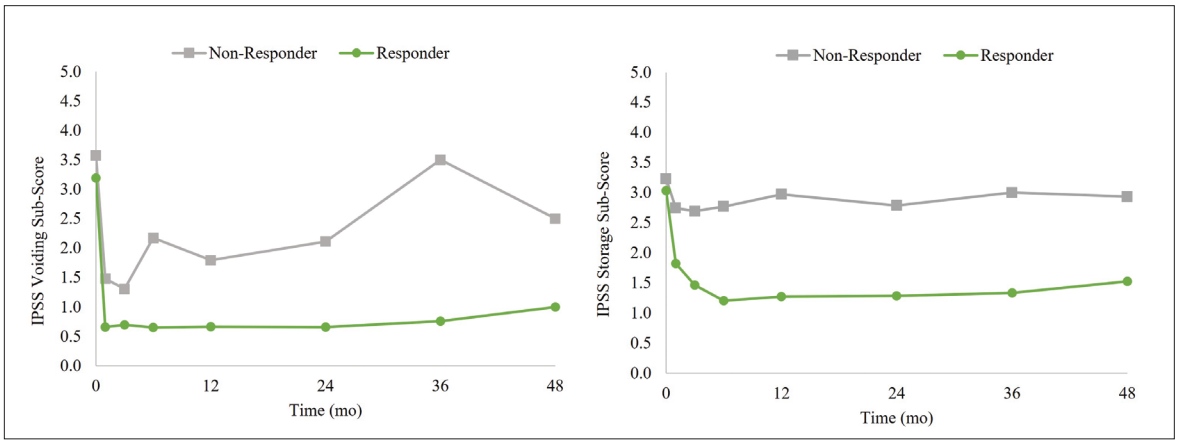

Figure 2. International Prostate Symptom Score (IPSS) voiding and storage subscores over time in non-responders and responders.

seen post-treatment are maintained through at least four years of followup. Clinically meaningful improvement in IPSS was maintained in 78% of patients, with an average improvement of 12.1 points (55%) from baseline through four years. Flow rate improvements were also maintained through four years, with an average Qmax of 17.2 mL/sec (+5.6 mL/sec vs. baseline). These outcomes compare favorably with long-term outcomes reported with other MISTs.[15-17]

Interestingly, although improvement was seen in both the storage and voiding subscores of the IPSS tool in the entire cohort, those subjects that did not meet the criteria for being symptomatic responders (overall IPSS improvement ≥30%) appeared to have significantly lower improvement in the storage subscore. This may indicate potentially confounding detrusor overactivity or other irritative etiology that was not solely due to underlying BOO contributing to the unresolved symptomology. Although the guidelines only recommend pressure/flow urodynamic studies in the setting of diagnostic uncertainty, these studies provide invaluable insight into treatment pathways and setting expectations for patients regarding outcomes, and are particularly helpful in the setting of mixed OAB/BOO symptomology.

Limitations

Given the nature of the study as a feasibility study designed to gather initial safety and efficacy data on the Optilume BPH Catheter System, no comparator group was included in the study design. Although the lack of control group represents an important limitation

Table 3. Sexual function after treatment with Optilume BPH

Measure	Baseline	3-month	6-month	1-year	2-year	3-year	4-year
IIEF EF n Mean ± SD	 80 17.6±11.0	 79 17.8±10.9	 77 19.3±10.7	 75 19.8±10.2	 68 18.4±10.6	 63 21.0±9.7	 58 16.3±10.8
MSHQ-EjD function n Mean ± SD	 80 9.4±4.3	 79 8.7±5.6	 77 8.1±5.8	 75 9.1±5.7	 68 8.9±5.2	 62 8.7±5.1	 58 8.3±5.1
MSHQ-EjD Bother n Mean ± SD	 80 1.2±1.4	 79 1.2±1.5	 77 1.3±1.6	 75 1.2±1.5	 68 1.4±1.6	 62 1.1±1.3	 58 1.5±1.4

BPH: benign prostatic hyperplasia; IIEF: International Index of Erectile Function; MSHQ-EjD: Male Sexual Health Questionnaire - Ejaculatory Dysfunction; SD: standard deviation.

to the results presented herein, a randomized, sham-controlled study evaluating Optilume BPH against a sham procedure reported similar outcomes of IPSS improvement and confirmed the impressive improvements in flow rate through one year of followup.[10]

Other limitations include the reduced number of subjects reporting outcomes during the long-term followup period (59/80, 74%). This limitation was mitigated by the incorporation of a sensitivity analysis evaluating the full cohort using a LOCF methodology, which showed minimal differences in the reported outcomes when including the last known status of each patient.

CONCLUSIONS

The Optilume BPH Catheter System represents a unique modality among MISTs, combining mechanical and pharmaceutical aspects for the treatment of BPH. Long-term results appear to support the mechanism of an immediate functional improvement by way of creating an anterior commissurotomy and a sustained anatomic result due to the application of paclitaxel to the prostatic urethra during the dilation. The functional and symptomatic improvements seen after treatment with Optilume BPH are significant and have been sustained through four years in this early feasibility study.

COMPETING INTERESTS: This study was funded by Urotronic, Inc, the manufacturer of the Optilume BPH Catheter System. The authors do not report any competing personal or financial interests related to this work.

This paper has been peer reviewed.

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