Aquablation for benign prostatic hyperplasia in large prostates (80-150 cc): 2-year results

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Introduction: *To report 2-year safety and effectiveness of the Aquablation procedure for the treatment of men with symptomatic benign prostatic hyperplasia (BPH) and large-volume 80-150 cc prostates.*

Materials and methods: *Between September-December 2017, 101 men with moderate-to-severe BPH symptoms and prostate volumes of 80-150 cc underwent an ultrasound-guided robotically executed Aquablation procedure in a prospective multicenter international clinical trial (WATER II). Baseline, procedural and follow up parameters were recorded at baseline and scheduled postoperative visits. Herein we report 2-year safety and efficacy for this cohort.*

Results: *Mean prostate volume was 107 cc (range 80-150 cc). Mean IPSS improved from 23.2 at baseline to 5.8 at 2 years (17-point improvement, $p < .0001$). Mean IPSS quality of life improved from 4.6 at baseline to 1.1 at 2 years ($p < .0001$). Maximum urinary flow increased from 8.7 to 18.2 cc/sec. Two subjects underwent a repeat procedure for BPH symptoms over the 2-year follow up period. By 2 years or study exit, all but 2 of 74 subjects stopped taking alpha blockers. Similarly, all but 4 of 32 subjects stopped taking 5α-reductase inhibitors.*

Conclusions: *Two-year prospective multicenter follow up demonstrated that the Aquablation procedure is safe and effective in the treatment of men with LUTS due to BPH and prostates 80-150 cc with durable treatment efficacy, acceptable safety profile and a low retreatment rate. ClinicalTrials.gov number, NCT03123250.*

Key Words: Aquablation, BPH, LUTS, prostate surgery, robotics, urology

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Introduction

Robotically executed waterjet-based resection of the prostate (Aquablation therapy) has emerged as a recognized, commercially available, attractive alternative treatment to other resective procedures for men with moderate-to-severe lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) due to prostate volume-independent procedural

efficiency and a very low learning curve. For men with prostates 30-80 cc, the Aquablation procedure demonstrated symptom reduction and urodynamic improvements similar to TURP in a blinded randomized trial (WATER).[1] In this study, the rate of postoperative anejaculation was markedly lower in the Aquablation group and showed better ejaculatory function as measured by the Male Sexual Health Questionnaire (MSHQ-EjD). Results from WATER prompted the current study, WATER II, a prospective multicenter single-arm trial of Aquablation procedure for men with LUTS due BPH and larger prostates (80-150 cc). Previously we reported early[2] and 12-month outcomes.[3] Herein we report 2-year outcome durability of improvements in symptom scores and uroflow, BPH medication discontinuation, and the occurrence of late adverse events, including symptom recurrence prompting repeat surgical treatment for BPH symptoms.

Materials and methods

Trial design and participants

WATERII (NCT03123250) is a prospective, multicenter clinical trial conducted at 16 centers in the United States and Canada. Adult men age 45-80 were included if they had a prostate volume between 80 and 150 cc by transrectal ultrasound, baseline IPSS[4] ≥ 12, a maximum urinary flow rate (Qmax) < 15 mL/s, a serum creatinine < 2 mg/dL, a history of inadequate or failed response to medical therapy and mental capability and willingness to participate in the study. Men were excluded if they had body mass index ≥ 42 kg/m^2, a history of prostate or bladder cancer, clinically significant bladder calculus or bladder diverticulum, active infection, previous urinary tract surgery, urinary catheter use daily for 90 or more days, chronic pelvic pain, diagnosis of urethral stricture, meatal stenosis or bladder neck contracture, use of anticholinergic agents, and other general conditions that could prevent adequate study follow up. Patients with prior prostate surgery were not excluded. Men with urinary retention were excluded if the catheter was in place for more than 90 days. Each center obtained institutional review board/ethics committee approval prior to study start. In the US, the study was run under investigational device exemption from US Food and Drug Administration. The study was sponsored by the device manufacturer.

At baseline and selected follow up visits the following questionnaires were completed: IPSS, Incontinence Severity Index, Pain Intensity Scale, International Index of Erectile Function (IIEF-15[5]), the Male Sexual Health Questionnaire (MSHQ-EjD[6]), uroflowmetry and post-void residual (PVR) volume measurements. At year 2, IPSS and uroflowmetry were assessed. Serum prostate-specific antigen (PSA) was performed at baseline and at 6, 12, and 24 months. Transrectal ultrasound prostate size measurements were performed preoperatively and at 3 months postoperatively. Standard laboratory tests (blood count/serum chemistries) were performed at baseline and prior to hospital discharge.

Though originally planned as a 1-year study, study follow up was extended to 5 years in order to collect further information on long-term safety and efficacy. Safety was assessed according to the cumulative incidence of adverse events. Efficacy was assessed with IPSS scores and uroflow measures. All sites participating in the early phase of this study enrolled subjects in this late follow up extension.

The Aquablation procedure was performed using the AquaBeam Robotic System (PROCEPT BioRobotics, Redwood City, CA, USA).[7] Briefly, after induction of general or spinal anesthesia, a 24F single-use handpiece was inserted into the prostatic urethra and secured into place using a bed-mounted arm. Using real-time transrectal ultrasound guidance, the surgeon defined the target anatomic resection contour on a computer console. Contours were selected to avoid damage to the bladder neck, ejaculatory ducts, and urinary sphincter. Tissue was then treated utilizing an automated, high-velocity waterjet controlled by the robot. For larger prostates, the Aquablation procedure typically required two treatment passes of the AquaBeam probe for larger tissue removal.

Post-Aquablation, the bladder was irrigated, and hemostasis was achieved via low-pressure tamponade with a Foley balloon catheter inflated to 40-80 cc of saline either at the bladder neck (98 cases) or within the prostatic fossa (3 cases) with traction greater than 600 grams (5.9 Newtons) with a catheter tensioning device, followed by continuous bladder irrigation as previously described. No cases utilized electrocautery for hemostasis.

Adverse events were judged for relatedness to the study device or procedure and adjudicated by a clinical events committee (CEC) up to 1 year. Events occurring after year 1 were reported by investigators but not adjudicated by the CEC. Three[2] and 12-month[3] outcomes were previously reported. Herein we report the extended 2-year outcomes and cumulative adverse event rates.

Data monitoring

All study data were collected using an electronic data capture system. Study data were 100% source-verified by study monitors.

Statistical analysis

Changes in continuous measures were assessed using t tests and/or repeated measures analysis of variance.

Exact binomial methods were used to calculate confidence intervals for proportions. All statistical analysis was performed using R.[8]

Results

In the original study between September and December 2017, 101 men were enrolled at 16 sites (24 surgeons). Consent for the extension study at 16 sites was obtained in 86 subjects (85%). Of the 15 subjects not followed up, five declined to continue in the study at various timepoints, three were lost to follow up prior to 1 year, and seven were lost to follow up prior to 2 years. All lost to follow up patients had three documented attempts to make contact before they were deemed lost to follow up. Reasons for non-participation in the extension study were not collected; some subjects participating in the original study could not be reached for further follow up.

Baseline patient characteristics (n = 101) are summarized in Table 1. Mean age was 68 years (63-72) and baseline IPSS was 23 (12-35). Sixteen subjects (16%) had used a urinary catheter in the 45 days prior to enrollment. Mean prostate volume was 107 cc (80-150). There were no remarkable differences in all patients enrolled compared to the cohort with 2 year follow up. Study procedures were performed under general anesthesia in 18% and spinal anesthesia in 82% of cases. Mean operative time was 37 minutes (range 15-97 minutes). There were six (6%) peri-operative transfusions likely resulting from electrocautery not being used for hemostasis.

The mean (SD) IPSS improved from 23.2 (6.3) at baseline to 5.8 (4.5) at 2 years (a 17.4-point improvement, $p < 0.0001$, Figure 1). Two-year IPSS scores were independent of both baseline IPSS and prostate size. IPSS QOL decreased from 4.6 (1.1) at baseline to 1.1 (1.4) at 2 years (a 3.4-point reduction, $p < .0001$). In patients reporting catheter use in the 45 days prior to enrollment, IPSS decreased from 26.3 (7.4) at baseline to 4.8 (4.6) at 2-year follow up. No patient using a catheter prior to surgery used a catheter prior to follow up visits. There were no differences in outcomes from 1 to 2 year or between subgroups of prostate sizes.

TABLE 1. **Baseline characteristics (n = 101)**

Characteristic	**Statistic**
Age, years, mean (SD), range	67.5 (6.6), 52-79
Body mass index, mean (SD), range	28.4 (4.2), 22-41
Race	
Asian	5 (5.0%)
Black	6 (5.9%)
White	88 (87.1%)
Other	2 (2.0%)
Ethnicity	
Hispanic or Latino	9 (8.9%)
Non-Hispanic or Latino	92 (91.1%)
Prostate-specific antigen, g/dL; mean (SD), range	7.1 (5.9), 0.34-29
Use of catheters in 45 days prior to enrollment	14 (14.3%)
Prostate size (TRUS), cc; mean (SD), range	107.4 (22.1), 80-150
Middle lobe	84 (83.2%)
Intravesical component	81 (96.4%)
Intravesical protrusion, mm; mean (SD)	1.8 (0.8)
Baseline questionnaires	
IPSS score, mean (SD), range	23.2 (6.3), 12-35
IPSS QOL, mean (SD), range	4.6 (1.0), 2-6
Sexually active, N (%) [MSHQ-EjD]	77 (76.2%)
MSHQ-EjD*, mean (SD), range	8.1 (3.9), 1-15
SHIM*, mean (SD), range	15.1 (7.4), 2-25

*sexually active men only

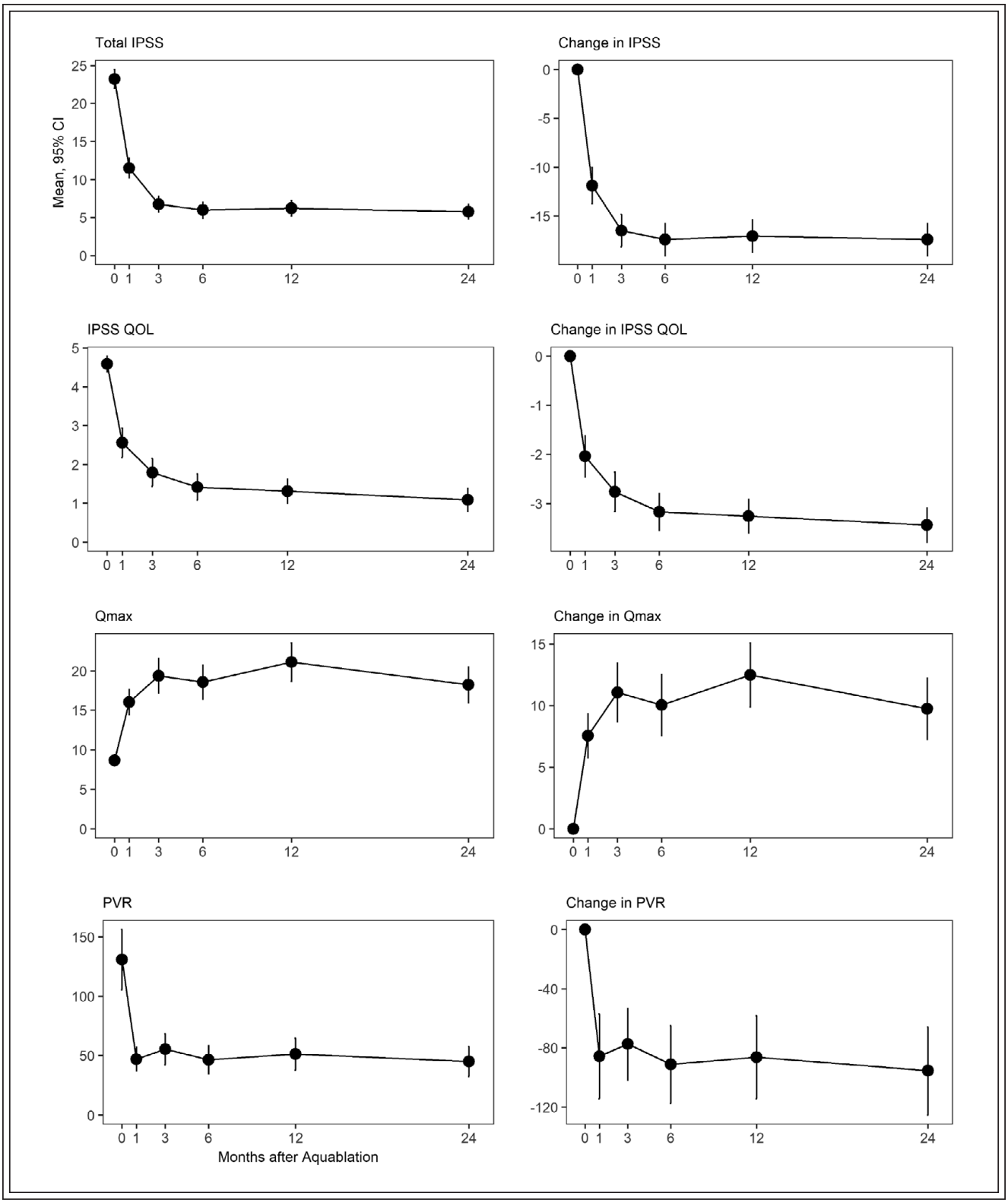

Figure 1. Improvement in parameters after Aquablation: IPSS; IPSS quality of life (QOL); Qmax (maximum urinary flow rate, cc/sec); Post-void residual (cc). Graphs on left show population means. Graphs on right show change from baseline.

Maximum urinary flow rate increased from 8.7 (3.4) to 18.2 (10.6) cc/sec (an improvement of 9.7 (11.3) cc/sec at 2 years, $p < .0001$) and post-void residual urinary volume decreased from 131 (125) cc at baseline to 45 (59.5) cc at 2 years. Mean (SD) serum PSA decreased from 7.1 (5.9) at baseline to 4.4 (4.3) and 4.9 (5.1) at 1 and 2 years, respectively. Amongst men with a PSA ≥ 4, PSA decreased by 42% and 38% at 1 and 2 years, respectively ($p < .0001$).

At baseline, 74 (73%) subjects were taking alpha blockers, primarily for LUTS due to BPH. By 2 years or study exit, all but 2 subjects discontinued alpha blockers. Three men not taking alpha blockers began them anew during study follow up; in 1 case alpha blockers were prescribed briefly for kidney stones, and 2 other cases, alpha blockers were started at days 26 and 28 days after Aquablation for ongoing BPH symptoms.

TABLE 2. **Number of events, number of subjects with event and rate by days since surgery.**

	< 1 month			1-3 months			3-12 months			12-24 months		
Event type	**Events**	**Subjects**	**Rate**	**Events**	**Subjects**	**Rate**	**Events**	**Subjects**	**Rate**	**Events**	**Subjects**	**Rate**
Bladder stones							3	3	3%			
Bleeding	23	20	20%				4	3	3%	3	3	4%
Cardiac	4	3	3%	1	1	1%						
Cerebrovascular accident	1	1	1%				1	1	1%			
Dysuria	12	10	10%	2	2	2%	2	1	1%			
Ejaculatory dysfunction				12	12	12%	3	3	3%	2	2	2%
Elevated PSA							2	2	2%	1	1	1%
Erectile dysfunction										1	1	1%
Gastrointestinal symptoms	6	4	4%									
Hematospermia							2	1	1%			
Kidney dysfunction				2	1	1%	1	1	1%			
Meatal stenosis	3	3	3%	5	4	4%	2	1	1%			
Multisystem organ failure	1	1	1%									
Other	16	10	10%	1	1	1%	14	12	12%	2	2	2%
Pain	9	6	6%									
Prostate cancer							1	1	1%			
Rising PSA										1	1	1%
Scrotal edema	3	3	3%									
Skin infection	1	1	1%	1	1	1%	1	1	1%			
Urethral stricture	1	1	1%	1	1	1%						
Urinary frequency	2	2	2%	1	1	1%				1	1	1%
Urinary incontinence	5	5	5%							1	1	1%
Urinary retention	2	2	2%	2	2	2%	1	1	1%	1	1	1%
Urinary tract infection	5	5	5%	4	3	3%	16	9	9%	2	2	2 %
Urinary urgency	6	4	4%				4	3	3%			

At baseline, 32 (32%) subjects were using 5α-reductase inhibitors (ARIs). By 2 years or study exit, all but 4 discontinued these. During follow up 5 subjects not using ARIs at baseline started them. Of these, 1 subject discontinued finasteride but restarted at day 83 post-Aquablation related to an episode of syncope/hydronephrosis, 3 subjects started finasteride at days 1, 233 and 507, respectively, for BPH symptoms, and 1 started finasteride at day for a rising PSA.

Between year 1 and year 2, the number of urologic events was small, Table 2. Two subjects (2.0%) had recurrent BPH symptoms that required surgical retreatment with TURP and HOLEP (1 case each), resulting in an annualized surgical BPH retreatment rate of 1.0%. One additional patient underwent a radical prostatectomy for prostate cancer. Compared to subjects not undergoing a repeat BPH surgical procedure, these 2 subjects had a slightly smaller prostate volume (91 versus 108 cc, p = .0162), higher baseline IPSS score (29 versus 23, p = .1816), lower baseline Qmax (6.7 versus 9.7 cc, p = .0137), and slightly lower operative time (31 versus 38 minutes, p = .2329). No other parameters were different between these two subject groups. No subject underwent a surgical procedure for urethral stricture, bladder neck contracture or urinary incontinence. There were no bleeding events requiring transfusion or take back for fulguration after 28 days.

Discussion

Our study provides strong evidence that the Aquablation procedure provides excellent mid-term (2-year) long-term relief of LUTS related to BPH. Our study is especially notable in that we enrolled men with a large prostate size (target range 80-150 cc, mean 107 cc, 83% with a large median lobe), a group that typically cannot undergo TURP. Nonetheless, improvements in LUTS were clinically important (mean ~17-point reduction in IPSS, 3.4-point reduction in IPSS QOL) and concomitant large improvements were seen in uroflow measures (improvement in Qmax of 10 cc/sec), both being durable at 2 years. Most subjects were able to stop taking alpha blockers and no subject requiring a catheter preoperatively required it during follow up. These changes are both expected for a resective prostate procedure and similar in magnitude to those seen for Aquablation in a large randomized trial of smaller (30-80 cc) prostates.1 Our results are also consistent with prior publications,12–14 some of which included men with large prostate sizes. Over 2 years, only 2 (2%) of men underwent a retreatment resective procedure for BPH symptoms.

Advantages of the Aquablation procedure include relatively rapid procedure times (37 minutes), with a small proportion of this time spent on robotic ablation (mean 8 minutes). We observed little relationship between procedure times and prostate size, suggesting the procedure is relatively independent of prostate size. These procedure times are lower than other procedures for large prostates (e.g., 95 minutes for open prostatectomy,[9] 91 minutes for HoLEP,[10] 93 minutes for PVP[11]).

Post-Aquablation bleeding requiring transfusion occurred in 10 patients (10%), a rate that is reasonably low compared to alternatives for men with large prostates. There were no late (> 28 days) bleeding events.

Our study provides convincing 2-year evidence that the Aquablation procedure is safe, easily reproducible and effective treatment of LUTS related to BPH. More important, it is feasible and effective for the subgroup of large prostates, for which treatment options are limited. For the majority of practicing urologists (> 98%) who do not perform HoLEP, Aquablation may be a reasonable choice to avoid the need for open prostatectomy. Other advantages include an extremely short learning curve (most surgeons in our study had little or no experience with Aquablation prior to study start), procedure reproducibility through image guidance and robotic execution, shorter operative time and shorter length of stay, all of which are potentially associated with decreased procedure-related morbidity.

Advantages of our study include its prospective multicenter design with careful preoperative and scheduled postoperative visits and assessments. Prospective trials of men with large prostates and 2-year follow up are uncommon. A trial limitation was the lack of a control group, preventing direct comparisons to other treatment approaches.

Conclusion

The Aquablation procedure is a safe and effective, robotically executed and globally reproducible surgical option for the treatment of BPH-related LUTS in men with large prostate glands with durable outcomes at 2 years coupled with short operative times, limited hospitalization and low retreatment rates.

Disclosures

Mihir Desai, Mo Bidair, and Eugene Kramolowsky are consultants for PROCEPT BioRobotics. Mihir Desai is also a consultant with Auris Surgical. Kevin Zorn and Naeem Bhojani have been paid for a training session at AUA 2018. No other author has a conflict of interest with PROCEPT BioRobotics. □

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