Aquablation versus transurethral resection of the prostate: 1 year United States – cohort outcomes

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KASIVISVANATHAN V, HUSSAIN M ON BEHALF OF THE U.S. WATER INVESTIGATORS. Aquablation versus transurethral resection of the prostate: 1 year United States – cohort outcomes. *Can J Urol* 2018;25(3):9317-9322.

Introduction: *The purpose of this analysis was to compare Aquablation to transurethral resection of the prostate (TURP) with respect to efficacy and safety at 1 year for the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia (BPH) in the United States (U.S.) cohort from the Waterjet Ablation Therapy for Endoscopic Resection of prostate tissue (WATER) study.*

Materials and methods: *WATER is a double-blinded, multicenter prospective randomized controlled trial for patients with moderate-to-severe lower urinary tract symptoms related to BPH. Men were randomized to TURP or Aquablation. The efficacy and safety outcomes at 1 year were evaluated for the U.S. cohort. The efficacy objective was reduction in International Prostate Symptom Score (IPSS). The safety objective was the occurrence of Clavien-Dindo persistent grade 1 or grade 2 or higher operative complications.*

Results: *Ninety patients were randomized and treated between December 2015 and December 2016. Change in IPSS at 1 year between Aquablation and TURP was similar (14.5 versus 13.8, respectively, p = 0.7117). The number of subjects experiencing persistent Clavien-Dindo grade 1 or Clavien-Dindo grade 2 or higher adverse events was lower in the Aquablation group compared to the TURP group (20% versus 47% respectively, p = 0.0132). Amongst sexually active subjects, the rate of anejaculation was lower in patients treated with Aquablation than TURP (9% versus 45%, respectively, p = .0006).*

Conclusions: *Surgical prostate resection using Aquablation showed improvement in lower urinary tract symptoms at 1 year comparable to TURP, but with a lower risk of adverse events and ejaculatory dysfunction.*

Key Words: aquablation, transurethral resection of the prostate, lower urinary tract symptoms

Accepted for publication May 2018

Acknowledgement
The authors would like to thank Barry Templin from PROCEPT BioRobotics for providing the data and for statistical support in this manuscript. The study was funded by PROCEPT BioRobotics.

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Introduction

Lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) are highly prevalent, with up to 42% of men over the age of 50 reporting moderate to severe symptoms.[1,2] These symptoms can be bothersome and warrant medical treatment, though many men fail medical management and seek surgical treatments.[3,4]

Despite the availability of a number of ablative and non-ablative surgical treatments for men with BPH

and bothersome LUTs, including laser enucleation, photovaporization, microwave thermotherapy, and needle ablation, surgical standard of care for men is transurethral resection of the prostate (TURP) with electrocautery.[5,6] TURP carries side effects with risks of retrograde ejaculation, bleeding, clot retention, urethral stricture, urinary incontinence and erectile dysfunction.[7-11] Of note, a particularly frequent side effect following TURP is retrograde ejaculation which has been reported in up to 68% of men.[12]

The full cohort results of the Waterjet Ablation Therapy for Endoscopic Resection (WATER) of prostate tissue study, evaluating the safety and efficacy of robotically guided waterjet-based prostate resection (Aquablation) at 6 months have been published.[13] At 6 months, large and comparable International Prostate Symptom Score (IPSS) improvements were seen with Aquablation and TURP. Aquablation was deemed non-inferior to TURP in efficacy, though demonstrated superiority in safety. Here, we evaluated the safety and efficacy at 1 year of Aquablation compared to TURP in the United States (U.S.) cohort.

Materials and methods

The design and methods of the WATER study (NCT02505919) have been previously described.[13] WATER is a double-blind, international multicenter clinical trial comparing the safety and efficacy of the Aquablation and TURP in the surgical treatment of LUTS due to BPH. Twelve of the 17 participating sites were based in the U.S. The study was approved by the institutional review board at each site. Key inclusion criteria included men aged 45-80 years of age with a prostate size between 30 cc-80 cc (measured with transrectal ultrasound), moderate-to severe symptoms as indicated by an IPSS[14] ≥ 12, and a maximum urinary flow rate (Qmax) < 15 mL/s.[13] Key exclusion criteria included men taking bladder anticholinergics, anticoagulants or with severe cardiovascular disease, and prostate cancer. The subjects enrolled in the U.S. are included in this analysis. All participants provided informed consent using study-specific forms.

Subjects were randomly assigned in a 2:1 ratio to Aquablation or TURP. Randomization was obtained through a web-based system and was stratified by study site and baseline IPSS score category with random block sizes.

Aquablation was performed using the AquaBeam System (PROCEPT BioRobotics, Redwood Shores, CA, USA).[15] After Aquablation was complete, hemostasis was achieved using either low-pressure inflation of a Foley balloon catheter in the prostatic fossa or focal, non-resective, electrocautery.[16] Use of catheter and bladder irrigation was carried out at the discretion of the local investigator.

TURP was performed according to standard practice. Following TURP, a urethral urinary catheter was placed and subjects received continuous bladder irrigation. Choice of catheter and duration of bladder irrigation was also carried out at the discretion of the local investigator.

Assessment at baseline and conduct of study treatment were provided by an unblinded research team (surgeon and coordinator) though the participant was unaware of which treatment they were assigned to throughout the study. A separate blinded team (physician and coordinator) conducted the follow up visits and assessments.

The primary efficacy outcome of the current study was the change in IPSS from baseline to 1 year. The difference in IPSS change was evaluated using a t-test; additional models controlled for baseline IPSS. The primary safety outcome of this study was the proportion of subjects with adverse events up to 1 year rated by the clinical events committee as possibly, probably or definitely related to the study procedure classified as Clavien-Dindo[17] grade 2 or higher or any grade 1 event resulting in persistent disability (ejaculatory or erectile dysfunction or incontinence). The difference in rates were performed using a two-sided Fisher's test. The clinical events committee was independent and blinded to treatment assignment. Analyses were carried out on a modified intention-to-treat basis.

Other objectives include, but not limited to: resection time and total operative time, length of hospital stay, reoperation or re-intervention rate, and uroflow measurements.

Independent study monitors verified all data prior to analysis and a data monitoring committee regularly reviewed safety data throughout the study.

Results

A total of 142 subjects were evaluated at 12 sites in the U.S. between December 2015 and December 2016 where 93 were randomized. Baseline characteristics were similar between groups, Table 1. Three subjects (2 TURP, 1 Aquablation) voluntarily withdrew prior to treatment, leaving 90 in the modified intent-to-treat population, Figure 1, resulting in 60 treated with Aquablation and 30 treated with TURP. Mean prostate size was 53 cc and 87% were sexually active. Eighty-seven (97%) patients completed 1 year follow up.

TABLE 1. **Baseline characteristics**

Characteristic	**Aquablation n = 61**	**TURP n = 32**
Age, years, mean (SD)	64.5 (7.4)	65.3 (7.1)
Body mass index, mean (SD)	28.2 (4.3)	29.6 (4.8)
Prostate size (TRUS)*, gm; mean (SD)	54.2 (16.3)	50.8 (13.9)
Prostate-specific antigen, g/dL; mean (SD)	3.5 (3.2)	2.9 (2.3)
Cystoscopy findings		
Lobes present		
Lateral lobe only	31 (50.8%)	17 (53.1%)
Middle lobe only	0 (0.0%)	1 (3.1%)
Both lateral and middle	30 (49.2%)	14 (43.8%)
Degree of middle lobe obstruction		
None	15 (24.6%)	9 (28.1%)
Mild	9 (14.8%)	5 (15.6%)
Moderate	18 (29.5%)	10 (31.2%)
Severe	11 (18.0%)	4 (12.5%)
Bladder neck obstruction	15 (24.6%)	11 (34.4%)
Baseline questionnaires		
IPSS score, mean (SD)	22.1 (6.2)	21.7 (6.6)
IPSS QOL, mean (SD)	4.7 (1.1)	4.9 (0.8)
Sexually active, n (%) [MSHQ-EjD]	56 (93.3%)	26 (86.7%)
MSHQ-EjD mean (SD)**	8.1 (3.7)	8.8 (3.6)
IIEF-5, mean (SD)**	16.2 (6.4)	16.2 (7)

*volume = prostate length × width × height × π/6
**sexually active men only
IPSS = International Prostate Symptom Score; QOL = quality of life; MSHQ = Male Sexual Health Questionnaire; EjD = ejaculatory dysfunction; IIEF-5 = International Index of Erectile Function

Subjects underwent the index study procedure under general anesthesia in 96% of cases and spinal anesthesia in 4%. In TURP, monopolar instruments were used in 14 (46.7%) patients and bipolar instruments in 16 (53.3%) patients. Mean operative time (defined as pre-treatment visualization to insertion of indwelling catheter after resection was complete) was slightly shorter for Aquablation (27.6 minutes in Aquablation, 37.4 minutes in TURP, p = 0.0037). Mean resection time (first pedal activation to end of pedal use) was lower in the Aquablation group (3.9 minutes in Aquablation, 29.8 minutes in TURP, p < 0.0001). Postoperative hemoglobin levels dropped from 14.8 g/dL at baseline to 12.8 g/dL at discharge in the Aquablation group and from 14.7 g/dL at baseline to 13.6 g/dL at discharge in the TURP group (p = 0.0111); no subjects in either arm required blood transfusion. Less irrigation fluid was used intraoperatively during Aquablation compared to TURP (3.1 liters versus 13 liters, p < 0.0001). Mean hospital length of stay was 1.4 days in the Aquablation group and 1.3 days in the TURP group. Thirty percent and 23% of Aquablation and TURP patients, respectively, were discharged with a catheter.

There was no difference in reduction in IPSS at 1 year for Aquablation compared to TURP (14.5 points versus 13.8 points, respectively, p = 0.7117), Figure 2. The IPSS quality of life score improved similarly in both groups at 1 year (decreases of 3.1 points ersus. 3.4 points, respectively, p = 0.5760). In both groups, mean maximum urinary flow rates increased markedly post-procedurally by 30 days with optimal flow rates at 90 days post procedure. This benefit persisted at 1 year post procedure and was similar for both groups (increases of 11 mLs/s versus 10 mLs/sec, respectively), Figure 2. At 1 year, post-void residuals decreased in both arms similarly (decreases of 54 mLs

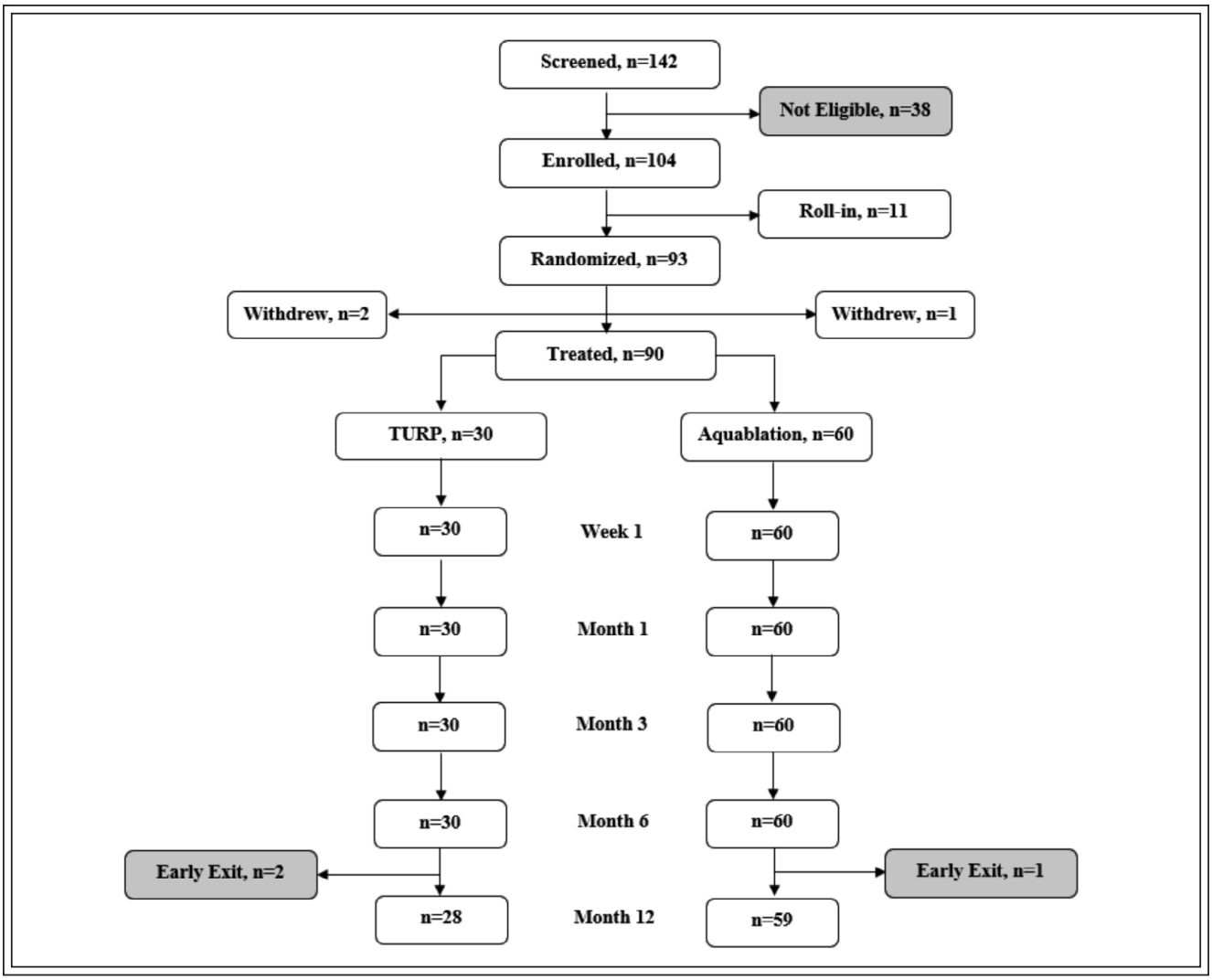

Figure 1. CONSORT diagram.

versus 39 mLs, respectively). At 1 year PSA reduced in both arms by a comparable amount (-1.0 ng/mL and -0.7 ng/mL, respectively).

Significantly fewer men experienced persistent Clavien-Dindo grade 1 or Clavien-Dindo grade 2 or higher adverse events following Aquablation compared to TURP (20% versus 47%, respectively, p = 0.0132) through 1 year. The rate of Clavien-Dindo grade 2 or higher was lower for Aquablation (13.3%) than TURP (30.0%). The Clavien-Dindo grade 1 persistent events was lower for Aquablation (6.7%) than TURP (30.0%) which included ejaculatory dysfunction, erectile dysfunction, and incontinence. No subjects in either arm experienced incontinence or erectile dysfunction. Amongst sexually active subjects, the rate of anejaculation was lower in patients treated with Aquablation than TURP (9% versus 45%, respectively, p = .0006).

One TURP subject (3.3%) and one Aquablation subject (1.7%) underwent surgical retreatment for BPH within 1 year from the study procedure.

Discussion

The main findings of this study were that Aquablation improved LUTS at 1 year at a level comparable to the standard of care TURP, but had fewer adverse events, notably fewer men experiencing retrograde ejaculation. Improvements at 1 year were seen in IPSS, flow rate, post-void residual and quality of life from urinary symptoms. The international study-wide results of the WATER study with efficacy results at 6 months have been reported[13] and the U.S. cohort findings are consistent with these. Additional findings in this study were that the benefits seen in

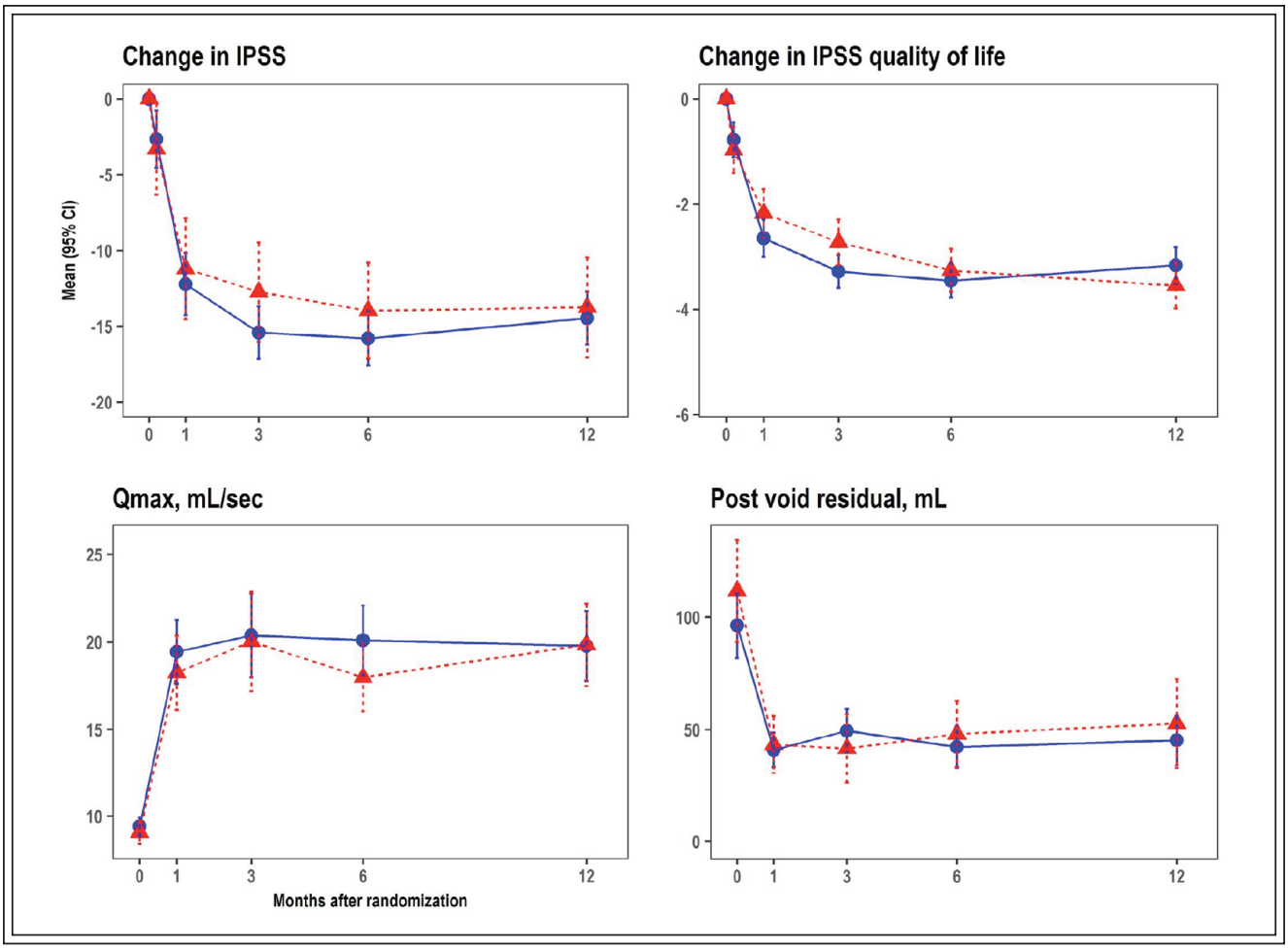

Figure 2. Change in International Prostate Symptom Score (IPSS, top left), IPSS quality of life (top right), maximum urinary flow (bottom left) and post void residual (bottom right) by treatment and time. Solid blue = Aquablation; dotted red = TURP.

improving LUTS appear to persist through to 1 year post-procedure.

Improvement in urinary flow rate and post-void residual seen in the study are consistent with those seen in the literature for ablative prostate surgical techniques, notably laser enucleation[18] and laser photovaporisation.[19] In comparison to non-ablative surgical options for BPH, Aquablation appeared to have more favorable improvements in IPSS; convective water vapor energy (Rezum, 3.3 points higher)[20] and UroLift procedure (3.7 points higher).[21] Of note a slightly greater drop in hemoglobin resulted from the Aquablation procedure than the TURP procedure though this did not result in increased transfusion rates. The hemostasis method was being optimized throughout the conduct of the study, so this is likely to stabilize with further experience of the technique. A major advantage of the Aquablation procedure is related to the preservation of ejaculatory function, which is thought to be due to the accurate tissue destruction sparing the verumontanum while utilizing a heat-free mechanism to remove tissue. In TURP, ejaculatory dysfunction is very common and is thought to relate to heat damage to the ejaculatory duct.[19]

Strengths of the study include the blinding of participants to intervention and the blinding of assessors during follow up which reduces bias in reporting of outcomes. It was also confirmed that blinding was preserved in the study. The multicenter design increases the generalizability of the results. Efficacy in the TURP control group, as reflected by both symptom score and uroflow improvements, were large and consistent with expectations, adding overall validity to the trial's outcomes. Surgeons that participated in the study were very experienced with TURP. Despite having far less experience with

Aquablation, efficacy outcomes were still comparable, highlighting that the learning curve with the technology is not significant. It is also encouraging that the large U.S. cohort of the study had results consistent with the overall study group. Of note, limitations in this study include the short follow up. Further follow up is required to assess the durability of Aquablation in the medium to long term. The study was also limited to enrolling prostates with a maximum size of 80 cc due to the fact that most international guidelines do not recommend TURP for glands greater than 80 cc. Aquablation has recently been used in 80 cc-150 cc prostates and demonstrated a reasonable safety profile[22] highlighting extended roles for the technology beyond the cohort of men analyzed in this study, which are the subject of ongoing research.

Conclusions

In conclusion, whilst TURP has been the surgical standard of care for improving LUTS in < 80 cc prostates, Aquablation, with its shorter mean operative and resection time, comparable efficacy and reduced adverse events, is a reasonable alternative with good 1 year outcomes for men with prostates of between 30 cc-80 cc. Additionally, it is a particularly good option for men who wish to maintain their ejaculatory function.

Disclosure

Dr. Veeru Kasivisvanathan has received funding from the American Urological Association for a scholarship supported by PROCEPT BioRobotics for a clinical visit to a U.S. institution. □

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