WATER: A Double-Blind, Randomized, Controlled Trial of Aquablation® vs Transurethral Resection of the Prostate in Benign Prostatic Hyperplasia

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Abbreviations and Acronyms

BPH = benign prostatic hyperplasia

EjD = ejaculatory dysfunction

IIEF = International Index of Erectile Function

I-PSS = International Prostate Symptom Score

LUTS = lower urinary tract symptoms

MSHQ = Male Sexual Health Questionnaire

PSA = prostate specific antigen

TURP = transurethral resection of the prostate

Purpose: We compared the safety and efficacy of Aquablation and transurethral prostate resection for the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia.

Materials and Methods: In a double-blind, multicenter, prospective, randomized, controlled trial 181 patients with moderate to severe lower urinary tract symptoms related to benign prostatic hyperplasia underwent transurethral prostate resection or Aquablation. The primary efficacy end point was the reduction in International Prostate Symptom Score at 6 months. The primary safety end point was the development of Clavien-Dindo persistent grade 1, or 2 or higher operative complications.

Results: Mean total operative time was similar for Aquablation and transurethral prostate resection (33 vs 36 minutes, $p = 0.2752$) but resection time was lower for Aquablation (4 vs 27 minutes, $p < 0.0001$). At month 6 patients treated with Aquablation and transurethral prostate resection experienced large I-PSS improvements. The prespecified study noninferiority hypothesis was satisfied ($p < 0.0001$). Of the patients who underwent Aquablation and transurethral prostate resection 26% and 42%, respectively, experienced a primary safety end point, which met the study primary noninferiority safety hypothesis and subsequently demonstrated superiority ($p = 0.0149$). Among sexually active men the rate of anejaculation was lower in those treated with Aquablation (10% vs 36%, $p = 0.0003$).

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Conclusions: Surgical prostate resection using Aquablation showed noninferior symptom relief compared to transurethral prostate resection but with a lower risk of sexual dysfunction. Larger prostates (50 to 80 ml) demonstrated a more pronounced superior safety and efficacy benefit. Longer term followup would help assess the clinical value of Aquablation.

Key Words: prostatic hyperplasia, transurethral resection of prostate, lower urinary tract symptoms, robotic surgical procedures, water

MODERATE to severe LUTS due to BPH affect 30% of men older than 50 years[1,2] with a rate as high as 90% by age 85 years.[3] Medical treatment often fails in men with moderate to severe symptoms and they seek surgical treatments.

Surgical approaches include ablative treatments such as TURP with electrocautery, photovaporization and laser enucleation, and nontissue ablative techniques such as microwave thermotherapy, or needle ablation or clips. While TURP remains the treatment reference standard, it carries risks of bleeding, clot retention, bladder neck contracture or urethral stricture, urinary incontinence, erectile dysfunction and retrograde ejaculation.[4–8] Retrograde ejaculation is especially common after TURP (more than 60%).[9] NonTURP ablative techniques have similarly high efficacy rates (exceeding those of nonablative techniques) but still suffer from certain risks.

High pressure water jet technology, which was originally used in industry to cut metal, ceramic and glass, has been described for tissue specific liver resection[10,11] and bladder tumors.[12] Initial studies of a robotically guided water jet for prostate resection termed Aquablation suggest high levels of efficacy with a potentially decreased risk of sexual side effects possibly due to more accurate tissue targeting.[13,14]

We evaluated the safety and efficacy of robotically guided, water jet based prostate resection compared to electrocautery based TURP in a double-blind randomized trial.

METHODS

Trial Design and Participants

WATER (Waterjet Ablation Therapy for Endoscopic Resection of Prostate Tissue) (ClinicalTrials.gov NCT02505919) is a prospective, double-blind, multicenter, international clinical trial comparing the safety and efficacy of Aquablation and TURP as surgical treatment of LUTS due to BPH in men 45 to 80 years old with a prostate between 30 and 80 gm as measured by transrectal ultrasound, moderate to severe symptoms as indicated by I-PSS[15] 12 or greater and a maximum urinary flow rate less than 15 ml per second.

Men were excluded from analysis if they had a history of prostate or bladder cancer, neurogenic bladder, bladder calculus or clinically significant bladder diverticulum, active infection, treatment for chronic prostatitis, diagnosis of urethral stricture, meatal stenosis or bladder neck contracture, a damaged external urinary sphincter, stress urinary incontinence, post-void residual urine greater than 300 ml or urinary retention, self-catheterization use or prior prostate surgery. Men receiving anticoagulants or bladder anticholinergics and those with severe cardiovascular disease were also excluded.

TURP was chosen as the control group because it represents the gold standard surgical treatment of moderate to severe BPH. All participants provided informed consent using study specific forms prior to any test that went beyond standard care.

Randomization and Intervention

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

TURP was performed according to standard practice. After TURP a urethral urinary catheter was placed and patients received continuous bladder irrigation. Catheter choice and bladder irrigation duration were in accordance with local preferences at each site.

Aquablation was performed using the AquaBeam® System.[13] A 24Fr hand piece probe similar to a rigid cystoscope was inserted in the prostatic urethra and locked into place using a bed mounted, rigid arm. Under real-time prostate visualization with transrectal ultrasound the surgeon used a console to mark the target resection contour. Under surgeon control tissue ablation was performed robotically with a high velocity water jet to resect adenomatous tissue while avoiding the verumontanum and the ejaculatory ducts.

After Aquablation was complete, hemostasis was achieved using focal, nonresective electrocautery or low pressure inflation of a Foley balloon catheter in the prostatic fossa.[16] Catheterization and bladder irrigation were left to local investigator discretion. Otherwise post-treatment management, which included continuous bladder irrigation in all subjects, was similar across groups.

Blinding and Followup

Baseline evaluation and study treatment were done by an unblinded research team (coordinator and surgeon) who did not reveal the treatment assignment to the subject. A separate blinded team (coordinator and physician) performed the followup visits and will do so out to the

Table 1. *Baseline and operative characteristics*

	Aquablation	TURP	p Value
No. pts	117	67	—
Mean ± SD age	66.0 ± 7.3	65.8 ± 7.2	0.8706
Mean ± SD body mass index (kg/m^2)	28.4 ± 4.1	28.2 ± 4.5	0.7934
No. race (%):			
Asian	3 (2.6)	2 (3.0)	0.7063
Hispanic	2 (1.7)	3 (4.5)	
Black	2 (1.7)	2 (3.0)	
White	109 (93.2)	59 (88.1)	
Other	1 (0.9)	0	
Mean ± SD TRUS prostate size (ml)*	54.1 ± 16.2	51.8 ± 13.8	0.3062
Mean ± SD PSA (gm/dl)	3.7 ± 3.0	3.3 ± 2.3	0.4260
No. urological history (%):			
Incontinence	10 (8.5)	5 (7.5)	1.0
Retention	14 (12)	8 (11.9)	1.0
Urinary tract infection	20 (17.1)	9 (13.4)	0.6746
Bladder spasm	3 (2.6)	2 (3)	1.0
Decreased ejaculation	52 (44.4)	23 (34.3)	0.2131
Erectile dysfunction	47 (40.2)	30 (44.8)	0.6415
Hematuria	12 (10.3)	7 (10.4)	1.0
Painful urination	11 (9.4)	4 (6)	0.5777
No. lobes present (%):			
Lateral lobe only	50 (42.7)	31 (46.3)	0.7577
Middle lobe only	9 (7.7)	3 (4.5)	
Lateral + middle	55 (47.0)	88 (47.8)	
Lobes touching	96 (82.1)	59 (88.1)	0.8421
No. middle lobe obstruction (%):			
None	23 (19.7)	15 (22.4)	0.9727
Mild	25 (21.4)	15 (22.4)	
Moderate	35 (29.9)	22 (32.8)	
Severe	14 (12.0)	7 (10.4)	
No. bladder neck obstruction (%)	30 (25.6)	24 (35.8)	0.1795
No. bladder trabeculation (%)			
None	10 (8.5)	9 (13.4)	0.2307
Mild	50 (42.7)	36 (53.7)	
Moderate	49 (41.9)	19 (28.4)	
Severe	5 (4.3)	3 (4.5)	
No. bladder diverticulum (%):	4 (4.3)	0	0.1604
No. sexually active + MSHQ-EjD (%)	93 (80.2)	54 (83.1)	0.6951
Baseline questionnaire score:†			
Mean ± SD I-PSS	22.9 ± 6.0	22.2 ± 6.1	0.4276
Mean ± SD I-PSS quality of life	4.8 ± 1.1	4.8 ± 1.0	0.8009
Mean ± SD EQ-5D TTO index	0.87 ± 0.1	0.89 ± 0.1	0.1057
Mean ± SD MSHQ-EjD‡	8.1 ± 3.7	8.8 ± 3.6	0.3080
Mean ± SD IIEF-5‡	17.2 ± 6.5	18.2 ± 7.0	0.4388
Mean ± SD IIEF-15‡	41.6 ± 21.6	40.4 ± 23.5	0.7674
Mean ± SD mins (IQR):			
Operative	32.8 ± 16.5 (21—41)	35.5 ± 15.3 (25—44)	0.2752
Instrument in/out	23.3 ± 8.7 (17—27)	34.2 ± 14.6 (25—43)	<0.0001
Resection	3.9 ± 1.4 (3—4.3)	27.4 ± 12.5 (18—34)	<0.0001
Mean ± SD L intraop fluid use (IQR)	5.2 ± 4.9 (2—7.5)	13.1 ± 6.6 (9—16)	<0.0001
Mean ± SD days hospital stay (IQR)	1.4 ± 0.7 (1—2)	1.4 ± 0.7 (1—2)	0.3357§

* Volume = prostate length × width × height × π/6.
† In 181 treated men.
‡ In sexually active men only.
§ Wilcoxon test.

completion of the trial. The supplementary materials (http://jurology.com/) provide details on blinding.

Data and Study Monitoring

Independent study monitors verified all study data in electronic case report forms prior to analysis. All adverse events were adjudicated by an independent clinical events committee blinded to treatment assignment. A data monitoring committee periodically reviewed safety data.

Study End Points and Statistical Analysis

The study primary efficacy end point was the change in I-PSS from baseline to 6 months. The difference in the I-PSS change was evaluated using Student's t-test. Additional models controlled for baseline I-PSS. Non-inferiority was declared when the lower 95% 2-sided confidence limit of the difference in score change at 6 months exceeded −4.7 points.

The study primary safety end point was the proportion of subjects with adverse events rated by the clinical

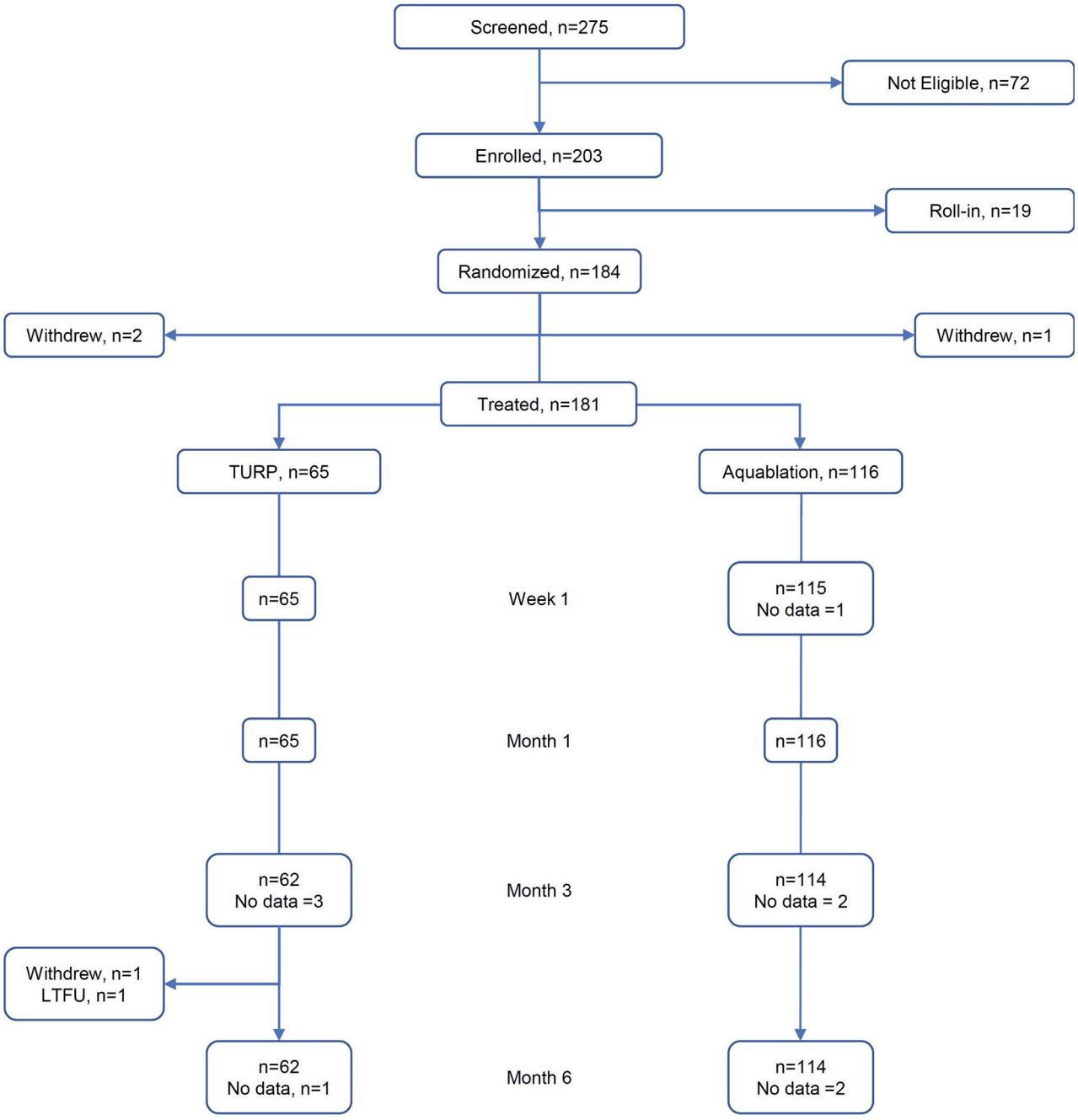

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. *LTFU,* lost to followup.

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, such as ejaculatory or erectile dysfunction or incontinence, as evidenced through 3 months after treatment.

A sample size of 177 randomized subjects had greater than 80% power to detect noninferior change scores with a noninferiority margin of 4.7 points, assuming a 16-point improvement in I-PSS, an effect size of 1.5 points worse in the Aquablation group and a SD of 6 points. Sample size for the safety end point assumed rates of 65% for TURP and 40% for Aquablation with a 12% estimated loss to followup rate and a standard comparison of proportions test. Preplanned subgroup analysis included baseline I-PSS (less than 20 vs 20 or greater), prostate size (less than 50 vs 50 gm or greater) and age (less than 65 vs 65 years or greater). Primary safety end point testing was performed using the Miettinen and Nurminen approach.[18] After superiority was determined subsequent testing, including testing within subgroups, was performed with a 2-sided Fisher test.

Secondary end points included resection time and total operative time, hospital stay, the reoperation or repeat

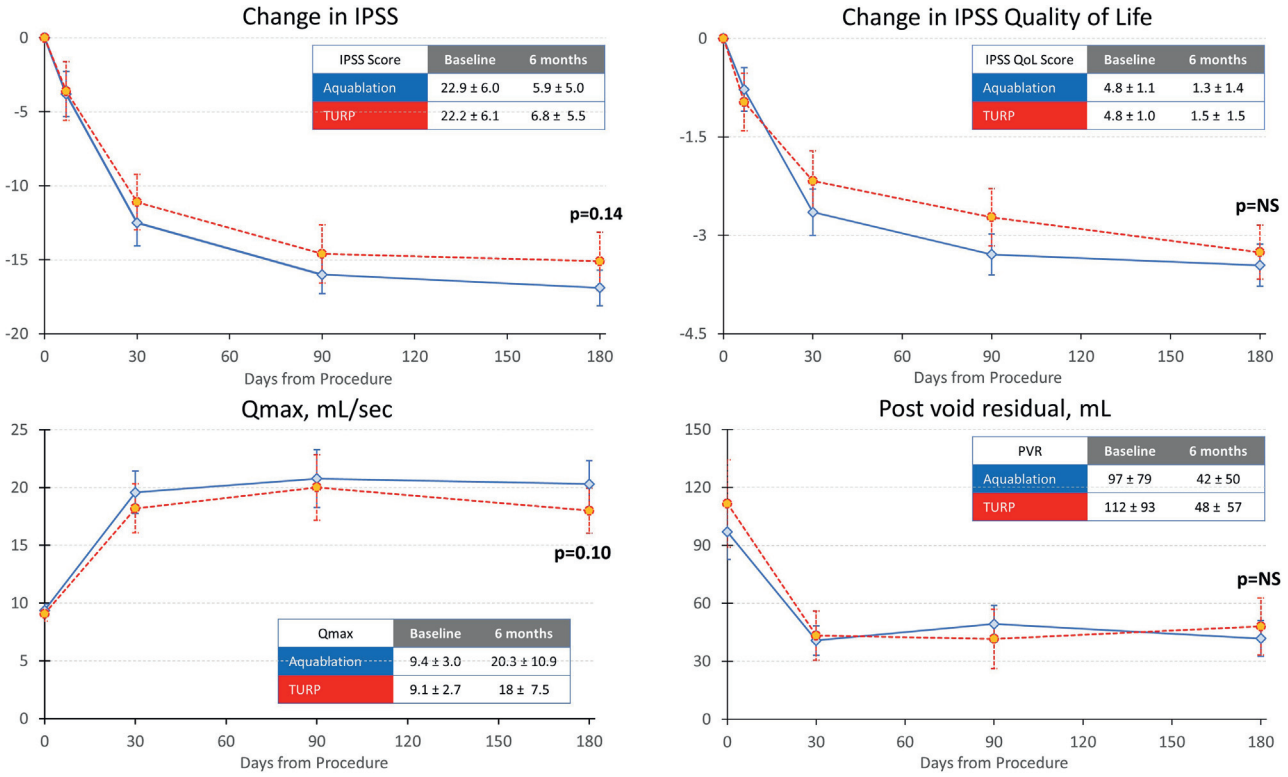

Figure 2. Change in I-PSS, I-PSS quality of life, maximum urinary flow (*Qmax*) and PVR by treatment and time

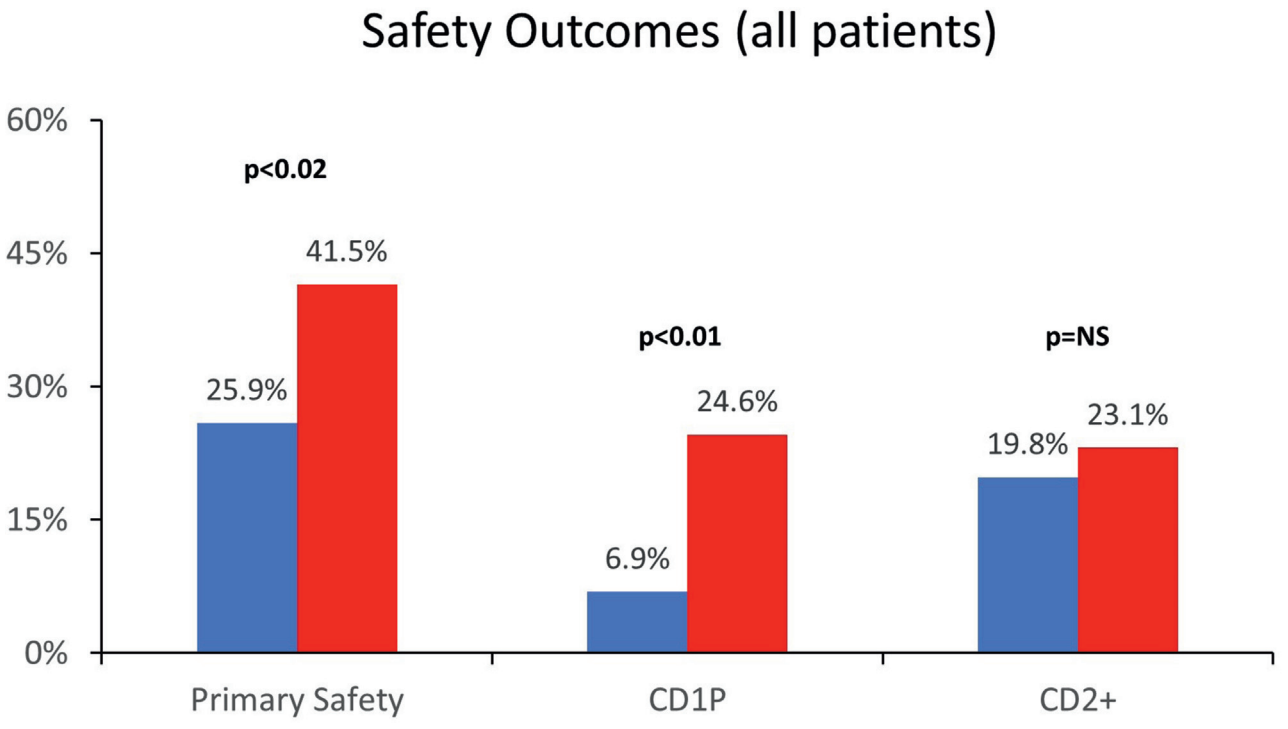

Figure 3. Safety outcome in all patients. *CD1P*, incontinence, erectile dysfunction and ejaculatory dysfunction. *CD2+*, all Clavien-Dindo grade 2-5 events. *NS*, not significant.

Table 2. *Events at month 3 categorized by Clavien-Dindo grades by group as possibly, probably or definitely related to procedure and/or device*

Clavien-Dindo	No. Adverse Events/No. Pts (%)		p Value (Fisher test)
	Aquablation	TURP	
Grade 1:	63/39 (33.6)	41/27 (41.5)	0.3350
Bladder spasm	3/3	1/1	1.0000
Bleeding	12/11	7/7	0.7995
Dysuria	12/12	5/5	0.7912
Pain	5/5	3/3	1.0000
Retrograde ejaculation	8/8	16/16	0.0012
Urethral damage	1/1	1/1	1.0000
Urinary retention	11/9	4/4	0.7730
Urinary tract infection	2/2	0/0	0.5371
Urinary urgency, frequency, difficulty, leakage	4/4	1/1	1.0000
Other	5/5	3/3	1.0000
Grade 2:	20/19 (16.4)	15/11 (16.9)	1.0000
Bladder spasm	4/4	2/2	1.0000
Bleeding	1/1	0/0	1.0000
Dysuria	0/0	1/1	0.3591
Pain	1/1	2/2	0.2932
Urinary tract infection	9/9	5/5	1.0000
Urinary urgency, frequency, difficulty, leakage	2/2	3/2	0.6191
Other	3/3	2/2	1.0000
Grade 3a:	4/4 (3.4)	2/2 (3.1)	1.0000
Bleeding	1/1	1/1	1.0000
Urethral stricture or adhesions	3/3	1/1	1.0000
Grade 3b:	3/3 (2.6)	3/3 (4.6)	0.6684
Bleeding	2/2	2/2	0.6191
Urethral stricture or adhesions	0/0	1/1	0.3591
Urinary retention	1/1	0/0	1.0000
Grade 4:	1/1 (0.9)	0/0	1.0000
Arrhythmia	1/1	0/0	1.0000

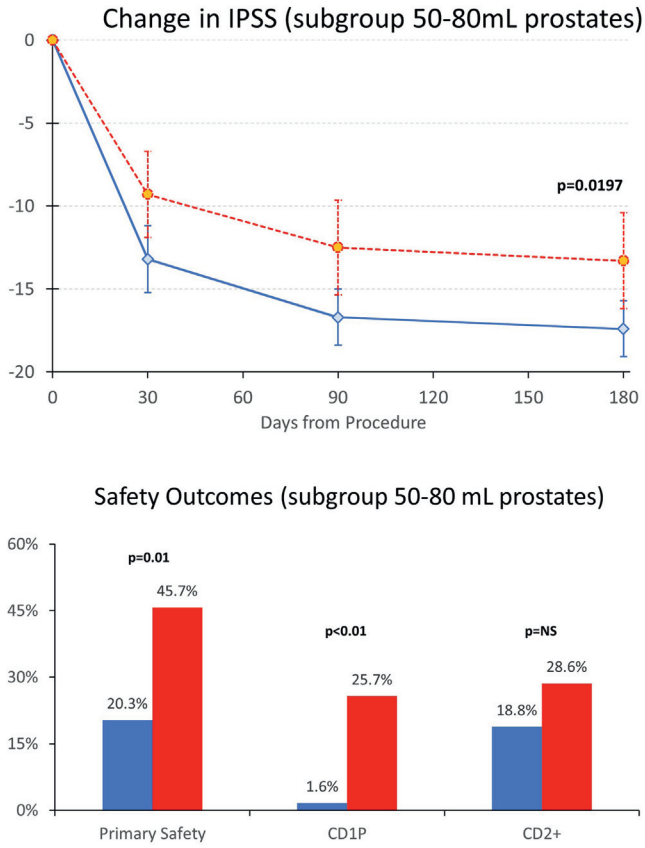

Figure 4. Posttreatment findings in patients with baseline prostate size between 50 and 80 ml. I-PSS change after Aquablation (blue curve) and TURP (red curve). Safety outcomes in patients with incontinence, erectile dysfunction and ejaculatory dysfunction (*CD1P*) and all Clavien-Dindo grade 2-5 events (*CD2+*). Blue bars represent Aquablation. Red bars represent TURP.

intervention rate, the proportion of sexually active subjects who reported worsening sexual function through 6 months on IIEF-5 (6-point decrease[19]) or MSHQ-EjD (2-point decrease[20]) and the proportion of subjects with a serious device or procedure related adverse event. The reoperation or repeat intervention rate was defined as any invasive procedure, eg cystoscopy, of the lower urinary tract to treat problems potentially related to BPH. The definition excluded required study evaluations and bladder catheterization only without a surgical intervention.

Since IIEF and MSHQ assume that a man is sexually active, those who were not sexually active at baseline or the study visit were excluded from this analysis. Additional end points included a change in incontinence measured by the Incontinence Severity Index,[21] pelvic pain, quality of life using EQ-5D (EuroQOL-5D),[22] bladder catheterization duration, Work Productivity and Activity Impairment,[23] and the relationship between the prostate size reduction measured on transrectal ultrasound and the change in symptoms scores. The latter will be reported elsewhere.

RESULTS

A total of 275 subjects were evaluated at 17 sites in the United States, United Kingdom, Australia and New Zealand between October 2015 and December 2016. Excluding 72 screen failures and 19 roll in subjects, 184 men were randomized. Baseline characteristics were well balanced across the groups and consistent with moderate to severe BPH (table 1). Mean prostate size was 53 ml and 81% of the men were sexually active. Two men assigned to TURP and 1 assigned to Aquablation voluntarily withdrew prior to treatment, leaving 181 in the intent to treat population (fig. 1).

The index study procedure was performed using general anesthesia in 94% of cases and spinal anesthesia in 6%. For TURP monopolar and bipolar loops were used in 36 (55.4%) and in 29 cases (44.6%), respectively. Mean operative time, defined as pretreatment visualization to indwelling catheter insertion after resection was complete, was similar in the Aquablation and TURP groups (33 and 36 minutes, respectively, $p = 0.2752$, table 1). Mean resection time from first pedal activation to the end of pedal use was lower in the Aquablation group (4 vs 27 minutes, $p < 0.0001$). Resection time

strongly depended on prostate size in TURP with 0.3 minutes per additional gm of prostate size but only modestly in Aquablation with 0.04 minutes per additional gm.

Postoperative hemoglobin decreased from 14.9 to 13.0 in the Aquablation group and from 14.7 to 13.7 in the TURP group ($p = 0.0002$). One Aquablation case but no TURP case required blood transfusion. Less irrigation fluid was used intraoperatively during Aquablation compared to TURP (5.2 vs 13.2 L, $p < 0.0001$). Mean hospital stay was 1.4 days in each group with no geographic variation and the urinary catheter was removed a median of 1 day after surgery in each group.

Compliance with study visits was high. Of the patients 178 (98%) completed the 3-month followup and 175 (97%) completed the 6-month followup. Blinding questionnaires at each study visit confirmed no evidence of unblinding.

At 6 months mean I-PSS had decreased from baseline by 16.9 points for Aquablation and 15.1 points for TURP (fig. 2). The mean difference in the change score at 6 months was 1.8 points greater for Aquablation (noninferiority $p < 0.0001$ and superiority $p = 0.1347$). At 6 months 100% of Aquablation vs 98% of TURP cases showed I-PSS improvement. Using a threshold of at least 50% for the I-PSS change score 90% of Aquablation and 79% of TURP cases met this threshold. Men with a prostate greater than 50 ml had superior improvement in I-PSS after Aquablation than after TURP ($p = 0.0197$). The I-PSS quality of life score improved similarly in the Aquablation and TURP groups at 6 months with a decrease of 3.5 vs 3.3 points ($p = 0.4582$). At month 3 the decrease was statistically larger in the Aquablation group.

The 3-month primary safety end point rate was lower in the Aquablation group than in the TURP group (26% vs 42%, $p = 0.0149$, fig. 3). The rate of persistent grade 1 events at month 3 was also lower after Aquablation (7% vs 25%, $p = 0.0004$) and the rate of grade 2 and greater events was similar in the 2 groups at 20% for Aquablation and 23% for TURP ($p = 0.3038$, table 2). Safety results remained consistent at 6 months. Among sexually active men without the condition at baseline anejaculation was less common after Aquablation than after TURP (10% vs 36%, $p = 0.0003$). The anejaculation rate after Aquablation was somewhat lower when posttreatment cautery was avoided (7% vs 16%, $p = 0.2616$).

In men with a prostate greater than 50 ml the primary safety end point was lower after Aquablation than after TURP (20% vs 46%, $p = 0.0111$, fig. 4). The rate of persistent grade 1 events was substantially lower (2% vs 26%, $p = 0.0003$) and the rate of Clavien-Dindo grade 2 and greater events trended in favor of Aquablation (19% vs 29%, $p = 0.3146$). Among sexually active men without the condition at baseline anejaculation was less common after Aquablation than after TURP (2% vs 41%, $p = 0.0001$).

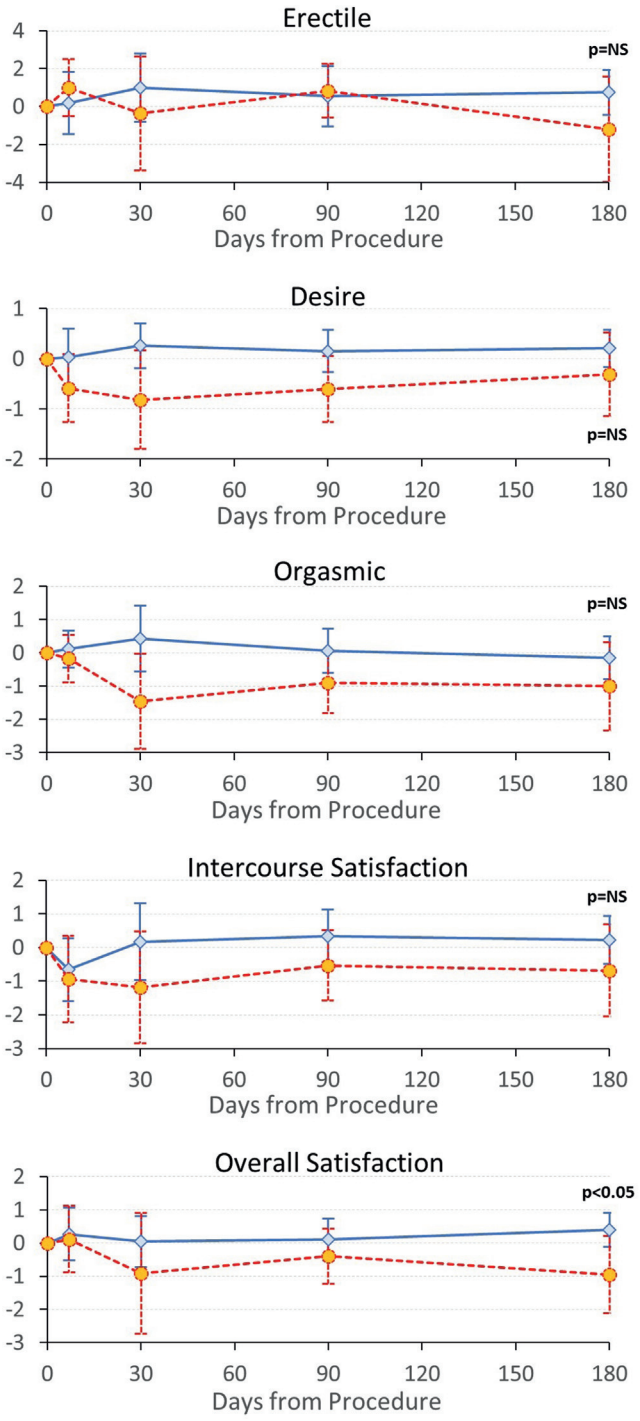

Figure 5. IIEF-15 subdomain score change by treatment and time. IIEF-15 comprises 15 questions with response ranging from 0 to 5. Erectile, intercourse satisfaction and all other domains are derived from 6 questions, 3 questions and 2 questions each, respectively. Overall satisfaction was superior in Aquablation group. *NS*, not significant. Blue curves indicate Aquablation. Red curves indicate TURP.

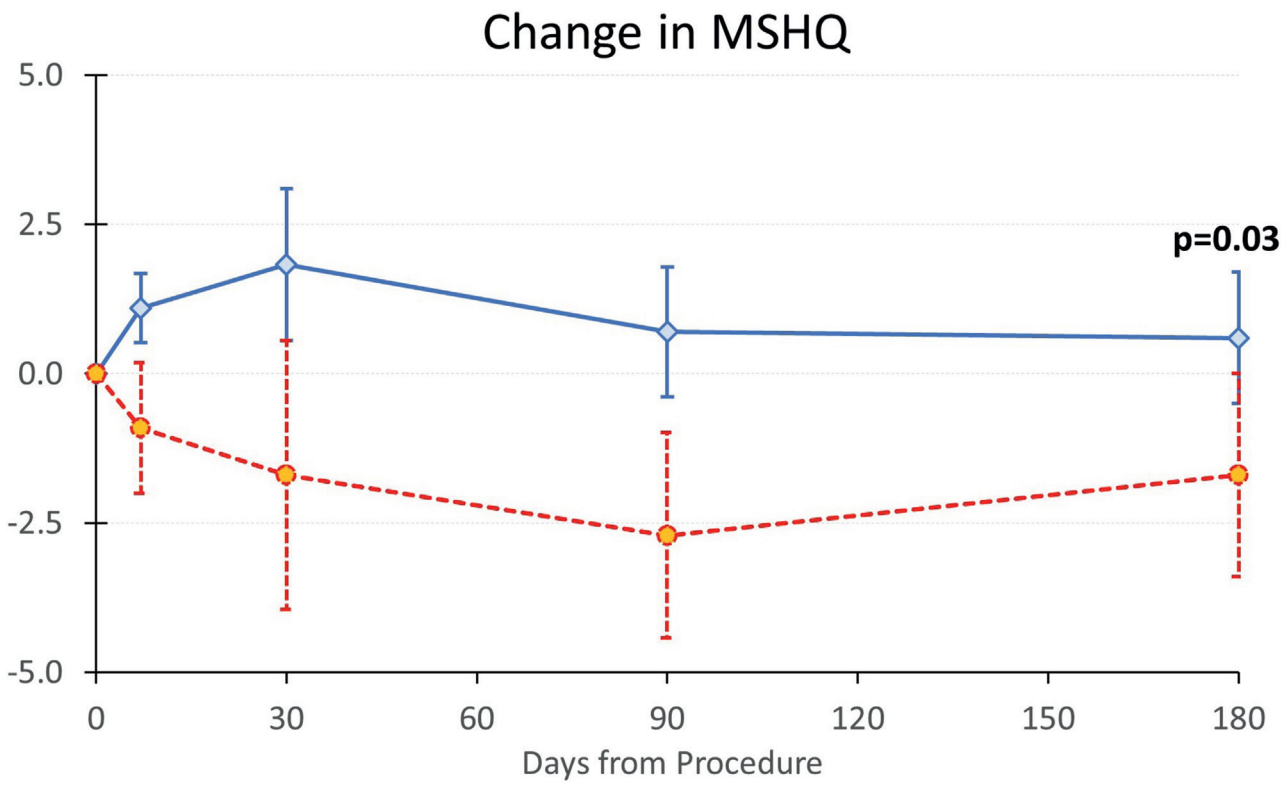

Figure 6. MSHQ-EjD score change by treatment and time in men who were sexually active at baseline and visit. Score was calculated using first 3 questions and ranged from 1—anejaculation to 15—normal ejaculation ability, strength and volume. Blue curve indicates Aquablation. Red curve indicates TURP.

Additional Secondary End Points

Reoperation for BPH was performed in 1 TURP case but not in any Aquablation case. There were threshold decreases in MSHQ-EjD or IIEF-5 scores in 33% of Aquablation and 56% of TURP cases ($p = 0.0268$). In sexually active men mean erectile function scores on IIEF-15 were stable after Aquablation but decreased slightly after TURP except for overall sexual satisfaction, for which Aquablation was significantly better ($p = 0.0492$, fig. 5). Ejaculatory function scores on MSHQ-EjD were stable after Aquablation but significantly worse after TURP ($p = 0.0254$, fig. 6).

Flow Rate and Other End Points

In each group the mean maximum urinary flow rate increased markedly from baseline to 6 months and mean post-void residual volume also decreased markedly (fig. 2). The amount of tissue removed after TURP was 13 gm. Transrectal ultrasound performed preoperatively and at month 3 showed a smaller prostate size reduction for Aquablation (17.3 vs 24.0 cc, mean 31% vs 44% reduction, $p = 0.0072$). At 6 months PSA was decreased in the Aquablation group vs the TURP group (−1.2 vs −1.1 ng/ml, 30% vs 36% median reduction, $p = 0.7205$).

At 6 months mean incontinence symptom scores improved by 1.2 points in the Aquablation group and 0.6 in the TURP group. The mean score improvement at the 1, 3 and 6-month visits was 0.6 points greater in the Aquablation group ($p = 0.0786$). At 3 months dysuria frequency was similar but severity trended favorably toward Aquablation ($p = 0.1277$). Pelvic pain levels were low and similar throughout followup, and time off from work was brief in most cases.

Of the 85 subjects (47%) who were receiving α-blockers at baseline 71% and 90% who underwent Aquablation and TURP, respectively, had stopped taking these drugs (for difference $p = 0.06$). Of the 41 subjects (23%) who were receiving 5α-reductase inhibitors at baseline 67% and 82%, respectively, had stopped these medications by month 6 ($p = 0.3092$). No subject who was not on α-blockers or 5α-reductase inhibitors had started them by month 6.

DISCUSSION

In this trial of prostate resection the robotic, ultrasound guided, surgeon controlled water jet improved BPH related urinary symptoms non-inferiorly compared to the reference standard

surgical treatment, TURP. These improvements were seen across study sites where there had been no previous experience with Aquablation at 14 of the 17 sites.

Retrograde ejaculation after TURP is a common and accepted side effect caused by heat related damage to the ejaculatory duct.[9] We observed a reduced rate of anejaculation after Aquablation compared to after TURP. The rate was even lower when post-Aquablation nonresective cautery was avoided. The decreased rate after Aquablation might be explained by tissue resection contours that were programmed to avoid damage near the verumontanum.

Improvements in objective urinary flow measures such as the maximum flow rate and post-void residual urine were in line with expectations for prostate resecting procedures. Moreover, other assessments of the acute impact of surgery, including hospital stay, work index and quality of life measurements, showed that Aquablation was well tolerated.

Other ablation technologies are available for the surgical treatment of moderate to severe BPH. Technologies providing high level improvement include resection techniques such as laser enucleation,[24] TURP, laser photovaporization[9] and Aquablation. Although it was not a direct comparison, improvements after Aquablation in our study appeared to be higher than after nonresective techniques, including convective water vapor energy (rezūm®, 11 points higher)[25], UroLift® procedure (11 points)[26] and microwave thermotherapy (11 points[27,28]) as well as after single drug or multidrug medical therapy (4 to 10 points higher).[29] This is probably because nonablative and nonresective treatments do not as effectively de-obstruct the bladder outlet.

Advantages of our study include its concurrent, randomized, multicenter and blinded design with confirmed preservation of blinding, of which all likely minimized bias related to patient reported outcomes. There was no evidence of variation in the degree of effect across study sites or geographies. Additionally, efficacy in the TURP control group as reflected by symptom score and uroflow improvements were large and consistent with expectations, adding overall validity to the trial outcomes. TURP resection time, PSA reduction and resected weight were lower than in previous reports but this did not appear to negatively impact TURP efficacy. Longer followup of the TURP arm would determine whether removing the right tissue vs maximizing the amount of tissue removed affects outcome durability.

CONCLUSIONS

This study provides what is to our knowledge the first randomized comparison of Aquablation of the prostate and TURP in men with LUTS due to BPH. Each group achieved significant symptom relief compared to baseline with similar rates of Clavien-Dindo 2 or greater complications. The risk of anejaculation was lower with Aquablation. Larger prostates (50 to 80 ml) demonstrated a more pronounced safety and efficacy benefit. These results suggest that Aquablation of the prostate may be an effective and safe approach to the surgical management of LUTS secondary to BPH with a substantially lower rate of ejaculatory dysfunction compared to TURP. Longer followup would help assess the clinical value of Aquablation.

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