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ORIGINAL ARTICLE

Comparison of < 100 cc prostates and > 100 cc prostates undergoing aquablation for benign prostatic hyperplasia

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Abstract

Introduction Surgical options for benign prostatic hyperplasia (BPH) become limited when treating large prostates due to steep learning curves and less effective treatment. Aquablation (AquaBeam System, PROCEPT BioRobotics, Inc., USA) could remedy this. We compare the effectiveness of Aquablation in large prostates between 80 cc and 100 cc and very large prostates > 100 cc.

Methods WATER II (NCT03123250) is a prospective, multicenter, international clinical trial of Aquablation for the surgical treatment of LUTS/BPH in men of age 45–80 years with prostates between 80 cc and 150 cc. Aquablation was performed using the AquaBeam System. The reported analysis compares the subgroup of patients with a baseline prostate size of < 100 cc versus those with a prostate size of > 100 cc. Students' *t* test was used for continuous variables and Fisher's test for ordinal/binary variables.

Results Of 114 screened patients, 101 meeting eligibility criteria were enrolled at 13 US and 3 Canadian sites between September and December 2017. Mean operative time was 31.2 ± 8 min in the < 100 cc subgroup and 41.7 ± 14.9 min in the > 100 cc subgroup. The average length of stay following the procedure for the < 100 cc subgroup was 1.5 ± 0.7 days versus 1.7 ± 1.1 days for the > 100 cc subgroup. Mean changes in International Prostate Symptom Score (IPSS), IPSS quality of life, and IPSS voiding and storage subscores were substantial, occurring soon after treatment and averaging (at 3 months) 16.5, 2.8, 10.6, and 5.8 points, respectively (all $p < 0.0001$).

Conclusion Aquablation clinically normalizes outcomes between patients of the < 100 cc and > 100 cc prostate cohorts. It is safe and effective in patients with large prostate glands (> 100 cc) with a smoother learning curve.

Keywords Aquablation · Benign prostatic hyperplasia · Large prostate

Introduction

Benign prostatic hyperplasia (BPH) is the most common benign urologic condition in men, and its incidence is age-related. Moderate to severe lower urinary tract symptoms (LUTS) due to BPH affect 30% of men over 50 and rise above 90% in men over 80 [1]. Although not life-threatening, LUTS associated with BPH impacts quality of life [2] and may lead to serious complications such as infection, calculus formation, bleeding, urinary retention, and deterioration of renal function if left untreated [3]. In most cases, initial management is usually non-surgical treatments and includes watchful waiting, medical therapy (alpha1-selective adrenergic receptor antagonists alone, combination with 5-alpha-reductase inhibitors for larger prostates, or phosphodiesterase type 5 inhibitor), and phytotherapy.

Surgical approaches should be considered for patients with persistent symptoms despite non-surgical treatments as well as in situations of urinary retention, gross hematuria, bladder stone formation, recurrent urinary tract infections, or upper urinary tract deterioration [4]. The historic gold standard for the treatment of BPH is transurethral resection of the prostate (TURP) for smaller glands and open prostatectomy

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for larger glands. More modern surgical approaches include ablative treatments such as transurethral laser photo-vaporization (PVP) as well as non-tissue ablative techniques such as Rezum and UroLift [1].

While this surgical arsenal can be used for the treatment of small to moderate-sized BPH, some of these options become somewhat limited when treating large (> 80 cc) and very large (> 100 cc) prostates. Many are not recommended per CUA/EAU/AUA guidelines [5–7]. For patients with large prostate volumes, effective surgical approaches include open and laser enucleation techniques such as holmium laser enucleation of the prostate (HoLEP), thulium laser enucleation of the prostate (ThuLEP), and thulium vapoenucleation of the prostate (ThuVEP). These approaches are likely to have superior safety profiles compared to open simple prostatectomy (OSP) with regard to complication rates [8]. However, there is a considerable learning curve associated with these modalities which precludes their widespread adoption [9]. Alternatively, PVP has been used to treat patients with large glands, but again requires a steep learning curve [10, 11]. There is also evidence demonstrating a higher retreatment rate for very large prostates using this technique [12]. For patients with prostates too large to be removed endoscopically, OSP remains an appropriate and effective treatment. A caveat of this procedure is that it requires abdominal-wall access and has been shown to be associated with longer hospitalization and catheterization times with higher risks of bleeding [8, 13]. There is thus a need for novel surgical approaches with smooth learning curves and effective treatment of large prostates in the context of BPH.

Aquablation (AquaBeam System, PROCEPT BioRobotics, Inc., USA) could be this novel tool and was added to the BPH surgical armamentarium following FDA approval in December 2017. Aquablation is a robotically executed, surgeon-guided, high-pressure water jet technology integrating real-time ultrasonography. High-pressure water jet technology, which is already in use in the metal, ceramic, and glass industries, has been described for tissue-specific liver resection [1, 4] and bladder tumors [15]. In prostatic disease, early studies have shown non-inferior symptom relief benefit of Aquablation as compared to TURP, but with considerably lower resection times and low risks of sexual side effects [16–18]. In a subgroup of larger prostates (50–80 cc) superior symptom-reduction efficacy by International Prostate Symptom Score (IPSS) was reported for Aquablation compared to TURP, the gold standard for minimally invasive treatment of LUTS for prostates < 80 cc [18]. With that in mind, Desai et al. focused on large prostates (80–150 cc) in a second trial and concluded that Aquablation appears to provide a reasonable surgical alternative in patients with larger prostate volumes and leads to relatively low operating time, hospital stays, and acceptable complication and transfusion rates [19].

We seek to confirm this and determine if the effectiveness of Aquablation remains for prostates over 100 cc comparing with smaller prostates between 80 cc and 100 cc. This will allow us to determine if previously studied advantages of Aquablation translate to all subgroups of large prostates.

Methods

Trial design and participants

WATER II (NCT03123250) is a prospective, multicenter, international clinical trial of Aquablation for the surgical treatment of LUTS/BPH in men 45–80 years of age with a prostate volume between 80 cc and 150 cc as measured by transrectal ultrasound. Participants were enrolled at 13 US and 3 Canadian sites between September and December 2017. The WATER II trial enrollment was initiated while under review with FDA. Participants were required to have a baseline IPSS ≥ 12, and 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 trial. Men were excluded if they had a body mass index ≥ 42, 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 consecutive days, chronic pelvic pain, urethral stricture, meatal stenosis or bladder neck contracture, use of anticholinergic agents specifically for bladder problems, and other general conditions that could prevent adequate trial follow-up. Patients were not excluded for prior prostate surgery or if in retention unless the catheter was in place for more than 90 days. The trial was performed with Institutional Review Board or Ethics Committee approval from each participating institution and all participants signed a study-specific informed consent form.

Intervention

Aquablation was performed using the AquaBeam System (PROCEPT BioRobotics, Redwood City, California, USA), as described previously [18]. Following the Aquablation treatment, the bladder was thoroughly irrigated to remove residual prostate tissue and blood clots that tend to accumulate during resection. Hemostasis was achieved using

tissue tamponade with a low-pressure Foley balloon catheter, which was inflated with 40–80 cc of saline either at the bladder neck or within the prostatic fossa with adequate traction using transrectal ultrasound (TRUS) guidance.

Study parameters

At baseline, subjects completed IPSS [20] as well as several validated questionnaires (Incontinence Severity Index, International Index of Erectile Function (IIEF-5) [21], the Male Sexual Health Questionnaire (MSHQ-EjD) [22], uroflowmetry and post-void residual (PVR) volume measurements, and underwent standard laboratory blood assessment. Questionnaires, uroflowmetry, PVR, and laboratory tests were also required at postoperative visits at 1 and 3 months. Adverse events rated by the clinical events committee as possibly, probably or definitely related to the study procedure were classified as Clavien-Dindo (CD) [23] grades through 3 months post-treatment. CD is a standardized classification system for grading adverse events occurring as a result of a surgical procedure.

Data study and monitoring

Study data were entered into an electronic data capture system by site coordinators, were monitored, and source-verified by monitors hired by the study sponsor (PROCEPT BioRobotics). Adverse events were collected throughout follow-up and evaluated by an independent clinical events committee. A data monitoring committee reviewed safety data periodically.

Statistical analysis

Students' *t* test was used for continuous variables and Fisher's test for ordinal/binary variables. All statistical analyses were performed using R programming language. p value ≤ 0.05 was considered statistically significant. The reported analysis will compare the subgroup of patients with a baseline prostate size of < 100 cc versus those with a prostate size of > 100 cc.

Results

Baseline characteristics and procedure outcomes

Of 114 screened patients, 101 subjects meeting eligibility criteria were enrolled at 13 US and 3 Canadian sites between September and December 2017. Of those, 97 (96%) subjects completed the 3-month follow-up visit. There were 42 subjects with a baseline prostate size < 100 cc (mean 88 ± 6 cc) and 59 subjects with a baseline prostate size > 100 cc (mean 121 ± 15 cc). Demographics and baseline IPSS were similar across groups (Table 1). Study procedures were performed under spinal anesthesia in 85% of cases.

Mean operative time, defined as hand-piece placement until final urinary catheter placement, differed by 10 min between groups ($p < 0.0001$). As expected, all procedural parameters (resection time, instrument in/out time, number of passes, TRUS time, and resection time) were statistically greater in the > 100 cc group. Specifically, resection time averaged 9.1 min in the > 100 cc group and 6.4 min in the < 100 cc group ($p < 0.0001$). None of the patients in either subgroup underwent post-Aquablation non-resective cautery for hemostasis. The average length of stay following the procedure for the < 100 cc subgroup was 1.5 ± 0.7 days versus 1.7 ± 1.1 days for the > 100 cc subgroup ($p = 0.1816$). One patient was excluded from days to discharge analysis with an extended hospital stay for non-prostate related reasons caused by an undiagnosed large patent foramen ovale. The decrease in hemoglobin levels was slightly higher in the > 100 cc subgroup (mean drop -3.3 vs -2.5; $p = 0.02$).

Table 1 Baseline characteristics by prostate size

	<100 cc, $n = 42$	>100 cc, $n = 59$	p value
Characteristic			
Age, years, mean (SD)	68 (7.1)	67 (6.2)	0.5592
Body mass index, mean (SD)	28.0 (3.7)	28.5 (4.5)	0.5186
Prostate specific antigen, g/dL; mean (SD)	6.3 (5.5)	7.7 (6.2)	0.2555
Prostate size (TRUS), cc; mean (SD)	88.3 (6.2)	120.9 (15.1)	< 0.0001
Baseline questionnaires			
IPSS score, mean (SD)	22.7 (6.4)	23.6 (6.3)	0.4867
IPSS QOL, mean (SD)	4.1 (1.0)	4.6 (1.1)	0.9280
Sexually active, *N* (%) [MSHQ-EjD]	31/42 (73.8%)	46/59 (78%)	0.4782
MSHQ-EjD mean (SD)[a]	7.8 (4)	9.5 (3)	0.0834
IIEF-5, mean (SD)[a]	13.4 (7.9)	15.8 (7.5)	0.1951

[a]Sexually active men only

Volume reduction

Mean prostate volume for the < 100 cc group was 88 ± 6 cc and 121 ± 15 cc for the > 100 cc group. The percentage of volume reduction by group was 42% (< 100 cc) and 41% (> 100 cc), $p = 0.9426$ for difference. An additional analysis of looking at only those prostates with median lobes within each subgroup showed no difference in volume reduction, 48% (< 100 cc) and 46% (> 100 cc).

Clinical outcomes

Mean changes in IPSS, IPSS quality of life, and IPSS voiding and storage subscores were substantial, occurring soon after treatment and averaging (at 3 months) 16.5, 2.8, 10.6, and 5.8 points, respectively (all $p < 0.0001$). Changes in each of these scores across groups were not statistically different (p = 0.2198, 0.2879, 0.1255, 0.7854, respectively, Fig. 1). The increase in Qmax between groups was similar. The PVR at 3 months was lower in the < 100 cc group; however, this is confounded with a lower baseline PVR in the < 100 cc group (Fig. 2). There were six transfusions prior to discharge in the study population. Two transfusions occurred in the < 100 cc group, and four transfusions occurred in the > 100 cc group ($p = 1$). Ejaculatory dysfunction, as adjudicated by the CEC, was similar in both groups; 17% of the < 100 cc patients compared to 14% of the > 100 cc patients ($p = 1.0$). Clavien–Dindo grade 2 and higher adverse events were similar in both groups as well, 35.7% of the < 100 cc patients compared to 32.2% of the > 100 cc patients ($p = 1.0$) (Table 2).

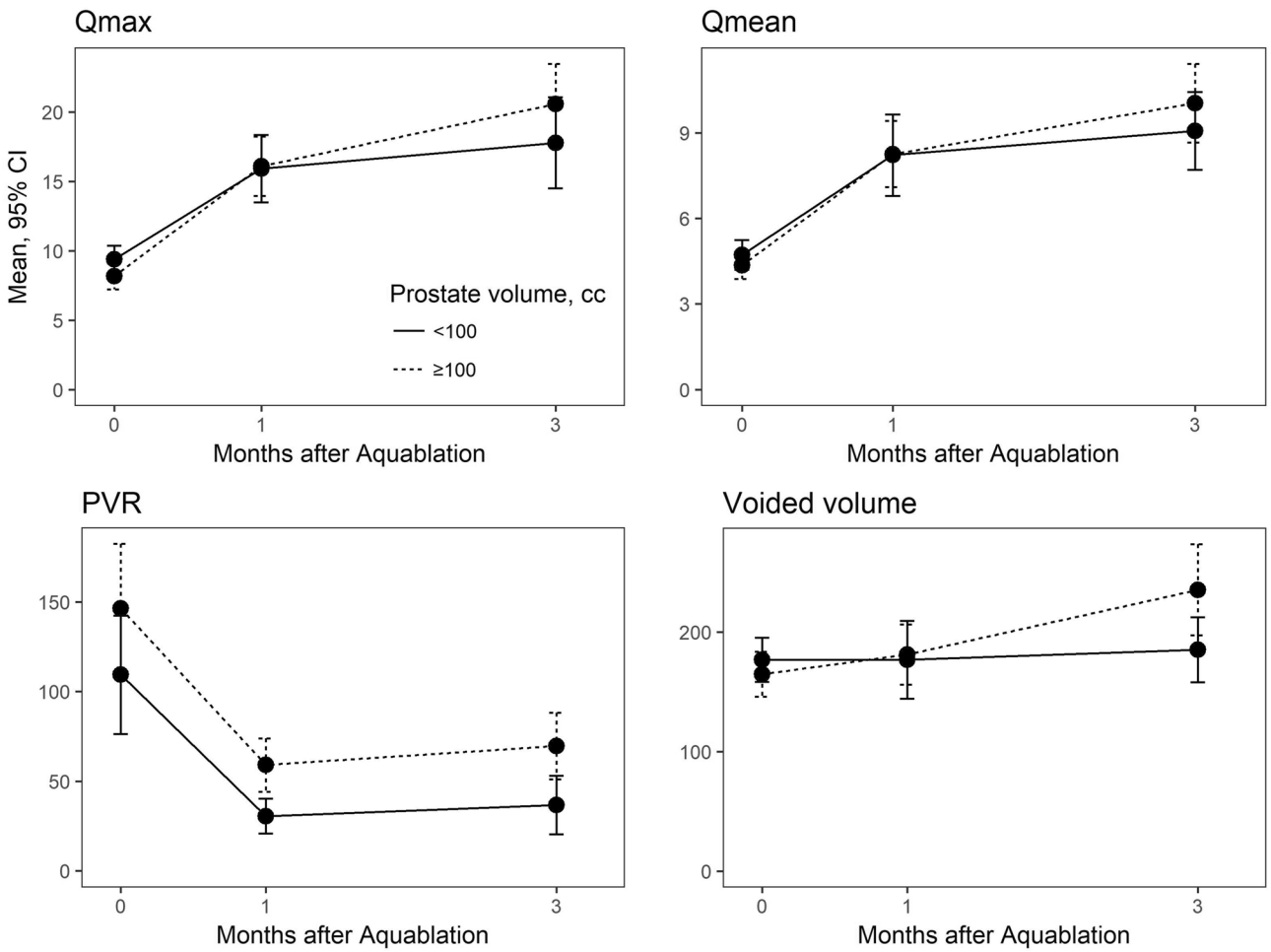

Fig. 1 Maximum urinary flow rate, post-void residual volume, and voided volume

Table 2 Times by prostate volume

	<100 cc, $n=42$			>100 cc, $n=59$			
	Mean	Standard deviation	Range	Mean	Standard deviation	Range	*P* value
Resection time (minutes)	6.4	2.8	[2.5-12]	9.1	2.9	[4–17]	< 0.0001
Operative time (minutes)	31.2	8	[15-52]	41.7	14.9	[15–97]	< 0.0001
In and out (minutes)	25.5	7.1	[11-44]	34.8	14.5	[12–94]	< 0.0001
Number of passes	1.5	0.6	[1–3]	1.9	0.6	[1–3]	0.0007
Transrectal ultrasound (minutes)	45.6	15.4	[24-83]	60.9	19	[25–111]	< 0.0001
Time from discharge to catheter removal (days)	2.2	1.8	[− 1 to 66]	2.1	2.6	[− 1 to 13]	0.7823

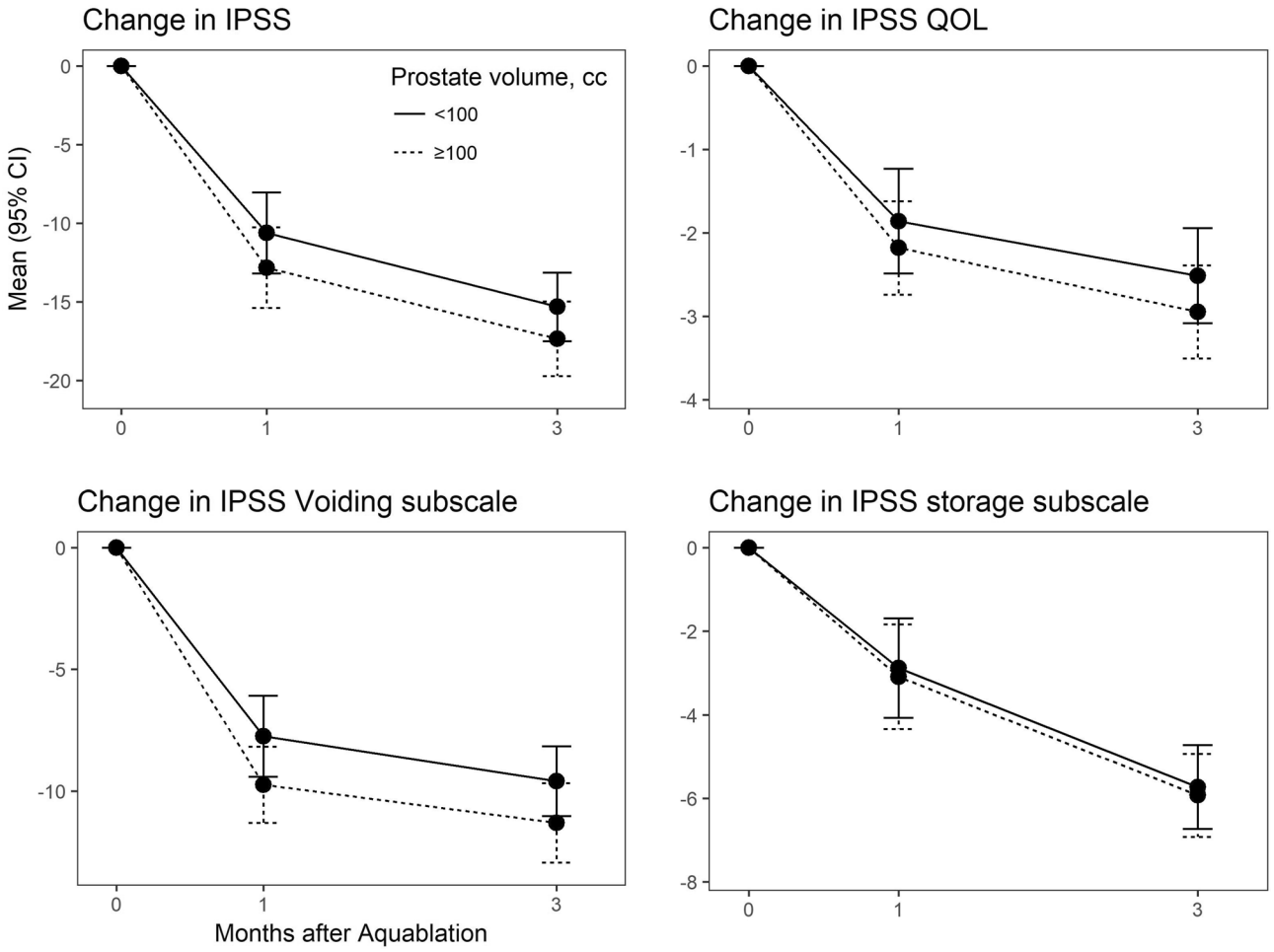

Fig. 2 Change in international prostate symptom score, quality of life, voiding subscale, and storage subscale. No statistical difference between arms at any timepoint for any variable

Discussion

Benefits previously observed with Aquablation compared to other surgical modalities for small to moderate-sized prostate glands can be transferred to large-sized glands. As this is the case, the benefit of using Aquablation to surgically manage large prostates is much more significant when compared to other surgical options. This represents a potentially

important paradigm-shift in the surgical treatment of large prostates.

Our findings demonstrate certain statistically significant procedural differences between < 100 cc and > 100 cc prostates when treating LUTS due to BPH with Aquablation; however, safety and efficacy outcomes remained similar regardless of prostate size. Albeit statistically significant, the overall differences between both groups in all categories are minimal compared to other surgical modalities and represent clinically negligible changes.

First, although procedural outcomes presented statistically significant differences, these represented relatively insignificant clinical differences. Operative time was slightly over 10 min longer for the large prostate group and resection time was just under 3 min longer. Comparing to the WATER trial looking at a cohort of patients with a smaller mean prostate size (30–80 cc) undergoing Aquablation, the mean operative time of our < 100 cc subgroup was actually a minute faster and our > 100 cc subgroup was only under 10 min longer [24]. In this cohort, the mean operative time for prostate glands larger than 100 cc was under 42 min; Aquablation times are significantly lower than other surgical modalities when dealing with such large glands. The average operative time for large prostates done via OSP is 95 min [25], with HoLEP 91 min [26] and with PVP 93 min [10]. It is important to consider that these times are taken in the context of established and developed techniques in the hands of surgeons more experienced in these surgeries. Despite only recently being approved and thus only providing surgeons with a short learning time, Aquablation takes half the operative time needed for other surgical modalities. This suggests that procedural outcomes will only improve as surgeons gain experience and the technique is improved. It is also indicative of the potential minimal learning curve required to reach advantageous procedural outcomes when using Aquablation. The rapidity of the procedure can be explained by the ultrasound guidance, which urologists are very familiar with, and the automated robotic execution of the resection. Planning takes the same time regardless of the size of the prostate.

Second, clinical outcomes in both groups were similar, as shown by Qmax (< 100 cc 9.4–17.8 compared to > 100 cc 8.2–20.6) and IPSS Scores (< 100 cc 22.7–7.4 compared to > 100 cc 23.6 to 6.3). The scores were comparable to those found with HoLEP (IPSS drop from 20 to 5.3 and Qmax increases from 8.4 to 22.7 ml/s [27]) and PVP (IPSS drop from 23 to 6 and Qmax increases from 6 to 16 ml/s [10]). There was a trend towards better outcome improvements for the larger prostates. The lower PVR at 3 months for the less than 100 cc subgroup was likely due to the > 100 cc group starting with a PVR 34% higher. Aquablation thus presents non-inferior clinical improvements compared to other modalities. Differences in transfusion rates were statistically not significant between both groups and no electrocautery hemostasis was performed for any patient in these cohorts. Blood loss was higher in the > 100 cc group and met the statistical threshold of significance, but this was anticipated as prostate size is a predictor of more hemoglobin drop as reported in an unpublished pooled analysis of the trial data by Mihir Desai et al. at AUA 2018. However, this was not clinically relevant. The CD classification of complications was also similar for both arms of our analysis of the trial data, further highlighting the similar complication profile and clinical outcomes of both arms. These results highlight a significant advantage of using Aquablation when dealing with very large prostates, as overall clinical outcomes are less impacted by size than other surgical options.

Third, the ejaculatory function rates were similar in both groups with over 80% of patients maintaining antegrade ejaculation. This is lower than the 90% antegrade ejaculation preservation reported by the WATER trial focusing on small to moderate-sized prostate treated with Aquablation [18]—with a greater number of passes and greater defects in bigger prostates, this was to be expected. However, unless ejaculatory duct sparing is performed, the rate of retrograde ejaculation with Aquablation (between 14 and 17%) is markedly lower to open prostatectomy (almost all patients [28]), HoLEP (76.3% [29]) and PVP (41.9% [29]). As maintenance of sexual quality of life, specifically antegrade ejaculation, is a major concern in many patients, the higher probability of preserving antegrade ejaculation represents a significant improvement compared to established surgical techniques.

Fourth, while there was a significant reduction in volumes for both groups, no statistically significant differences were observed in both arms of our analysis of the trial data. The higher absolute reduction in the > 100 cc group is due to the higher number of passes on average for this subgroup. The presence of a prostatic median lobe did not impact volume reduction although it traditionally increases the difficulty level in other types of procedures. No statistically significant differences were observed in both arms of our analysis of the trial data when a median lobe was present.

Last, length of stay following the Aquablation procedure was 1.5 ± 0.7 days in < 100 cc subgroup and 1.7 ± 1.1 days in > 100 cc subgroup which is comparable to HoLEP (1–1.3 days [30]) and PVP (1–2 days [11]) and much shorter than open simple prostatectomy (3–7 days [8]). It took a bit over 2 days for catheter removal in both groups, which is standard when comparing to alternative surgical modalities. Time to removal of the catheter will only improve with time as more experience is accumulated. As noted with the procedural time, further experience with the Aquablation system and postoperative optimization should lead to shorter postoperative hospitalization times. In our analysis of the

trial data, two patients were sent home the same day of surgery and it is plausible that in the near future this procedure could become a same day procedure.

Limitations

One of the limitations is that the trial was designed as a non-randomized single arm study. The impact of our analysis of the trial data would have been greater if the study compared Aquablation to HoLEP, PVP or open prostatectomy. Standardized reporting of events categorized by CD scores was limited in the literature. In addition, surgeon experience with Aquablation is still relatively limited and additional experience will probably improve outcomes. With that said, the major limitation of this report is the length of follow-up of 3 months. Longer term follow-up data from this cohort will be necessary to demonstrate the durability of the treatment outcomes in the < 100 cc subgroup and > 100 cc subgroup.

Conclusion

Aquablation clinically normalized outcomes between patients of the < 100 cc prostate cohort and the patients of the > 100 cc prostate subgroup treated for LUTS due to BPH. It is safe and effective in patients with large prostate glands (> 100 cc) with a short and potentially smoother learning curve [16]. This represents an important finding as other surgical modalities are associated with worse outcomes in larger prostate glands or a much steeper learning curve.

Aquablation is now an option for this patient subpopulation presenting with large prostates with both FDA and Health Canada approval. The updated Canadian Urological Association BPH guidelines have also included Aquablation as an option for surgical management of LUTS due to bladder outlet obstruction [6].

For patients with large prostates needing surgery, Aquablation could represent a more readily accessible and less daunting treatment option. As the technique does not require expert hands, its availability should be superior to other alternative surgical modalities without any clinical trade-off. It can also be hypothesized that Aquablation is much more cost-effective than alternative surgical options with its shorter procedure times and similar length of stay; such economic benefits of the modality should be assessed in the near future.

Author contributions NB: Protocol/project development, data interpretation, manuscript writing/editing. DDN: data interpretation, manuscript writing/editing. kaufman: review. DE: protocol/project development, review. KCZ: protocol/project development, review.

Compliance with ethical standards

Conflict of interest Study data were entered into an electronic data capture system by site coordinators, were monitored, and source-verified by monitors hired by the study sponsor (PROCEPT BioRobotics).

Human or animal studies This research involves humans.

Informed consent Informed consent was obtained from all patients.

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