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BPH-RELATED VOIDING DYSFUNCTION (R LEE, SECTION EDITOR)

The WATER Study: a Review

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Abstract

Purpose of Review The purpose of this review is to detail and discuss the results of the WATER study. This study compared the efficacy and safety of Aquablation to transurethral resection of the prostate (TURP) for the treatment of male lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).

Recent Findings The WATER study compared Aquablation using the AquaBeam system to the current gold standard, TURP. It demonstrated that Aquablation was non-inferior to TURP when comparing the primary efficacy study endpoint of reduction in International Prostate Symptom Score at 6-month follow-up. Additionally, it proved superior for the primary safety endpoints at 3 and 6 months.

Summary Aquablation has been shown to provide non-inferior symptom relief when compared with TURP. Additionally, it demonstrated a significantly superior safety profile and lower risk of sexual dysfunction. Ongoing trials including the Open WATER study and WATER 2 study are completing follow-up in 2019 with the promise of determining the safety and efficacy of Aquablation in larger prostates (80–150 g).

Keywords Aquablation · Benign prostatic hyperplasia · Minimally invasive surgical procedures · Transurethral resection of the prostate · Lower urinary tract symptoms · Water

Introduction

Lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) continue to significantly impact ageing men [1]. In developing countries, population ageing will cause the rates of each to dramatically increase [2]. The prevalence of LUTS due to BPH is reported to be 56% of men between 50 and 79 years of age, and this increases to 90% of men by 90 years of age [2, 3]. LUTS have been shown to negatively impact the quality of life and convey an increased risk of urinary tract infections, urinary retention, renal failure and non-urologic conditions such as falls [2, 4].

Patients with mild-moderate symptoms may see satisfactory improvement with medical therapies including alpha-adrenergic receptor blockers and 5-alpha reductase inhibitors [1]. However, a proportion of these patients, and those with severe symptoms, will require surgical treatment. Current surgical options include tissue ablative (TURP, laser enucleation) and non-ablative (UroLIFT, prostatic stenting) techniques. TURP has well-known risks of bleeding, bladder neck contracture, incontinence, erectile dysfunction and retrograde ejaculation, but remains the current treatment gold standard [5, 6]. The electrocautery nature of TURP also makes retrograde ejaculation particularly common, occurring in more than 60% [7].

In an effort to reduce the risks associated with TURP, new minimally invasive techniques have been developed. The aim of these novel techniques is to reduce LUTS caused by BPH while minimising the associated risks. This article reviews the results of the WATER study and current literature for Aquablation to date.

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Aquablation

The AquaBeam system (PROCEPT BioRobotics Inc., Redwood Shores, CA, USA) selectively ablates prostatic tissue using a non-thermal, high-pressure water jet. The ablation occurs after real-time surgical planning using transrectal ultrasonography and cystoscopy [8]. The system consists of three components—a robotic handpiece, console and conformal planning unit (CPU) [8]. When the patient presents for surgery, they are given a general anaesthetic and intravenous antibiotic prophylaxis. They are prepped and draped in the dorsal lithotomy position. A bi-planar transrectal ultrasonography (TRUS) transducer is inserted providing real-time images of the prostate in sagittal and transverse views on the CPU. This is used to define the extent and boundaries of the tissue resection.

Transurethral insertion of a 22Fr rigid cystoscope with a visual obturator provides access to the bladder [8, 9••, 10]. The obturator is removed and replaced with the robotic handpiece containing an integrated bespoke cystoscope. The tip of this is positioned at the bladder neck under endoscopic vision. After positioning, the handpiece is locked to a robotic arm which is then fixed securely in place.

The CPU is then used to measure and adjust the length, depth and sweep angle parameters providing a three-dimensional area of resection [8, 9••, 10]. Once surgical planning is complete, Aquablation is activated with a foot pedal. This begins an automated process which continues until the resection is complete. After resection, haemostasis is achieved by inserting a Foley 22Fr 3-way catheter into the bladder and placing it on traction using a non-invasive novel traction device [9••, 10]. The catheter balloon filled with 40 mL of saline provides direct compression to the prostatic cavity [8, 9••]. It remains on traction for 2–5 h post-operatively depending on the amount of bleeding observed within the catheter tubing. Alternatively, haemostasis can be achieved through monopolar or bipolar electrocautery according to the surgeon's preference [8, 9••]. Continuous bladder irrigation is performed as required and then weaned over a 24-h period. A trial removal of catheter occurs the following morning.

The WATER Study

The WATER (Waterjet Ablation Therapy for Endoscopic Resection of Prostate Tissue) study is a prospective, double-blind, randomised controlled trial comparing the safety and efficacy of Aquablation to TURP for the surgical treatment of BPH [11••]. The study was carried out in 17 centres across four countries between October 2015 and December 2016. It included men aged 45 to 80, with moderate to severe LUTS (defined as International Prostate Symptom Score (I-PSS) > 11 and maximum urinary flow rate (Qmax) < 15 ml/s). Additionally, prostate size was measured by TRUS and patients were included if it was between 30 and 80 g in size. A total of 184 men were randomised in a 2:1 ratio favouring Aquablation. Sixty-five men were in the TURP arm, 116 in the Aquablation arm and three voluntarily withdrew from the study. Initial evaluation and treatment (Aquablation/TURP) were carried out by an unblinded team, whereas the patient and follow-up team were blinded.

Baseline characteristics were consistent with typical BPH patients, and no significant differences existed between the groups. The mean age was 66, and 81% reported being sexually active [11••]. The mean prostate size was 53 mL, I-PSS was 22.6, and I-PSS-QOL was 4.8 [11••]. The primary endpoints of the study were twofold reduction in I-PSS at 6 months and development of persistent grade 1 Clavien-Dindo complications, or any that were grade 2 and above.

Efficacy measures demonstrated the mean operative time was similar between the groups [11••]. However, the mean resection time was significantly less in the Aquablation group (4 versus 27 min, $p < 0.0001$). This difference was exacerbated in larger prostates as the mean resection time in TURP was highly dependent on prostate size unlike Aquablation. TURP took 0.3 min/g of the prostate, whereas Aquablation was only 0.04 min/g [11••]. Other significant perioperative endpoints included post-operative haemoglobin change which favoured TURP showing a decrease from 14.7 to 13.7 compared with Aquablation which decreased 14.9 to 13.0 ($p = 0.002$) [11••]. One patient in the Aquablation group required a blood transfusion, whereas no patients did in the TURP group. Finally, no significant difference was observed in the mean length of hospital stay.

Post-treatment measures were observed at both the 3- and 6-month follow-ups (Table 1). Adherence to follow-up was high with 97% of patients being seen at the 6-month follow-up visit [11••]. The primary efficacy endpoint at 6 months demonstrated non-inferiority with a mean decrease in I-PSS by 16.9 for Aquablation and 15.1 for TURP. In subgroup analyses in men with baseline prostate size greater than 50 g, Aquablation showed superiority with respect to improvement in I-PSS ($p = 0.0197$). I-PSS-QOL also improved similarly between groups at 6-months showing mean decreases of 3.5 for Aquablation and 3.3 for TURP. Qmax and post-void residual volume also improved and again showed the non-inferiority of Aquablation compared with TURP.

At 3-months, the primary safety endpoint was significantly better in the Aquablation group compared with the TURP group (26% vs 42%, $p = 0.0149$) [11••]. Additionally, the rate of persistent Clavien-Dindo grade 1 complications was significantly lower in the Aquablation group (7% compared with 25%, $p < 0.01$). In particular, anejaculation was much more common after TURP (36%) than Aquablation (10%) ($p = 0.0003$). The difference in anejaculation was exacerbated in men with prostates between 50 and 80 g (41% versus 2%, $p =$

Table 1 Post-treatment measures at 6-month follow-up

	Aquablation ($n = 116$)	TURP ($n = 65$)	Sig (p value)
Post-operative haemoglobin change (g/dL)	− 1.9	− 1.0	0.0002
Change in I-PSS	− 16.9	− 15.1	0.14
Change in I-PSS-QOL	− 3.5	− 3.3	0.4582
Qmax (ml/s)	+ 10.9	+ 8.9	0.10
Post-void residual (ml)	− 55	− 64	NS
Anejaculation rate	10%	36%	0.0001

0.00010). There was no significant difference between groups for Clavien-Dindo grade 2 or higher complications. These safety endpoints remained consistent at 6-month follow-up.

Subgroup analyses in men with a prostate size between 50 and 80 g demonstrated even larger differences in safety endpoints. In this subgroup, the primary safety endpoint was higher in TURP than Aquablation (46% vs 20%) [11••]. Only 2% of Aquablation patients had a persisting Clavien-Dindo grade 1 complication compared with 26% of TURP patients. Clavien-Dindo grade 2 and higher complications were more common in TURP patients, but this did not reach statistical significance.

Discussion

The WATER study is a landmark trial introducing new technology in the management of BPH. The AquaBeam system remains the only commercially available system that avoids delivery of thermal energy to the prostate but still achieves acute resection of adenoma. The trial has cemented the AquaBeam system's role as a serious option in the treatment of BPH.

All three authors have the first-hand experience in the technique. Although no specific data has been published on the learning curve, it is much shorter than the traditional TURP. This view is based on the availability of the novel graphic user interface and step-by-step guidance given by the software as the operating surgeon delivers the treatment. Precise selection of tissue by the surgeon based on ultrasound imaging allows avoidance of anatomical structures such as the verumontanum and external urethral sphincter. The availability of this real-time data throughout the procedure is a valuable aid to teaching as well as treatment.

The data also confirms a reduced rate of anejaculation versus TURP, further elicited in a subgroup analysis of WATER study data published by Plante et al. [12]. This is important when counselling patients in their choice of therapy for BPH, as our patients are seeking to maintain sexual function as they age and doing so successfully [13]. Anejaculation is more prevalent in both TURP as shown by the WATER study and is greater than expected for patients treated with medical management for BPH [14]. With respect to erectile function, studies are ongoing comparing Aquablation with TURP.

The statistically significant difference in post-operative haemoglobin favouring TURP is also consistent with our experience and should be taken into account during patient selection. In our experience, post-operative haematuria has been reduced through the use of a novel catheter traction device provided by PROCEPT. Engagement with ward nursing staff and the provision of dedicated teaching sessions regarding post-operative care and the use of the traction device have been vital in minimising both nurse and patient distress due to haematuria or difficulties with traction.

Although the mean operative time in the Aquablation arm was 45 min, remarkably, resection time averaged only 5 min. Setup time is a major component of total theatre time, but once local staff are familiar with the procedure this drops significantly. We have found having the same theatre team allocated to each Aquablation list useful in streamlining this process. Typically, in a single full-day operating list, seven cases can be easily completed, allowing for anaesthetic time, turnover and staff breaks. Many urologists now face the problem of functioning in a resource constrained system, and one advantage we have seen with Aquablation is efficiency. We have the ability to treat more patients with BPH compared with traditional techniques. Our experience has been that Aquablation has been a valuable adjunct in the arsenal of treatments for BPH available to us as Urologists.

Ongoing Trials

The WATER II trial is a prospective single-arm, open label, interventional clinical trial examining the safety and efficacy of Aquablation for the surgical treatment of BPH in large prostate sizes (80–150 g) [15]. It began in September 2017 in 17 centres across the USA and Canada, and enrolment is completed. Its primary safety and efficacy endpoints are similar to the WATER study, and follow-up will occur over a 12-month period initially. Initial outcomes from the trial have shown significant improvement in I-PSS at 3 months with a mean change from 24 to 7. Additionally, it has seen significant increases in I-PSS-QOL and Qmax with a corresponding decrease in post-void residual volume. This data has reported a

Clavien-Dindo grade 2 and higher complication rate of 34% which is higher than the WATER study, but possibly to be expected considering the larger prostate size [15].

The Open WATER trial is a prospective observational study in the form of a global post-market registry for Aquablation [16]. It began enrolment in September 2017 in four centres across four different countries including our own. Its primary outcome is I-PSS change at 3-month follow-up.

Conclusions

Bothersome LUTS due to BPH is a significant issue which affects ageing men. The WATER study demonstrated that Aquablation is non-inferior to the current gold standard TURP in the management of bothersome LUTS due to BPH. Additionally, it demonstrated a significantly superior safety profile and lower risk of sexual dysfunction. Future studies will evaluate long-term outcomes of Aquablation and its efficacy in larger prostates (80–150 g).

Compliance with Ethical Standards

Conflict of Interest Peter J. Gilling is an investigator for the WATER Trial.

Jordan A. Mann and Jared L. White declare that they have no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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