Update on minimally invasive surgery and benign prostatic hyperplasia

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Abstract Transurethral resection of the prostate (TURP) became the gold standard surgical treatment for benign prostatic obstruction without undergoing randomized controlled trials against the predecessor standard in open suprapubic prostatectomy. TURP has historically been associated with significant morbidity and this has fuelled the development of minimally invasive surgical treatment options. Improvements in perioperative morbidity for TURP has been creating an ever increasing standard that must be met by any new technologies that are to be compared to this gold standard. Over recent years, there has been the emergence of novel minimally invasive treatments such as the prostatic urethral lift (PUL; UroLift System), convective WAter Vapor Energy (WAVE; Rezum System), Aquablation (AQUABEAM System), Histotripsy (Vortx Rx System) and temporary implantable nitinol device (TIND). Intraprostatic injections (NX-1207, PRX-302, botulinum toxin A, ethanol) have mostly been used with limited efficacy, but may be suitable for selected patients. This review evaluates these novel minimally invasive surgical options with special reference to the literature published in the past 5 years.

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1. Introduction

Minimally invasive surgery for benign prostatic hyperplasia (BPH) is a dynamic field, with novel treatment modalities emerging in experimental and clinical use with various safety and efficacy profiles. This review aims to update the readership on minimally invasive surgical treatments for BPH, by assessing relevant literature published in the past 5 years.

Several reviews on minimally invasive surgical treatments for lower urinary tract symptoms (LUTS) due to BPH have been published within the last 2 years, perhaps an

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indication of the interest and progress in this dynamic field of surgical device technology [1,2]. Transurethral resection of the prostate (TURP) and open simple prostatectomy (OSP) have been the historical reference-standard procedures for decades. Although both operations are highly effective and offer durable improvements in urinary functional outcomes, they are also associated with risk of considerable perioperative complications and morbidity [3]. A number of new technologies are at various stages of experimental and clinical trial ranging from animal models and early clinical trials through to complete commercialization. A number of these procedures can be performed as quickly as within minutes, in the office or outpatient setting, or with only local anaesthesia or oral sedation [4].

For the purposes of this review, we have examined minimally invasive procedural treatments for LUTS due to BPH, as defined by the ability for the procedure to be performed either in an office or outpatient setting with minimal recovery time and morbidity for the patient. We examined technologies such as the prostatic urethral lift (PUL, UroLift System, NeoTract, CA, USA), convective water vapor treatment (Rezum System, NxThera, Maple Grove, MN, USA), temporary implantable nitinol device (TIND, Genesis Medical, London, England and MediTate, Or Akiva, Israel), aquablation (AQUABEAM System, PROCEPT Bio-Robotics, Redwood Shores CA, United States of America), histotripsy (Vortex Rx System, HistoSonics, Ann Arbor MI, United States of America) and intraprostatic injections. Traditional or standard cavitating prostate operations such as TURP and laser prostatectomy have not been included within the scope of this study, nor has robotic simple prostatectomy been considered within the scope of this review.

2. PUL

PUL involves the transurethral placement of small permanent intraprostatic implants (comprising of nitinol, polypropylene, and stainless steel) to retract the obstructive lateral prostatic lobes away from the prostatic urethral lumen, creating an anterior channel, hence treating benign prostatic obstruction without tissue destruction. This minimally invasive treatment has been reported by several studies to improve International Prostate Symptom Score (IPSS) by over 52%, with a weighted mean improvement of 9.22–11.82. In a prospective, sham controlled, pivotal trial the mean IPSS improvement was 11 points, 88% greater than sham controls. The procedure has been shown to achieve durable outcomes out to 3 years [5].

One of the most favoured advantages of UroLift is its ability to treat LUTS due to BPH whilst preserving sexual function, both erectile and ejaculatory. It is an attractive treatment option for men wanting to avoid the side effects and complications of long-term drug therapy (α-blockers or 5-α-reductase inhibitors) and standard surgical BPH operations [6].

Roehrborn et al. [7] published the 3-year results of the L.I.F.T. Study, a multi-centre, randomized, patient and outcome assessor blinded trial of the PUL in men with bothersome LUTS due to BPH. This study involved 206 patients at 19 centres in North America and Australia, with IPSS ≥13, peak flow rate (Q_{max}) <12 mL/s, and prostate volume between 30 mL and 80 mL. The improvement in IPSS was 88% greater in the PUL compared with the sham group at 3 months. At 3 years, the mean total IPSS improvement was significantly improved by 41.1%, quality of life (QoL) by 48.8%, and Q_{max} by 53.1%. There were no de novo cases of sustained ejaculatory or erectile dysfunction and all sexual function assessments showed average stability or improvement after PUL. Patients recovered quickly post-operation and were able to return to normal physical activities. Fifteen of the 140 patients originally randomized to PUL required surgical reintervention for treatment failure within the first 3 years.

Bozkurt et al. [8] reported on 17 patients who underwent treatment with PUL, and reported results out to 12 months. Similar to the results from other studies, PUL was shown to offer rapid improvement in LUTS and QoL and Q_{max}. There was a 4.2-point increase in Q_{max}, a 0.9-point improvement in QoL and a 32% decrease in postvoid residual urine volume. Sexual function was preserved, with no statistically significant difference (p > 0.05) in the International Index of Erectile Function (IIEF) and Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EJD) scores [8].

Perera et al. [9] performed a systematic review and meta-analysis of symptomatic, functional, and sexual outcomes following the PUL procedure. At the time of that literature search (May 2014), 10 articles comprising six independent patient cohorts were included for analysis. Pooled estimates from between 452 and 680 patients suggested overall improvement following PUL, including symptoms (large gain; standardised mean gain range of 1.3–1.6, IPSS difference of −7.2 to −8.7 points), Q_{max} (3.8–4.0 mL/s), and QoL (2.2–2.4 points). Sexual function was preserved with a small improvement estimated at 12 months (standardised mean gain range of 0.3–0.4). It was concluded that PUL is a well-tolerated, minimally invasive therapy for BPH that provides favourable symptom, sexual health, and functional outcomes during follow-up to 12 months [9].

A prospective, randomized, controlled trial (BPH6 Study) at 10 European centres involving 80 men, showed that significant symptom relief was achieved in both TURP and PUL treatment arms. However, PUL was associated with better preservation of ejaculation and quality of recovery compared with TURP (p < 0.01). The study demonstrated non-inferiority of PUL, and superiority of PUL over TURP in terms of a composite BPH6 endpoint which incorporated symptom relief, quality of recovery, erectile function preservation, ejaculatory function preservation, continence preservation, and safety [10]. Although advantageous in terms of important aspects of QoL and minimal to mild complications, PUL does not appear to improve IPSS, QoL or Q_{max}, more than TURP and holmium laser enucleation of the prostate (HoLEP) [11].

In September 2013, the US Food and Drug Administration approved the UroLift. In September 2015, the UK National Institute for Clinical and Health Excellence also approved the UroLift as an effective, safe and cost-effective treatment for use in the UK health system, when implemented in a day-case setting [6,12]. It has been postulated that even earlier management with PUL may even reduce overall cost...
for those patients managed with medication. It was concluded that since PUL achieved rapid LUTS improvement with low risk of complications, the procedure was a safe and cost-effective option for early treatment of LUTS due to BPH [5].

The UroLift System Tolerability and Recovery When Administering Local Anaesthesia (LOCAL) Study is ongoing, to evaluate procedure tolerability and surgical recovery following the PUL procedure when performed under local anaesthesia. It is estimated to be complete in September 2018 (ClinicalTrials.gov Identifier: NCT01876706).

A limitation of the clinical application of the UroLift procedure is that it had been recommended for the treatment of obstructing lateral prostate lobes, but not for obstructing prostatic median lobe. However, there is currently a study in place to evaluate the safety and effectiveness of using UroLift in patients with prostatic median lobe enlargement — recruitment is currently in progress, and the estimated study completion date is February 2018 (ClinicalTrials.gov Identifier: NCT02625545).

3. Convective water vapor treatment

The Rezum System utilizes convective water vapor energy (WAVE) to ablate prostatic tissue. This minimally invasive surgical treatment can be performed in an office or hospital setting using oral pain medication, and is applicable to all prostate zones including the median lobe. It has been shown to be safe and efficacious in both Phase I and II studies [11,13]. Dixon et al. [14] studied safety and efficacy outcomes of the Rezum System from pilot studies of 65 men, and reported statistically significant clinical improvements at 1, 3, 6, and 12 months for IPSS (decreasing by 6.8, 13.4, 13.1, and 12.5, respectively) and Qmax (increasing by 2.0, 4.7, 4.3, and 4.6 mL/s, respectively). At 12 months, there was a 56% improvement in IPSS (p < 0.001), 61% improvement in QoL and 87% improvement in Qmax (p < 0.001). The procedure was safe with an acceptable side effect profile. Sexual function was maintained, and the majority of adverse events were of short duration and related to the endoscopic instrumentation. There was only one case of urinary retention in this study [14].

A multicentre, randomized, controlled trial (Rezum II Study) using convective Water Vapor Energy (WAVE) to treat LUTS due to BPH was conducted in 197 men aged ≥50 years, with IPSS ≥13, Qmax ≤15 mL/s, and prostate size 30–80 mL. Patients were randomised in a ratio of 2:1 between thermal therapy with the Rezum System (n = 136) and control (n = 61). The primary end-point compared IPSS reduction at 3 months and treatment subjects were followed for 12 months. WAVE treatment was shown to provide rapid and durable improvements in LUTS due to BPH whilst preserving erectile and ejaculatory function. WAVE and control IPSS decreased by 11.2 ± 7.6 and 4.3 ± 6.9, respectively (p < 0.0001). IPSS significantly decreased at 2 weeks postoperation (from 22 to 18.6, p = 0.0006) and by 50% or greater at 3, 6, and 12 months (p < 0.0001). Qmax increased by 6.2 mL/s at 3 months and this improvement was sustained to 12 months (p < 0.0001). Adverse events were mild to moderate and resolved quickly [13]. IIEF and MSHQ-EjD scores were not different from the control group at 3 months or from baseline at 1 year. Ejaculatory bother score improved 31% over baseline (p = 0.0011). Also, 32% of subjects achieved minimal clinically important differences in erectile function scores at 3 months, and 27% at 1 year, including those with moderate to severe erectile dysfunction [15]. The 2-year results were not published at the time of the writing of this review but are expected to become available in 2017.

Regarding the action of WAVE technology, an MRI study demonstrated the delivery of convective WAVE technology created thermal lesions in the prostate tissue, which then underwent near complete resolution by 3 and 6 months after treatment. This was associated with a one-third reduction in overall prostate and transition zone volumes [16].

4. TIND

The TIND is a nickel-titanium alloy, or nitinol, device which is placed transurethrally into the prostatic urethra to exert outward pressure on the obstructive prostatic lobes for 5 days prior to removal. It aims to relieve bothersome LUTS due to BPH. The results of the first prospective in-human clinical trial were reported by Porpiglia et al. [17]. Thirty-two patients (age >50 years) with LUTS due to BPH, IPSS ≥10, ≤12 mL/s, and prostate volume of <60 mL, were treated with TIND. With patients under light sedation, TIND was implanted within the bladder neck and the prostatic urethra using a rigid cystoscope; TIND was removed 5 days later in an outpatient setting. Mean patient age was 69.4 years. The mean (standard deviation, sd) prostate volume was 29.5 (7.4) mL and the Qmax was 7.6 (2.2) mL/s. The median (interquartile range, IQR) IPSS was 19 (14–23) and QoL score was 3 (3–4). All the implantations were successfully completed without intraoperative complication. The mean operative time (sd) was 5.8 (2.5) min and the median (IQR) postoperative stay was 1 (1–2) day. All but one (96%) of the devices was removed 5 days after implantation in an outpatient setting. Four (12.5%) complications were recorded: one (3.1%) urinary retention, one (3.1%) transient incontinence due to device displacement, one (3.1%) prostatic abscess and one (3.1%) urinary tract infection. No independent prognostic factor for complications was identified. There were statistically significant differences in the IPSS, QoL score and Qmax when comparing pre- and post-operative results at each time point. After 12 months, the median IPSS was 9 (interquartile range 7–13), median QoL score 1 (interquartile range 1–2), and mean Qmax 12 mL/s (SD 4.7). The mean improvement in IPSS compared with baseline was 45%, and Qmax 67%. No patients required medical therapy or surgical procedures for BPH at the time of their last follow-up visit 12 months post-operation [17].

In conclusion, TIND implantation was demonstrated to be a feasible and safe minimally invasive option for the treatment of LUTS due to BPH. The functional results are encouraging and the treatment significantly improved patients QoL [17]. However, this is the first published in-human prospective clinical trial and further studies are required to confirm these results and assess durability of the procedure beyond 12 months. There are several clinical trials regarding the TIND Device, as registered on
Aquablation is a novel minimally invasive water ablation therapy combining image guidance and robotics for the removal of prostatic tissue as a treatment for LUTS due to BPH. Under real-time image-based ultrasonic guidance, AQUABEAM technology enables surgical planning and mapping, to achieve a heat-free resection of the prostate using a high-velocity saline stream. Aquablation is a relatively automated procedure which shows promise in Phase II studies with few side effects but requires general anaesthesia [11].

In eight canine models, Faber et al. [18] evaluated the safety and efficacy of aquablation (PROCEPT Aquablation System) treatment to the prostate. The objective of the high-velocity saline stream was to selectively ablate prostatic glandular tissue while sparing collagenous structures such as blood vessels and capsule. After ablation, a laser beam was captured by a low-pressure water jet to produce surface haemostasis. The extent and depth of ablation was predetermined by endoscopic and transrectal ultrasound guidance. There was no active bleeding in any of the dogs during or after Aquablation. Complications included two dogs with infection successfully treated with antibiotics, a false passage created during catheter placement, and two bladder neck perforations (from mechanical insertion), one leading to euthanasia. Histologic evaluation at 6 weeks revealed a normal cellular architecture and full re-epithelialization of the treatment cavity [18].

Gilling et al. [19] reported on the first study of ablation in humans: a prospective, non-randomised, single-centre trial. The mean age was 73 years (range 59–85) years and prostate size was 54 mL (range 27–85) mL. Forty percent (6/15) of men had a large prostatic median lobe. At baseline, the men had moderate-to-severe LUTS, with mean IPSS 23 and Qmax 8.4 mL/s. All aquablation treatments were performed under general anaesthesia, and follow-up was conducted at 1, 3 and 6 months. Mean procedural time was 48 min with an aquablation treatment time of 8 min. All procedures were able to be completed with no serious or unexpected adverse events. Ninety-three percent (14/15) of patients had their catheters removed on postoperative day 1, and most patients went home on the first postoperative day. No serious adverse events occurred within 30 postoperative days. There were no blood transfusions and no significant changes in serum sodium. One patient received a repeated procedure within 90 days. There was a statistically significant improvement in mean IPSS from 23.1 at baseline to 8.6 at 6 months ($p < 0.001$) and $Q_{\text{max}}$ from 8.6 mL/s at baseline to 18.6 mL/s at the 6 months ($p < 0.001$). Mean prostate size decreased by 31% to a mean of 36 mL from 54 mL ($p < 0.001$). No cases of urinary incontinence or erectile dysfunction were reported [19].

The preliminary results from this initial study show aquablation of the prostate is technically feasible with a safety profile comparable to other BPH technologies. The combination of surgical mapping by the operating surgeon and the high-velocity saline appears to deliver a conformal, quantifiable, and standardised heat-free ablation of the prostate. Advantages of this technique include reduction in resection time compared with other endoscopic methods, as well as the potential to preserve sexual function [19].

A Phase III prospective multicentre randomized blinded study comparing Aquablation using the AQUABEAM System and TURP for the treatment of LUTS due to BPH is in progress, and plans to follow patients out to 3 years (ClinicalTrials.gov Identifier: NCT02505919). The study began in September 2015; estimated completion date is September 2019.

Histotripsy is a nonthermal, noninvasive, pulsed ultrasound technology that homogenizes tissue within the targeted volume. It was investigated in several animal studies; in-human trials are currently in progress.

Darnell et al. [20] reported on histological changes in the prostate after histotripsy treatment in eight canine models. In vivo histotripsy of canine prostate produced a 31% decrease in prostate volume and a limited inflammatory and fibrotic response. A narrow (1.5 mm) band of fibrosis around the empty, re-epithelialized treatment cavity was observed 6 weeks after treatment. In four cases, an overall reduction in collagen content was measured. Further studies are planned to correlate these histologic findings with alteration in mechanical tissue properties and explore strategies for treatment of BPH with little resulting fibrosis [20].

There is one in-human prospective single-arm clinical trial on histotripsy in progress, as registered on clinicaltrials.gov, titled "Safety and Initial Efficacy Study of the Vortx Rx for Treatment of Benign Prostatic Hyperplasia". The trial, which started in July 2013 and planned to complete in June 2017, aims to assess and monitor the performance of the Vortx Rx (Histotronics’ Histotripsy BPH Device) in terms of initial safety and efficacy when used for the treatment of LUTS due to BPH in men aged ≥50 years old (ClinicalTrials.gov Identifier: NCT01896973).

Although this technology has had a number of complications in animal models, it has undergone technical improvements. The results of the first-in-human studies are being awaited [11].

Intra-prostatic injections with a variety of agents have been explored as a treatment of LUTS due to BPH and appear an attractive treatment proposal as they can be readily performed under local anaesthesia [11].
7.1. NX-1207 injections

NX1207 (Nymox Corporation, Quebec, Canada) is a drug that is administered by transrectal intraprostatic injection under ultrasound guidance. The substance leads to prostate volume reduction and symptomatic improvement. However, patient numbers are still low and currently treatment with NX1207 is still experimental, although results were interesting in Phase I and II studies [21,22]. A Phase III study “Evaluation of Re-Injection of NX-1207 for the Treatment of Benign Prostatic Hyperplasia (BPH)” has been performed, with primary completion date January 2013 (ClinicalTrials.gov Identifier: NCT01438775). In November 2014, it was reported that NX1207 had failed to reach its primary endpoints and further development of NX1207 as a treatment for BPH has been abandoned.

7.2. PRX-302 injections

PRX302 (topsalyisin; Sophiris Bio Corp, La Jolla, CA, USA), a modified recombinant protein, is an experimental intraprostatic injectable medication, proposed for the treatment of LUTS due to BPH. Results from the phase one and two studies were promising. In the phase two study (TRI-UMPH-1 Trial), there was statistically significant ($p < 0.05$) difference in IPSS and $Q_{\text{max}}$ at three months posttreatment with PRX302 compared with placebo according to results posted on ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT00889707). No significant safety problems were reported [22].

A phase three study entitled “Randomized, Double-blind, Vehicle-controlled, Multicenter Safety and Efficacy Study of Intraprostatic PRX302 for LUTS BPH (The PLUS-1 Trial)” is ongoing and aims to evaluate the safety and efficacy of a single treatment of PRX302 for LUTS due to BPH compared to placebo (Clinical Trials.gov Identifier: NCT01966614). The estimated completion date was December 2015, and published results are being anticipated.

7.3. Botulinum toxin injections

Botulinum toxin is a neurotoxin produced by the bacterium Clostridium botulinum. It inhibits the release of acetylcholine and other neurotransmitters from the nerve terminal. Botulinum toxin, specifically toxin type A (BoNT-A) has been used since the 1970s to reduce the muscular hypercontraction disorders. Since prostate gland as well as bladder is under the influence of autonomic innervation, theoretically, injection of BoNT-A into the prostate induces chemo-denervation and modulation of prostate function, thereby reducing LUTS. Furthermore, BoNT-A has been shown to induce prostate apoptosis, down-regulation of $\alpha_{1A}$ receptors, and reduce contractile function of prostate in animal studies. Open studies of intraprostatic BoNT-A injection have demonstrated promising results in improving voiding dysfunction, however, intraprostatic BoNT-A injection did not perform better than the placebo group in recent publications of placebo controlled studies [23].

A systematic review and meta-analysis assessing BoNT-A injection for treatment of LUTS due to BPH showed no difference in efficacy or procedure-related adverse events compared with placebo. Insufficient evidence of clinical benefit has been demonstrated and therefore clear recommendations for its use cannot be made [24].

By contrast, in a study of 32 men with LUTS due to BPH, 200 IU BoNT-A was injected into 5 points at the lateral and middle lobes of the prostate under ultrasound guidance. All clinical symptoms and indicators (IPSS, QoL, $Q_{\text{max}}$, post-void residual urine) improved at 1 month posttreatment, reached optimal levels 6 months posttreatment, and was durable at 12 months posttreatment. Therefore, in this study, ultrasound-guided BoNT-A injections were found to be safe and effective in the management of BPH [25].

A case report of BoNT-A injection into the bladder neck was performed in an elderly man who was in urinary retention but not medically fit enough for transurethral incision of the prostate (TUIP) or TURP. The result was satisfying as a minimally invasive, tolerated, and cost-effective approach. The authors of the case report considered it a promising treatment option, but recognised it may only be effective in selected patients [26].

8. Conclusion

The field of novel minimally invasive technologies for the treatment of LUTS due to BPH is an interesting and dynamic field, with novel procedures being proposed in various phases of experimental and clinical trial. Most minimally invasive technologies can be performed in an office or outpatient setting, with minimal recovery time and morbidity to the patient. The PUL (UroLift System) procedure has demonstrated consistent good functional results similar to TURP out to 3 years, and with the favourable advantage of improving LUTS due to BPH whilst simultaneously preserving erectile and ejaculatory function (unlike TURP). Performance of the WAVE (Rezum System) procedure appear promising with functional improvement of LUTS due to BPH shown in a randomized controlled trial. The results of the first-in-man prospective trial of the TIND procedure for treatment of LUTS due to BPH have been promising. Phase one, two and four studies are in progress and further validation of results awaited. Aquablation (AQUABEAM System) has had favourable results in first-in-man studies, and a phase three randomized controlled trial of Aquablation versus TURP is in progress. Histotripsy (Vortx Rx System) remains experimental, with mixed results in animal studies; one prospective human trial is in progress. Intraprostatic injections with PRX-302 showed interesting and somewhat promising results in phase one and two studies, but these results require validation in phase three studies. NX-1207 treatment has been abandoned due to failure to achieve primary endpoints. BoNT-A intraprostatic injections were not of benefit over placebo in systematic review and meta-analysis, although some individual studies showed favourable results. Further validation of the performance of these novel minimally invasive treatment options for LUTS due to BPH in well-designed studies are desired, in order to evaluate their role (or lack of such a role) in clinical practice.
Conflicts of interest

H W. Woo reports the following conflicts of interest: Boston Scientific-advisory board, NxThera-investigator, Neotract-stock. A Chung has no conflict of interest to declare.

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