

NOVEL SURGICAL TREATMENTS FOR BENIGN PROSTATIC ENLARGEMENT

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Transurethral resection of the prostate (TURP) has been the gold standard for the treatment of elderly men with lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH). However, over the last few years, advances in surgical treatment have led to the development of other treatment modalities. These innovations include convective WATER Vapor Energy (WAVE; Rezum System), prostatic urethral lift (PUL; UroLift System), Prostate Artery Embolisation (PAE) and Aquablation (AQUABEAM System). This review provides an update on these current minimal invasive surgical treatments. The evidence of their safety, tolerability and efficacy in clinical practice is reviewed.

REZUM SYSTEM (WATER VAPOUR THERMAL THERAPY)

The Rezum System (water vapour thermal therapy) uses a convective radiofrequency water vapour thermal energy system to ablate prostate tissue and give relief from LUTS. The system has a generator and a transurethral delivery device, that delivers water vapour circumferentially via 12 holes at the tip of an 18-gauge needle inserted via a cystoscopic instrument. One to 3 injections of water vapour are administered to prostate lobes, each lasting 9 seconds. The initial injections are delivered 1 cm distal to the bladder neck at the 3- and 9-o'clock positions, with further injections inserted distally every 10 mm of the prostate urethra until the proximal verumontanum is reached.

Rezum (Figure 1) convective energy transfer does not produce thermal injury to tissues outside the intended treatment area in the transition zone of the prostate as it doesn't create a temperature gradient between tissues as compared to other forms of thermoablation surgery. This minimally invasive surgical treatment can be performed in an office or hospital setting using oral analgesia or local anesthetic. It can be applied to all 3 lobes of the prostate making it more versatile than forms of treatment where the middle lobe needs treatment. It is contraindicated in patients with artificial urethral sphincters or penile prosthetic devices.

Initial Phase I clinical trials (n=30) demonstrated significant improvements in IPSS (10.7 from 23 at baseline) which was associated with a mean 26% reduction in total prostate volume at 3 months.¹ A further trial by Mynderse et al² in 44 individuals demonstrated a 28.9% reduction in prostate volume on gadolinium-enhanced magnetic resonance imaging at 6 months. This was followed up by further studies including Dixon et al³ and the Rezum II Study.⁴

Dixon et al³ performed a further study assessing the safety, efficacy and outcomes of the Rezum System (n=65). They observed statistically significant clinical improvements in IPSS scores at 1-, 3-, 6-, and 12-month intervals with falls of 6.8, 13.4, 13.1, and 12.5 in the IPSS score respectively. Similarly, Qmax increased by 2.0, 4.7, 4.3, and 4.6 mL/s, respectively over the same intervals. IPSS improved by 56% by 12

FIG 1. The Rezum System.

months ($p < 0.001$), quality-of-life (QoL) improved by 61% ($p < 0.001$) and Qmax by 87% ($p < 0.001$) in one year. Sexual function was maintained. The procedure was safe with acceptable short-term side effects. One case of urinary retention occurred.

The Rezum II Study⁴ was a multicentre, randomized, controlled trial assessed the efficacy of the Rezum WAVE therapy in treating men with LUTS secondary to BPH, with prostate volumes of between 30–80 mLs ($n = 197$). Patients were randomized in a 2:1 ratio between Rezum System ($n = 136$) and control ($n = 61$), which was simulated cystoscopy procedure with treatment sounds. The IPSS reduction at 3 and 12 months was used as end point. Rezum thermal therapy resulted in a reduction in IPSS by 11.2 ± 7.6 versus control 4.3 ± 6.9 ($p < 0.0001$). There was a reduction in the baseline IPSS score of 22 to 18.6 in 2 weeks ($18.6, p = 0.0006$) and by 50% or greater at 3, 6 and 12 months, $p < 0.0001$. The Q max flow rate increased by 6.2 mL/s at 3 months, remaining more or less the same at 1 year ($p < 0.0001$). Rezum treatment resulted in a 160% improvement in IPSS improvement. There was also maximal symptom relief of at least 50% improvement in IPSS, QoL, Qmax, and BPH Impact Index remained durable throughout 3 years ($P < .0001$). Median lobe treated patients also had similar responses. Retreatment rate was only 4.4% in the 3-year period. There were no reports of erectile dysfunction. Side effects observed were acute urinary retention (3.7%), hematuria (11.8%),

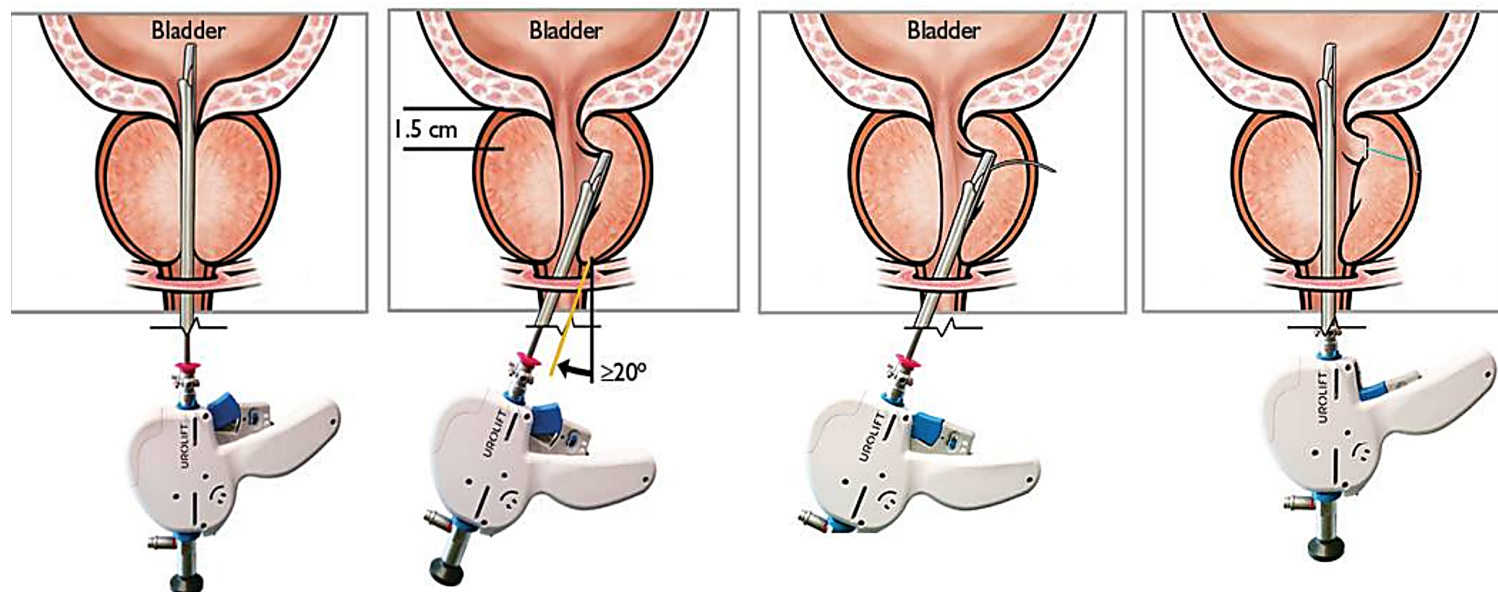
dysuria (16.9%), frequency and urgency (5.9%), and suspected urinary tract infection (3.7%). Where side effects were reported they were short lived and treated conservatively.

PROSTATIC URETHRAL LIFT (PUL) – UROLIFT

The UroLift system uses adjustable transurethral placed, permanent implants (made of nitinol, polypropylene, and stainless steel) to retract the obstructive lateral prostatic lobes away so as to unblock the urethra. The device relieves symptoms of urinary outflow obstruction without cutting or removing tissue. In September 2015, the UK National Institute for Clinical and Health Excellence approved day-case UroLift as an effective, safe and cost-effective treatment.⁵

The implant is delivered by a hand-held pistol grip to which a needle-shaped probe is attached (Figure 2). The surgeon inserts the probe into the prostatic urethra and a fine needle at the end of the probe deploys and secures an implant in a lobe of the prostate. One end of the implant is anchored in the urethra and the other firmly attached to outer surface of the prostatic capsule, thereby pulling the prostatic lobe laterally and away from the urethra. This is repeated on the other lobe of the prostate. Usually 4 implants are used and the procedure can be done under local or general anesthetic, as day-case.

The UroLift system has been reported by several studies to improve International Prostate Symptom

FIG 2. Prostatic Urethral Lift.

Score (IPSS) by more than 52% (mean weighted improvement of 9.22–11.82). In a review article by Rukstalis et al. 2015,⁶ a number of studies showed an IPSS score improvement of minimum of 52%. The pivotal trial showed an eleven-point IPSS score improvement which is 88% better than the controls cohort. A comparison study reported PUL/ UroLift to be superior to TURP in outcomes of IPSS score, Erectile function and continence preservation, recovery quality, safety and ejaculatory function. Furthermore, there were durable outcomes lasting up to 3 years. The UroLift system can treat LUTS due to BPH and can preserve both erectile and ejaculatory sexual function. This gives UroLift a clear advantage compared to medical management with alpha- blockers or 5 alpha reductase inhibitors or the standard bladder outlet obstruction due to BPH operations, TURP, laser prostate enucleation or ablation and open prostatectomy. McNicholas et al.⁷

The PUL/ L.I.F.T study had 206 patients from 19 centres in North America and Australia, with IPSS ≥ 13 , peak flow rate (Qmax) ≤ 12 mL/s, and prostate volume between 30 and 80 mLs. Roehrborn et al.⁸ The IPSS score improved by up to 88% greater in PUL arm vs the sham arm at 3 months. However, at 3 years, the mean total IPSS improvement was only

41.1%, QoL 48.8%, and Qmax 53.1%. No cases of prolonged ejaculatory or erectile dysfunction and all sexual function assessments showed stability or improvement after UroLift. Recovery was relatively quick, with early return to normal daily physical activities. 11% of UroLift patients required surgical reintervention for treatment failure within the first 3 years. Furthermore, a systematic review by M. Perera et al⁹ in 2014 also confirmed that PUL improves urinary symptoms and flow while preserving sexual function for men with BPH for up to 12 months follow up.

A multicentre European units RCT involving 80 men in different (BPH6 Study) Sonksen et al,¹⁰ showed that significant symptom relief in both TURP and PUL treatment arms. UroLift was associated with better preservation of ejaculation and quality of recovery compared with TURP ($p < 0.01$). UroLift was superior to TURP in the BPH6 study in symptom relief, ejaculatory /erectile function and continence preservation, safety and recovery quality. However, there was no evidence that UroLift improves IPSS, Qmax or QoL more than TURP OR holmium enucleation of prostate (HoLEP). Small sample size with the failure to blind participants to enrolment arm was a limitation of this RCT.

PROSTATE ARTERY EMBOLIZATION (PAE)

PAE for benign prostate hyperplasia involves the introduction of microparticles (polyvinyl alcohol, trisacryl gelatin microspheres, or other synthetic biocompatible materials) into the prostatic arteries via a percutaneous transfemoral arterial approach under local anesthesia with image guidance. The resultant reduction in the prostate blood supply, causes partial prostatic necrosis and shrinkage, thereby improving symptoms of bladder outlet obstruction or prostatic hemorrhage. It is common for patients to experience pelvic pain during and after the procedure for a couple of days. This procedure is potentially suitable for patients who have moderate to severe LUTS, bleeding from prostate or those not suitable for major general anesthetic procedures.

The first experiments were done on dogs by Darewicz in 1980 in treatment of prostatic hemorrhage. This was followed by case reports for human patients in treatment of hematuria and LUTS by DeMeritt et al.¹¹ The largest prospective non-randomized case series was reported for 255 patients in Portugal by Pisco JM et al.¹² Clinical and urodynamic parameters improved with PAE in almost all patients (97.9%). Treatment success was described in 82% and 72% success rates at 1 and 3 months respectively in those who had undergone PAE. However, 15% of patients may have poor outcomes with reported complications including transient ischemic proctitis, penile ulcers and bladder wall necrosis, as a result of embolizing collaterals to adjacent organs.

A recent prospective randomized trial comparing the efficiency and safety of PAE with TURP Gao et al¹³ found no significant differences in functional urinary outcomes ($P < 0.001$). There was improvement in IPSS, QoL, Qmax, and post-void residual volume in both groups. The TURP group had earlier symptom improvement than in the PAE group. Furthermore, the reduction in prostate-specific antigen and prostate volume were significantly greater in the TURP group ($P < 0.05$). The PAE cohort had more overall adverse events and complications ($P = 0.029$), that is post-embolization syndrome, urinary retention and technical failures. The advantages of the PAE procedure must

be weighed against the potential for technical and clinical failures in a minority of patients.

The United Kingdom Observational Rope study of 2018 by Ray et al¹⁴ assessed the efficacy and safety of PAE for LUTS due to BPE. Further comparison with TURP was done. 305 patients were recruited from 17 UK centres, 216 undergoing PAE and 89 TURP. Complications and IPSS scores were primary outcomes which were then compared between the 2 groups. PAE reduced the IPSS by a median score of 10 after 1 year. This was lower than 15-point reduction in IPSS from the TURP arm of the study. PAE produced statistically significant changes in Qmax of 3mL/s (vs +7.5% in TURP) and 28% prostate volume reduction. The QoL IPSS score was not inferior in PAE vs TURP. The reoperation rate in PAE was 5% and 20% at 3 and 12 months respectively.

Two patients had penile ulcer form non-target embolizations which healed without any significant sequelae. One patient had sepsis and another required transfusion in the PAE arm. Whilst 80 % of TURP patients required at least one day admission in hospital, 71% of PAE procedures were done as day cases or outpatient procedures. The study concluded that PAE is a safe and effective alternative treatment to TURP with clinical and statistically significant changes in patient LUTS and QoL.

The National Institute for Health and Care Excellence NICE UK issued guidance on use of PAE with cautions on the potential risks of high radiation exposure, increased urine retention risk, prostatic bleeding (hematuria and haematospermia), groin haematoma, pain and retrograde ejaculation.

AQUABLATION

Aquablation uses high-velocity saline stream to selectively ablate prostatic glandular tissue while sparing blood vessels and capsule. It is a semi-automated ablation therapy procedure, developed in New Zealand, which combines image guidance and robotics to remove prostate tissue. Real-time image-based ultrasonic guidance and AQUABEAM technology enables surgical planning and mapping

to achieve a heat-free resection of the prostate using a high-velocity saline stream. In Phase II studies the procedure was reported to have few side effects and the results have been promising.

Faber et al¹⁵ evaluated the safety and efficacy of Aquablation treatment using PROCEPT Aquablation System in canine models. Assessment of extent and depth of ablation was predetermined by endoscopic and transrectal ultrasound guidance. No active bleeding in any of the dogs during or after Aquablation was observed. However, complications like urinary tract infection, false passages and bladder neck perforations were observed.

Following animal studies, Gilling et al¹⁶ reported on Aquablation in 15 humans in a prospective, non-randomized controlled single-centre trial. The average age was 73 years (Range 59–86 years). The incidence of middle lobe was 40%. Men had mean Qmax of 8.4 mL/s and mean IPSS of 23. Treatments were done under general anesthesia with on average 48 min per procedure and Aquablation time of only 8 minutes. Fourteen of the 15 patients had their catheters removed in 24-hours post-op and discharged on same day. One patient had a repeat procedure within 90 days. There was improvement in mean IPSS from 23.1 at start of treatment to 8.6 at 6 months ($p < 0.001$). Qmax increased from 8.6 mL/s at baseline to 18.6 mL/s at the 6 months ($p < 0.001$). Prostate size reduced by 31% to a mean of 36 mL from 54 mL ($p < 0.001$). No cases of urinary incontinence or erectile dysfunction were reported. The results showed that Aquablation of prostate was feasible, safe and comparable to other BPH treatment methods. Other advantages of this technique include reduction in resection time and the potential to preserve sexual function.

Gilling et al¹⁷ in 2018 compared the safety and efficacy of Aquablation and TURP. Aquablation reportedly demonstrated non-inferior symptom relief as well as a lower risk of sexual dysfunction compared to TURP. Furthermore, prostate glands between 50 and 80 mL in size demonstrated good safety and efficacy benefit. The trialists concluded that long-term follow up was required to further assess the clinical value of Aquablation. It is worth noting that this procedure also has received NICE approval in September 2018.

CONCLUSION

The studies reviewed have all confirmed proof of sustained and effective relief of male LUTS symptoms. Rezum therapy has received significant interest as it has been reported to have a greater degree of preservation of sexual function after the procedure. In addition, the treatment can be applied to median lobe of the prostate. Rezum has received NICE UK approval in August 2018 for UK NHS patients. UroLift has been proven to be a well-tolerated and effective minimally invasive treatment for LUTS due to BPE. It has the added advantage of preserving sexual function. It is a local anesthetic day procedure and can be performed on men who are not suitable for invasive surgery or general anesthetic. The clinical limitation of the UroLift procedure is the inability to treat obstructing middle lobe of prostate. In September 2013, the US Food and Drug Administration approved the UroLift followed by NICE in September 2015. The UroLift System Tolerability and Recovery When Administering Local Anaesthesia (LOCAL) Study is ongoing and it is estimated to be complete in late 2018 (ClinicalTrials.gov Identifier: NCT01876706). PAE is a procedure with good results for BPE patients with moderate to severe LUTS and bleeding from prostate after failure of medical therapy. The procedure requires highly trained and dedicated interventional radiology and urology specialists. It is largely still considered experimental and further studies are encouraged. Aquablation (AQUABEAM System) has good comparable results to TURP and further evaluation and studies are awaited to evaluate its efficacy. Phase 3 randomized controlled trial of Aquablation versus TURP is in progress. Further evaluation of current minimally invasive treatment options for LUTS due to BPH in well-designed studies are desired, in order to further evaluate their role in the ever-evolving environment of male LUTS.

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