Evolving and investigational therapies for benign prostatic hyperplasia

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Introduction: *Lower urinary tract symptoms (LUTS) are common and are often caused by benign prostatic hyperplasia (BPH). Traditional surgical methods of open enucleation and transurethral resection of prostrate (TURP) have been efficacious in alleviating these symptoms however, these are operator dependent and often come with significant side effects. In this review, we will discuss upcoming new surgical techniques in management of BPH.*

Materials and methods: *A systematic search of SCOPUS, MEDLINE, EMBASE and Cochrane databases were carried out using relevant key words.*

Results: *Intra-prostatic injections with a variety of agents have been explored as these can be readily performed under local anesthesia. Alcohol injections into the prostate have been abandoned due to potential side effects but there has been ongoing development of two alternative agents, NX-1207 and PRX-302. Both have shown good safety profiles and early efficacy in phase II studies. Thermal treatment with the Rezum device performed as an outpatient procedure has shown both safety and efficacy in phase I and II studies. Aquablation shows promise in phase II studies with few side effects and is a relatively an automated procedure, albeit requiring general anesthesia. Prostate artery embolization has been reported in a number of studies, but clinical outcomes have been unpredictable. Histotripsy has had a number of complications in animal models and despite technical improvement has not yet progressed beyond feasibility studies in humans.*

Conclusions: *Some of the new techniques and technologies available for BPH have been shown to be relatively safe and efficacious and await validation with phase III studies.*

Key Words: benign prostatic hyperplasia, NOX, alcohol ablation, aquablation, Rezum, histotripsy, embolization

Introduction

Benign prostatic hyperplasia (BPH) of prostate may lead to bladder outflow obstruction and symptoms in older men.[1] Surgical interventions such as resection, enucleation and vaporization have led to reasonable long term outcomes with acceptable safety. Most of these techniques are operator dependent and success depends upon the extent of de-obstruction of the bladder outlet.[2] Although the development of new techniques has been reasonably successful, there is a continued desire to develop better techniques. The latest developments are focused on two principles: an office based procedure without the need for general anesthesia; and minimizing incontinence and sexual dysfunction related side effects while retaining satisfactory clinical efficacy. This has subsequently led to the investigation of even more minimally invasive therapies such as intra-prostatic injections, a variety of ablation techniques ranging from the use of high frequency ultrasound to water vapor, and mechanical interventions based on intra-urethral stenting.[3,4] The aim of this review is to evaluate evolving minimally invasive therapies for the treatment of lower urinary tract symptoms (LUTS) in which ongoing clinical trials show early promise, namely, intra-prostatic injections, alcohol ablation, aquablation, the Rezum device, prostatic artery embolization (PAE), and histotripsy.

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Intra-prostatic injections

Intra-prostatic injections have been used in the treatment of BPH for decades; however two drugs which have shown particular promise recently are NX-1207 and PRX-302. Administration of NX-1207 is guided by transrectal ultrasound, whilst PRX-302 is a transperineal or transrectal TRUS guided intra-prostatic injection, with a short course of pre and post procedure prophylactic antibiotics.[5,6] NX-1207 is a protein which reduces prostate volume at a cellular level by inducing apoptosis, the exact mechanism of which has not been published by its manufacturer, Nymox Pharmaceutical Corporation.[5,7] NX-1207 is currently undergoing phase III clinical trials but two phase II multicenter studies with 175 and 85 men (severe LUTS and prostate volume 30 mL-70 mL), have shown statistically significant improvements in American Urological Association Symptom Index (AUASI) scores and prostate volume.[5,8] Prostate volume reduction of 6.8 mL led to improvements in AUASI scores ranging from 9.4 to 11 points at 3 months to 6.5 years.[5] In addition, > 50% of participants in all phase I and II trials did not require any further surgical intervention for BPH at 5 year follow up. Minimal complications have been reported, limited to those universal to all transrectal procedures – mild hematuria, dysuria or infection – and no significant difference has been shown when compared to placebo or equivalent transrectal procedures. No sexual dysfunction or urinary incontinence has been reported.[5,7]

Similarly, PRX-302, also known as topsalysin, reduces prostate volume by inducing cell death. It is activated by enzymatically active prostate-specific antigen (PSA) within prostate tissue, and the subsequent formation of a transmembrane heptameric pore leads to apoptosis.[6] A small phase II study (18 patients) and a larger phase IIB study with 92 patients have been conducted.[6,9] In the phase IIB trial which was a placebo controlled study, men with severe IPSS and prostate volume 30 mL-100 mL were included.[6] Although no significant difference in prostate volume was noted, there was a significant decrease in IPSS by 9 points compared to 6 points in the vehicle group at 90 days. This difference however, was not statistically significant at 12 months. Complications were limited to both transient and at most, moderate severity such as dysuria, micturition urgency and/or frequency, perineal pain and mild hematuria.[6] Again, no sexual function-related side effects were reported and initial phase I and II studies showed no difference in erectile function scores at baseline and follow up at 12 months.[6,9]

The main benefit of PRX-302 and NX-1207 lies in the relative ease of performing the procedure which can be performed by most urologists without a need for special training or special equipment, and the lack of side effects.[5] NX-1207 seems to be favorable as an office based catheter free procedure, and the results from the ongoing two large phase III studies should provide answers for durability of efficacy.

Alcohol ablation, also known as transurethral ethanol ablation of the prostate (TEAP), refers to the use of a flexible injection needle to inject dehydrated ethanol into the prostate under direct visualization using cystourethroscopy, for chemoablation of prostatic tissue.[10,11] This short procedure, up to 25 minutes long, can be done either with a peri-prostatic block with oral or intravenous sedation, or under spinal anesthesia.[10-12] The first clinical study proposing the safe and effective use of TEAP in the treatment of BPH was published in 1999 by Goya et al, with statistically significant improvements in mean AUASI (12.2 from 23.1), IPSS (3.2 from 5.1), Qmax (13.1 from 8) and PVR (49.3 from 129.1) at 3 months follow up but with a sample size of only 10 patients.[13] The phase I/II clinical trial in 2007 was a multi-center randomized trial (n = 79) in the United States and used three different doses of anhydrous ethanol which all demonstrated statistically significant improvement across a range of clinical outcomes.[12] After 6 months of follow up, prostate volume dropped to 39.8 g from 46.1 g resulting in improvement in IPSS of 10.6.[8] In a smaller study (35 men) with 4 year follow up, IPSS remained significantly lower than pre-injection values, with prostate volume decreasing from 52.67 ± 20.43 to 49.94 ± 21.28 grams.[10] Nine out of these patients had another intervention with four requiring a TURP.[10] Additionally, complications reported include hematuria, dysuria, urinary retention, infections such as UTIs and epidymo-orchitis, urinary incontinence and urethral lacerations.[10-12] There have also been documented cases of erectile dysfunction and ejaculatory problems despite the avoidance of bladder neck injections to minimize the risk of retrograde ejaculation.[10,12] Major complications such as wide-spread bladder necrosis leading to cystectomy however have largely led to abandonment of ethanol as a viable and safe intra-prostatic agent.

Aquablation

Aquablation involves a transrectal ultrasound guided, robot assisted high-velocity saline stream (inserted via a resectoscope) to ablate glandular prostatic tissue whilst eliminating the formation of heat energy.[14] The capsular

tissue is spared and ablation is monitored endoscopically and under transrectal ultrasound guidance. In the initial canine survival study, superficial anticoagulation using a low power laser was also performed after ablation.[15] This canine study (n = 8) also confirmed Aquablation's rapid procedure time with mean ablation only taking 60.5 seconds, as well as its relative safety due to both the radiological and histological sparing of collagenous tissue such as blood vessels and the surgical capsule.[15] Although two of the dogs developed significant complications – bladder perforation – it was thought this was related specifically to canine anatomy.[15] Procedures in humans, done mostly under general anesthesia, have been found to take up to 12 minutes of ablation time and require catherization for 24 hours.[14] Phase I and II clinical studies, the largest of which used 21 patients, had an improvement of IPSS by 13-19 from baseline whilst the prostate volume reduction was 57 grams to 35 grams.[14] These results were still significant at 6 months. In addition, there were no complications in any of these clinical trials, including bleeding, clot retention, retrograde ejaculation, urinary incontinence or erectile dysfunction.

The efficacy and safety of the treatment is still to be validated in larger multi-center trials which are underway. The main advantage of this procedure is the non-dependence on the technical competency of the operator (though the operator is required to determine the limits of ablation through the Graphical User Interface), also the actual surgical time and efficiency is largely independent of prostate size.

The Rezum system

The Rezum system uses radiofrequency to create thermal energy in the form of water vapor to ablate prostatic tissue without the thermal gradient produced by other ablative procedures.[16,17] The water vapor delivery device is inserted trans-urethrally under cystoscopic guidance and can be performed under local anesthetic with a mean procedure time of only 8 minutes.[16,17] First-in-man and phase I clinical trials (n = 30) have shown significant improvements in IPSS (10.7 from 23 at baseline). This corresponded to a mean 26% reduction in total prostate volume at 3 months.[16] Similarly, a larger study of 44 men found reductions in prostate volume of 28.9% on Gadolinium-enhanced MRI at 6 months.[17] Adverse effects have been limited to transient urinary retention, mild dysuria and hematuria with no reported rectal injuries, urinary incontinence or sexual function-related side effects.[17]

The main advantage of this procedure is its ability to be performed as an outpatient under local anesthesia. The reduction in volume has been moderate although ongoing multi-center trials are currently underway to confirm longer term efficacy.

Prostatic artery embolization

Percutaneous transluminal prostatic artery embolization (PAE) has been proposed as a non-surgical alternative to the TURP.[18-20] Reduction of prostate volume in PAE is achieved by the injection of an embolic agent – usually ethanol based – into the prostatic artery as the name suggests, and can be performed with unilateral or bilateral artery occlusion.[18-21] This requires CT angiography prior to the procedure, a trained interventional radiologist and a mean procedure time of 2 hours.[19,21] Like several other minimally invasive therapies for BPH, the benefits of PAE include the avoidance of a general anesthetic and lack of hemorrhage during treatment.[19-21] The first published cases by Carnevale et al in 2010, involved two patients who showed clinically significant improvements following the novel use of PAE for acute retention secondary to BPH.[22] There were prostate volume reductions of 27.8% and 47.8% at 6 month follow up. A phase II trial (n = 11), which confirmed the technical success rates of 75% and clinical success rate of 91%, was performed.[22] Subsequent trials were even more favorable with technical success rates consistently greater than 90%, along with statistically significant improvements in clinical parameters at up to 30 months of follow up.[19,20,23-26] The largest prospective non-randomized study included 255 patients with a mean follow up of 10 months, and a success rate of 72% after 24 months.[23] The IPSS improved from 24 to 9.1 at 36 months, but no significant difference in prostate volume was noted at a similar time interval.[23] The prostate volume was not correlated to functional outcomes. Similarly, a systematic review of the clinical studies did not find differences in clinical outcome between unilateral and bilateral prostatic artery occlusion, or size of particles used.[19,20,23-26] Documented complications were largely transient, and included dysuria, hematuria, hematospermia, rectal bleeding, hematoma at the site of access, acute urinary retention and minor infections such as urinary tract infections, prostatitis and balanitis.[19-26] Significant complications were largely theoretical and were related to the risks associated with inadvertent or untargeted ischemia affecting the bladder, rectum, anus and/or corpus cavernosum; however in the systematic review referred to previously, six cases of bladder ischemia were reported, with four cases requiring minor surgery.[19] There are no documented cases of urinary incontinence or sexual dysfunction.

Despite technical success rates of at least 90% across all individual studies to date, a high clinical failure rate (n = 131, 19%) has been reported in the review performed by Schreuder et al, with an unspecified proportion requiring subsequent TURP or re-embolization, which is of some concern.[19] A large multi-center study is currently underway in the United Kingdom to compare the efficacy of PAE to TURP.[18,27] Even if efficacy is proven, it seems unlikely this technique can be up taken by smaller centers due to the need for access to a sub-specialized interventional radiologist.

Histotripsy

Histotripsy is the use of extracorporeal ultrasound energy to induce extreme pressure changes within tissue to create localized and oscillatory clusters of microbubbles which cause mechanical fractionation.[28] The violent collapse of these microbubble clusters then lead to cellular destruction, specifically the conversion of tissue into acellular liquid, a process known as cavitation.[28] The reason for histotripsy's growing popularity aside from its non-invasive nature and relatively short procedural duration, is its high precision/localization due to significant differences in echogenicity between microbubbles and fractionated tissue making it ideal for the use of real time ultrasound monitoring.[29] Canine models have shown promising results in reducing prostate volumes by 12%-22%.[28-34] Complications documented in order of incidence include mild to moderate hematuria without clot retention, perforated prostatic capsule and significantly less commonly; pelvic urinomata, superficial rectal erosions, recto-prostatic fistulae with associated abscess formation, peritonitis and urethral perforation.[28-34] Human clinical trials are underway with the Vortx Rx device however these are currently suspending participant recruitment for their pilot study due to poor enrolment.[35] Given the safety concerns seen in the animal models, it seems highly unlikely this technology will progress to use in a clinical setting in its current form.

Conclusion

Currently, there are several promising techniques for BPH on the horizon, Table 1. Techniques such as PAE which have been in development since the 1980's have made significant progress with the availability of better imaging equipment. Some are progressing to phase III studies, such as NX-1207, aquablation and

TABLE 1. **Summary of clinical trials on evolving techniques focusing on efficacy**

Technology	Largest series published	Longest follow up	Symptom score improvement	ΔQmax	ΔProstate volume	Re-intervention rates
Intra-prostatic NX-1207 injection	Phase II (n = 175)[5]	6.5 yr	Mean AUASI vs. baseline at 90 days (all doses) = ↓9.35	n/a	↓6.8 mL in transition zone	45%
Intra-prostatic PRX-302 injection	Phase IIB (n = 92)[6]	12 mo	IPSS NS vs. placebo at 12 mo	NS vs. placebo at 12 mo	NS vs. placebo at 6 mo	n/a
Intra-prostatic ethanol injection	Phase II (n = 79)[12]	4 yr	IPSS vs. baseline at 6 mo (lowest dose) = ↓10.6	↑3.2 mL/s at 6 mo	↓6.3 g at 6 mo	20%
Aquablation	Phase I (n = 21)[14]	12 mo	IPSS vs. baseline at 6 mo = ↓14.1	↑13.1 mL/s at 6 mo	↓22 g at 6 mo	n/a
The Rezum system	Phase I (n = 30)[16]	12 mo	IPSS vs. baseline at 12 mo = ↓12.3	↑4.1 mL/s at 12 mo	↓26% at 3 mo	n/a
Prostatic artery embolization	Phase II (n = 255)[23]	36 mo	IPSS vs. baseline at 36 mo = ↓15.0	↑4.7 mL/s at 24 mo	↓ 13.7% at 30 mo	19%

n/a = not available

PAE, whereas the future of histotripsy technology is in doubt. Pilot studies have found significant differences in symptom scores compared to baseline with these devices however, as investigators of PRX-302 discovered, the placebo effect can also be significant. Treatments, in comparison to a placebo arm, may not have a statistically significant benefit. There may be several new techniques available to the urologist within a decade, and ultimately the technique's success will continue to depend on patient selection and skill of the operator.

Disclosure

Dr. Shiva Madhwan Nair and Dr. Marie Adrianne Pimentel have no disclosures.
Dr. Peter J. Gilling is an investigator for PROCEPT BioRobotics. □

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