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Review Article

Minimally invasive surgical therapies for benign prostatic hypertrophy: The rise in minimally invasive surgical therapies



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ABSTRACT

The prevalence of benign prostatic hypertrophy (BPH) causing bothersome lower urinary tract symptoms increases with our ageing population. Treatment of BPH traditionally begins with medical therapy and surgical intervention is then considered for those whose symptoms progress despite treatment. Minimally invasive surgical therapies have been developed as an intermediary in the treatment of BPH with the aim of decreasing the invasiveness of interventions. These therapies also aim to reduce morbidity and dysfunction related to invasive surgical procedures.

Multiple treatment options exist in this group including mechanical and thermo-ablative strategies. Emerging therapies utilizing differing technologies range from the established to the experimental. We review the current literature related to these minimally invasive therapies and the evidence of their effectiveness in treating BPH.

The role of minimally invasive surgical therapies in the treatment of BPH is still yet to be strongly defined. Given the experimental nature of many of the modalities, further study is required prior to their recommendation as alternatives to invasive surgical therapy. More mature evidence is required for the analysis of durability of effect of these therapies to make robust conclusions of their effectiveness.

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1. Introduction

Benign prostatic hypertrophy (BPH) causing bothersome lower urinary tract symptoms (LUTS) becomes more common in men with advancing age, presenting a growing issue in our ageing population. Lifelong hormonal exposure to androgens is thought to cause an ongoing growth response in the prostatic glandular tissue leading to compression of the prostatic urethra with bladder outlet obstruction and LUTS. The management of men with bothersome LUTS may be initiated with conservative measures or medical therapies.¹ Despite this, many patients have symptomatic

progression that are refractory to these therapies and that necessitates surgical intervention. Invasive surgical therapies such as transurethral resection of the prostate (TURP) and simple prostatectomy are the current gold standard surgical interventions for BPH. However, these invasive procedures are also associated with considerable peri-operative morbidity.² Further, risks to continence and erectile function limit its widespread use. As such, a range of minimally invasive surgical therapies (MIST) have been developed aimed at achieving amelioration of a patient's LUTS and avoiding the risk of adverse outcomes associated with more invasive measures.

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Since its introduction, data from the USA identified an increasing proportion of MIST performed annually with a decrease in the rates of TURP.³ Considering that over this time period, procedures for BPH have risen overall, the epidemiology of MIST procedures is one of rapid expansion. The American Urological Association has incorporated a handful of these therapies into their guidelines for BPH management based on heterogeneous study outcomes,⁴ whereas the National Institute for Health and Care Excellence Guidelines do not recommend their use over TURP for men with voiding LUTS secondary to BPH.⁵

The improved morbidity and complication profiles associated with MIST are countered by their higher rate of clinical failure requiring secondary intervention and less dramatic improvement to LUTS and urine flow rates. While these therapies are well tolerated and able to be used in higher-risk surgical candidates, validation of their utility and durability of effect is an ongoing process. We aimed to provide an objective, updated review of the literature regarding various established and emerging MIST options. We aimed to assess the evidence base for the efficacy and safety of varieties of MIST and their appropriate use in patients with BPH.

2. Transurethral incision of the prostate

Transurethral incision of the prostate (TUIP) intends to produce improvements in urinary function by following similar methods to TURP. However, during TUIP, debulking of the prostate adenoma is not performed. Instead, either an electrocautery device or laser⁶ is used to incise the prostate tissue from the bladder neck down to the verumontanum. This incision allows the crowded circumferential band of hypertrophied tissue to separate and the bladder outlet is “opened up.” TUIP is typically recommended for men with smaller prostatic glands (<30 cc). The presence of a large median lobe is a relative contra-indication as this may cause ongoing blockage if incised. Bilateral TUIP may be performed but with greater risk of ejaculatory dysfunction compared with a single midline incision. TUIP gives superior outcomes for ejaculatory function when compared with TURP.⁷ Outcomes relating to International Prostate Symptom Score (IPSS) have been shown to be similar between TUIP and TURP but with decreased improvement in peak flow rates.⁸

3. Thermo-ablative strategies

Thermo-ablative strategies in the treatment of BPH rely on the generation and conductance of thermal energies into the prostatic tissues to induce a coagulative necrosis and ultimately tissue destruction. Their respective safety and limited morbidity compared to TURP have been demonstrated. However, like alternate MIST options, these factors are counteracted by their reduced impact on IPSS and patient function, as limited durability of symptomatic improvement exists. Therapies utilizing laser energy for destruction of prostate tissue such as Holmium laser or “greenlight” photoselective vaporization of the prostate are considered as invasive measures. However, these may be used to facilitate the process of some MIST options as seen in TUIP.

3.1. Transurethral microwave therapy

Transurethral microwave therapy (TUMT) utilizes microwave radiation heat generation to produce coagulative necrosis in prostatic tissue. This microwave radiation is distributed via an intraurethral antenna which, when correctly placed, can deliver heat to targeted regions of the prostate. TUMT has been shown to

improve symptoms and sustain this effect but remains inferior to TURP in its efficacy. Specifically, recent literature reports improvements in IPSS at 12-months follow-up of 65% and 77% after TUMT and TURP, respectively.⁹ Similarly, urinary flow rates following TUMT provided a 70% increase and TURP provided a 119% increase.^{9,10}

Despite these promising similarities in urinary outcomes, the durability of TUMT is under question due to the high proportions of patients requiring retreatment. Thalmann et al⁹ provided a robust analysis of 200 patients who had received TUMT with minimum 2 years' follow-up. In their cohort, 22% of patients required retreatment with either repeat TUMT, TURP, or suprapubic catheterization.

Nevertheless, the benefits of TUMT are diverse and include improved sexual function, less hospitalization, decreased hematuria, and lowered requirement for transfusion when compared with more invasive measures.¹¹ Of these, sexual function outcomes of TUMT are promising with reports of an incidence of retrograde ejaculation of 21.2% on pooled analysis.⁷ Being performed under local anesthesia, TUMT has also displayed its usefulness in cohorts of patients who are frail or unsuitable for surgery.¹²

3.2. Transurethral evaporation of the prostate

Transurethral electrovaporization of the prostate (TUVP) is a similar MIST that utilizes heat from monopolar or bipolar high-voltage electrical current, resulting in tissue ablation.¹³ TUVP has demonstrated symptomatic benefits comparable to conventional TURP. With use, TUVP affords significant reductions in IPSS and improvements in peak urine flow rate of approximately 10 mL/s; however, results were not so promising for a reduction in post-operative morbidity or shorter hospital stay.¹⁴

A recent randomized control study comparing bipolar TUVP to monopolar TURP found that both were effective in reducing patient's IPSS (49.7% and 70.6% at 6 months' follow-up for TUVP and TURP, respectively) and improving peak flow rates, but with more statistically significant results in the TURP group.¹⁵ Use of TUVP was also found to lead to a decreased duration of catheterization, improvements to postprocedure hematuria risk, decreased hematocrit drop, and fewer perioperative complications, but had higher rates of secondary intervention for clinical failure.¹⁶

The relatively recent development of continuous energy bipolar TUVP has displayed benefits when compared with conventional TUVP and monopolar TURP. These mainly relate to decreased operating time, lowered rates of postoperative hematuria, and length of catheterization period but also showed a decrease in perioperative complication rates.¹⁶

3.3. Transurethral needle ablation

Transurethral needle ablation of the prostate is achieved by the placement of two electrodes into the target prostatic tissue and the creation of a radiofrequency signal between them. This results in thermal energy creation and ablation of tissues through coagulative necrosis.

Several randomized trials have been performed with only short-to-midterm follow-up available to date. As with other forms of MIST, concerns regarding durability are present. A 5-year follow-up demonstrated that 58% of patients had maintained symptom control; however, 21% needed retreatment.¹⁴ Meta-analytical data confirms an improved IPSS and urinary flow rate at 1 year; however, to a significantly lower magnitude when compared with TURP.¹⁷ Similar to TUMT and TUVT, transurethral needle ablation has a favorable morbidity profile when compared with TURP.

4. Mechanical

4.1. Urolift

Urolift (Urolift®, Neotract Inc., Pleasanton, CA, USA) or prostatic urethral lift (PUL) is a novel technique in the management of LUTS secondary to BPH that may be performed in the outpatient setting under local anesthesia. It is characterized by the placement of multiple nonabsorbable monofilament sutures into the prostatic urethra through to the lateral lobes and while kept under traction, establishes a large caliber urethral channel. Jones et al¹⁸ undertook a recent systematic review which included a total of 440 patients from seven series. The outcomes compared included peak urine flow rates, PVR, IPSS scores, and five-item version of the International Index of Erectile Function scores as their primary measures. Patients demonstrated an improvement to their mean peak urine flow rates from 8.4 mL/s to 11.3 mL/s with use of Urolift and a PVR mean decreased from 93 mL/s pre- to 84.7 mL/s postprocedure. The mean IPSS scores improved from 24.1 to 14 postprocedure. The five-item version of the International Index of Erectile Function scores remained stable, changing from 17.7 to 18.2 postprocedure. Ruktalis et al,¹⁹ published results of a blinded study where patients underwent a sham procedure then PUL 3 months later to assess the effectiveness of the PUL on IPSS, peak urine flow rates, at 24-months post-PUL. Their findings were consistent with previous studies,^{18,20,21} with IPSS scores decreasing by 9.6 points at 24 months, and peak urine flow rates increasing by 4.2 mL/s when compared with presham baseline. Sexual function and ejaculatory function were preserved in each of these studies, which may be an important consideration for patients being treated for their LUTS. Longer term follow-up for robust durability data is currently being collated.²²

4.2. Intraprostatic stents

With use of intraprostatic stenting, the transurethral approach is utilized to identify the point of maximal obstruction and a stent or coil is positioned under endoscopic vision. A variety of stent types are available ranging from temporary biodegradable options to permanent stents. Yildiz et al²³ have reported on 1-year follow-up data from 51 patients using the Allium Triangular Prostatic Stent (Allium Medical Solutions, Caesarea Industrial Park South, Israel). At 12-month follow-up; patients in this group experienced a mean decrease in IPSS scores from 26.4 to 7.7 and an average increase in peak urine flow rates from 5.5 mL/s to 16.0 mL/s. Two patients required removal of the stent due to significant complications (Clavien Grade 3). The most common reported complication was stent-related pain; however, this was intermittent and no patient required removal of the stent secondary to pain issues.²³ Despite the short-term improvement to symptoms, prostatic stents are characterized with potentially significant morbidity including stent migration and recurrent infection. Relatively higher complication rates associated with their use limit their utility as a long-term durable option in BPH management. Further large-scale studies are required to definitively establish the efficacy of these stents.^{24–26}

4.3. Intraprostatic injections (transurethral ethanol ablation of the prostate, PRX-302, NX-1207, botulinum toxin A)

A variety of pharmaceutical or chemical compounds have been investigated for use in intraprostatic injection and may be delivered via the transrectal, transperineal, or transurethral approach. These compounds are injected deep into the prostate to elicit either a chemical irritant response or initiate cellular apoptotic pathways that results in ablation of prostatic tissue.

Transurethral ethanol ablation of the prostate is one such method involving injection of pure ethanol. The largest cohort of patients reported in a multicenter, prospective trial showed improvement of both IPSS and quality of life scores (reduced by more than 50%) and improvement to peak flow by 36% at 3-months' postprocedure. These results were sustained to 1-year post-procedure.²⁷ A separate study with a 4-yr follow-up period suggested a sustained response in 73% of patients with the remaining 23% requiring retreatment.²⁸ There is a need for further evaluation with comparative data to further quantify the value of transurethral ethanol ablation of the prostate.

Agents that induce cellular apoptosis include NX-1207 (Nymox Pharmaceutical Corp, Hasbrouck Heights, NJ, USA) and PRX-302 (Sophiris Bio Corp, La Jolla, CA, USA) and have been designed for minimally invasive injections. NX-1207 has been shown to be safe for use in BPH with sustained reductions in symptom scores over long-term follow-up.²⁹ In this phase II trial, over half of the NX-1207 treated participants reported no further surgical intervention or medication requirements for their BPH.²⁹ Further phase II and III trials are underway to confirm the validity of these promising findings. Despite this, NX-1207 remains as experimental.

PRX302 is a compound, designed to promote apoptotic activity specifically in native prostate tissue. This protoxin has been altered to include a prostate-specific antigen selective sequence that activates following interaction with active prostate-specific antigen within the prostatic tissue. Initial studies investigating the safety and efficacy of PRX-302 revealed some benefit to symptoms scores and peak flow at the 12-month follow-up.³⁰ These findings were corroborated in a larger double blind, randomized control trial which found statistically significant improvement to IPSS after 90 days with some reduction of effect at 12 months.³¹

Botulinum neurotoxin-A (BoNT-A) is thought to modulate neurotransmitter activity at the neuromuscular junction. It has been utilized in other functional aspects of urology such as over-active bladder and proven safe for clinical use. Use of BoNT-A for BPH LUTS in clinical trials has shown a mixed pattern of results. Urodynamic effects investigated by de Kort et al³² showed benefit to postvoid residual volumes and symptom scores but no effect on urodynamic outcomes including peak flow. Two randomized controlled studies have been performed to investigate BoNT-A with heterogenous results. Maria et al³³ displayed improvement to postvoid residual volumes by 60% ($P < 0.0001$) and increased peak flow rates from 8.1 mL/s to 14.9 mL/s ($P = 0.00006$), which were sustained to the 12-month follow-up. Conversely, a study by Marberger et al³⁴ with the largest cohort of men treated with BoNT-A, reported nonsignificant improvements in both the control and treatment groups. Indeed, the role of BoNT-A in the treatment of LUTS is yet to be determined and requires further investigation. The National Institute for Health and Care Excellence guidelines suggest that treatment with BoNT-A only occur as part of a randomized control trial.⁵

5. Emerging MIST options

5.1. Aquablation

Aquablation (AquaBeam®, Procept BioRobotics, Redwood Shores, CA, USA) is novel technique for the treatment of LUTS secondary to BPH. It involves robotic-assisted hydrodissection of prostatic tissue with high velocity saline under transrectal ultrasound guidance. The procedure requires no heat unless electrocautery is required post-Aquablation for hemostasis. Gilling et al³⁵ published follow-up data at 6-months' post-Aquablation showing a reduction in mean IPSS Scores from 23.1 to 8.6,

mean Qmax increased from 8.6 mL/s to 18.6 mL/s, mean PVR decreased from 91 mL/s to 30 mL/s, and mean quality of life score decreased from 5.0 to 2.5. Currently, phase III clinical trials are underway comparing Aquablation to TURP, the current gold standard for treatment of BPH.³⁶

5.2. Prostatic artery embolization

Prostatic artery embolization (PAE) is a procedure performed under radiological guidance and involves highly selective injection into the prostatic arteries. Either unilateral or bilateral prostatic artery injection is performed with an embolic agent, most commonly which is typically nonspherical, polyvinyl alcohol based. Contemporary literature highlights considerable failure rates as high as 19%³⁷ with 15% of patients requiring TURP within the 1st year after treatment. Uptake may have been limited due to these factors and availability of specialist interventional radiologists required to perform the procedure. However, increasing experience with PAE has led to improved procedural success rates. PAE has gained interest recently with further studies showing acceptable outcomes in IPSS scores at 24-months' postintervention. Despite this, TURP results in significantly better ($P = 0.029$) outcomes in IPSS scores and quality of life scores at 1-months' and 3-months' postprocedure.³⁸ Another large prospective series by Pisco et al³⁹ reported a 63% reduction in IPSS at 36-months' follow-up with PAE.

Complications of PAE are not insignificant and include failure of the procedure, dysuria, hematuria, hematospermia, rectal bleeding, and urinary retention. Although rare, risks of inadvertent embolization and untargeted ischemia of the bladder, corpus cavernosum, or anus do exist and pose a significant compromise to patient outcomes. A recent meta-analysis identified six cases of bladder ischemia.³⁷ More long-term data is necessary to define the safety and feasibility of PAE.

5.3. Rezum

Rezum (NxThera, Inc., Maple Grove, MN, USA) is a thermo-ablative strategy that relies on water vapor to deliver energy. This system allows convective thermal energy to travel through the interstitium of the transition zone of the prostate, disrupting cell membranes, and causing instant cell death and necrosis. The vapor is delivered transurethrally during cystoscopy, frequently performed under local anaesthetic in the outpatient setting. The Rezum system also works without creating a discernable thermal gradient, reducing the risk of injury to surrounding tissues by dissipated heat.

A recent multicenter RCT reviewed the outcomes of Rezum compared with controls and displayed significant results in the reduction of IPSS ($P < 0.0001$) with sustainable results of 50% or more at 12-months' follow-up.⁴⁰ Peak flow rates in this group were increased by 6.2 mL/s at 3 months and were sustained at 12 months. Rezum also provides a relatively low risk of compromising sexual function.⁴¹

5.4. Histotripsy

Histotripsy is a relatively modern application of high intensity ultrasound technology that is used to create negative pressure changes in tissue. This causes fluid in the tissues to vaporize and release highly energetic gaseous microbubbles that cause disruption to integral cellular structures ultimately leading to tissue destruction. The resulting tissues are homogenized and display a liquefied core of cytoplasm and cellular debris.⁴² This technique has been used to create a cavitation effect in the prostate gland in a real time setting. Studies to date have been limited to canine models but have been promising in the cavitation effect resulting from histotripsy.⁴³ These models have also shown promise in preserving vital structures surrounding the prostate and of the prostatic urethra.⁴⁴

Table 1
Types of minimally invasive surgical therapies (MIST) and factors specific to each type

Type of MIST	Prostate size	Anesthetic	Relative contraindications
Transurethral incision of prostate	<30 cc	Local ± sedation ± regional anesthesia	• Large median lobe • Prostate size <30 mL
Transurethral microwave therapy	<100 mL	Local ± sedation	• Urethral stricture • History of prostate or bladder cancer • Neurogenic bladder
Transurethral evaporation of the prostate	—	Local anesthesia and sedation	• History of prostate or bladder cancer • History of bladder outlet surgery • Neurogenic bladder
Transurethral needle ablation	—	Sedation ± regional anesthesia	• Urethral strictures • Prostate cancer • Neurogenic bladder
Urolift or prostatic urethral lift	<100 cc	Local anesthesia and sedation	• Renal insufficiency • Previous prostate surgery • Large median lobe • Acute urinary tract Infection • Cystolithiasis
Intraprostatic stents	<100 cc	Local or regional anesthesia	• Penile or artificial urinary sphincters • Acute urinary tract infection
Intraprostatic injections	—	Local anesthesia and sedation	• Urethral stricture • Neurogenic bladder
Aquablation	—	General anesthesia (in trial currently)	• History of prostate or bladder cancer • Urinary retention history
Prostatic artery embolization	>30 cc	Local anesthesia and sedation	• Neurogenic bladder • Urethral stricture • Coagulation disorders • Presence of prostate cancer

Initiation of human pilot trials are on in progress and are sure to add valuable information to this experimental entity.⁴³

5.5. Recommendations and summary

The rise in MIST procedures represents a paradigm shift in the treatment of BPH. The aim of achieving a personalized medicine approach has led to the use of these “middle-ground” therapies that lie between medical therapy and invasive surgical intervention. The MIST group is varied and continually growing in its range of options based on patient and pathological factors (Table 1). As the evidence for their utility is gathered, many of the MIST options remain experimental or without a robust evidence base. MIST should be used in a select patient group, particularly those that place importance on preserved sexual and continence function rather than urinary improvement. More mature data will help to identify the role of MIST in the evolving treatment pathway of BPH.

Conflicts of interest

The authors declare no competing interests.

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