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BENIGN PROSTATIC HYPERPLASIA (K MCVARY, SECTION EDITOR)

Comparing Outcomes of Medical Management and Minimally Invasive Surgical Techniques for Lower Urinary Tract Symptoms due to BPH

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Abstract

Purpose of Review Compare outcomes of medical therapy as compared to minimally invasive surgical therapy (MIST) for treatment of bladder outlet obstruction

Recent Findings Treatment for lower urinary tract symptoms due to benign prostatic hyperplasia (LUTS/BPH) remains largely driven by patient symptomatology with medical therapy or watchful waiting as the first-line management strategies. However, most patients are not adherent to prescribed medical therapies and are hesitant to accept the risks associated with more invasive therapies. Minimally invasive surgical therapies are treatments providing short-term symptom relief superior to medical therapies without the sequela of more invasive procedures.

Summary Though there are few direct comparisons, MIST seems to relieve LUTS/BPH symptoms at least as well as medical therapy without the need for daily adherence.

Keywords LUTS · BPH · MIST · Bladder outlet obstruction

Introduction

Benign prostatic hypertension (BPH) is defined as a histopathological change consisting of both glandular and fibromuscular hyperplasia. It is estimated that 10% of men in their 50s and almost 90% of men over 80 have BPH [1]. BPH is often used as a shorthand to describe men with obstructive voiding symptoms, and the presence of BPH does not necessarily indicate that bladder outlet obstruction (BOO) or lower urinary tract symptoms (LUTS) are present [2]. BPH, BOO, and LUTS are different entities which can exist independently of one another, but often coexist as a symphony of causes and effects. LUTS can be divided into three categories: storage symptoms, voiding symptom, and post-micturition events. Storage symptoms can also be secondary to overactive bladder syndrome (OAB), a result of intrinsic bladder dysfunction, which occurs in 12–15% of men [1]. Detrusor dysfunction during the bladder filling phase is seen in nearly 50% of men with LUTS [3, 4]. Urinary symptoms are frequently what brings a patient in to see their physician. LUTS are the primary complaint in approximately 7% of all doctor visits and cited as a complaint in 14% of visits [5]. LUTS affect one-third of men over 55 and half of men over 65 and while LUTS due to BPH (LUTS/BPH) are generally thought of as a disease of older men the costs of treating this disease start accruing when patients are in their 40s.

The incremental annual financial burden of a diagnosis of LUTS/BPH is approximately $1500, and the total estimated cost of treating BPH is estimated around $4 billion annually in the USA, a number that is set to increase with an aging population. An analysis of the 12.2 million BPH patients shows 54.8% are managed medically, 35% are observed, another 9.1% have discontinued medical management, and 1% are treated surgically [1]. Compliance rates after 1 year in patients medically managed are exceedingly low. Cindolo et al. found

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that in Italian men who were started on long-term medical therapies, the percentage of patients that continued to fill their prescriptions after 1 year were 35%, 18%, and 9% for alpha-blockers, 5-alpha reductase inhibitors (5ARIs), and combination therapy, respectively [6]. Unwanted sexual side effects and unrealistic patient expectations are the most likely reasons for discontinuing medical therapies [6]. Patients often associate a lack of improvement with an indication to stop treatment and it can be difficult to properly council a patient that preventing progression of symptoms is a benefit. BPH is a progressive disease and observation can result in deterioration of symptoms, hospitalization, and potentially irreversible bladder damage, within 5 years [7].

Minimally invasive surgical therapies (MISTs) are procedures that can be completed in a single session under local sedation. They provide more pronounced short-term benefits compared to medical therapies without the negative sexual side effects and prolonged recovery of traditional definitive surgical interventions. The number and variety of MISTs is rapidly growing and evolving. The purpose of this study is to review contemporary medical and MIST BPH treatments with an emphasis on effectiveness, place in current treatment paradigms, and potential impact on those norms.

Medical Management

Medical therapy is the first-line treatment for patients with LUTS/BPH. The goal of medical management is to alleviate symptoms, improve quality of life (QoL), and prevent sequelae, but medications can have many side effects and require daily, continuous treatment [8]. There are three main pharmacologic classes used to treat LUTS/BPH, which can be used alone or in combination depending on the patient: alpha-adrenergic receptor blockers, 5ARIs, and antimuscarinic agents [8]. All medical therapies can reduce symptoms and improve QoL but only 5ARIs and combination therapies have been shown to halt disease progression.

Alpha-Blockers

Alpha-blockers are a drug class that inhibits the alpha-1a receptors, resulting in the relaxation of smooth muscle both within the bladder neck and the prostate itself. This increases the diameter of the previously tightened urinary channel and reduces the amount of pressure the bladder needs to generate to evacuate urine. Studies have shown that alpha-blockers reduce symptoms by 30–40% and increase flow rates by 16–25% [9]. However, one-third of men will experience no symptomatic relief and the treatment approach should be adjusted after 8 weeks without improvement [2]. All approved medications in this class are similar in terms of their efficacy but differ in their side effect profiles. Alfuzosin and tamsulosin are very well tolerated, while doxazosin and prazosin result in orthostatic hypotension, dizziness, and weakness in 5–10% of patients [9]. Alpha-blockers start to work almost immediately; however, their maximum efficacy takes a few weeks to achieve.

5-Alpha Reductase Inhibitors

The prostate grows under the influence of dihydrotestosterone (DHT) which is converted from testosterone via the 5-alpha reductase enzyme. 5ARIs prevent this conversion and thus can impede prostatic tissue growth and tip the balance in favor of apoptosis resulting in prostate size reduction, which has been shown to decrease disease progression [10–12]. The PLESS study showed patients taking 5ARIs experienced significant improvement in AUA-SS compared to placebo [13]. There are currently two drugs on the market, dutasteride and finasteride. Both drugs have side effect profiles consistent with androgen deficiency: erectile dysfunction, ejaculatory dysfunction, and decreased libido. PSA levels will also be artificially decreased by approximately 50% and a baseline PSA level should be checked prior to starting 5ARI treatment [2]. Symptomatic improvement, which is the result of a physical reduction in prostate size, can take anywhere from 6 months to 1 year.

Antimuscarinic Agents

Kaplan et al. in a randomized controlled trial showed that an antimuscarinic agent (tolterodine) significantly improved patient QoL scores when added to an alpha-blocker in patients who reported OAB symptoms [14]. A total of 879 patients were randomized to one of four arms: tolterodine and an alpha-blocker, tolterodine alone, an alpha-blocker alone, or placebo. Eighty percent of the patients in the combo therapy arm reported experiencing benefits by 12 weeks and compared with the placebo arm experienced significant reductions in urgency urinary incontinence (-0.88 vs -0.31, $P = .005$), urgency episodes without incontinence (-3.33 vs -2.54, $P = .03$), micturitions per 24 h (-2.54 vs -1.41, $P < .001$), and micturitions per night (-0.59 vs -0.39, $P = .02$) [14]. Side effects most commonly include dry mouth and constipation [4]. A newer OAB medication mirabegron, a beta-3 agonist, has been approved for use but studies evaluating its use in men with BPH are limited. Otsuki et al. demonstrated improvement in International Prostate Symptom Score (IPSS) and OAB symptom score after 8 weeks of treatment in 85% of patients who were newly diagnosed with OAB and 61.6% of patients who were previously unresponsive to antimuscarinics. There was no difference in improvement or adverse events between the mirabegron group and control group, newly diagnosed patients who were given an antimuscarinic medication [15]. This is the first drug in its class and has been shown to have a significant impact on OAB symptoms with fewer anticholinergic side effects, making this medication safer for elderly patients [16].

Combination Therapies

The combination of alpha-blockers and 5ARIs or antimuscarinic agents has been shown to have added benefit over each treatment alone in correctly selected patient populations. The MTOPS trial showed that a combination of doxazosin and finasteride resulted in a 66% decreased risk of clinical progression of BPH compared to placebo or either medication alone [13]. The COMBAT trial also showed significant reduction in IPSS scores of patients taking tamsulosin and finasteride compared to either medication alone [17]. Kaplan et al. showed that adding an antimuscarinic agent (tolterodine) to an a1-blocker significantly improved patient QoL scores compared with placebo or either medications alone [14]. There have been no reports of synergistic effects of combination therapy resulting in worse side effect profiles than either medication alone. Yet, adherence rates for combination therapy are significantly worse than monotherapy regimens [6]. One theory for this observation is the added complexity of taking multiple medications. The strategy of increasing compliance by decreasing the number of medications is well established in other medical fields [18]. Early reports with Duodart, a fixed-dose combination pill, have shown increased compliance rates compared with those historically reported for patients on combination therapy [19].

PDE5I

Recently, phosphodiesterase 5 inhibitors (PDE5Is) were added to the pharmacologic armamentarium to combat BPH. These medications will not reduce the prostate size and the exact mechanism of action on LUTS has yet to have been elucidated, but several randomized control trials have been published showing PDE5Is are an effective treatment for LUTS with the added benefit of also addressing ED. In Porst et al., patients were randomized to tadalafil or placebo and after 12 weeks patients in the tadalafil arm report greater reductions in IPSS (− 5.6) and improvement in erectile function score (6.7) compared with placebo [20]. Oelke et al. randomized 511 patients to placebo, tadalafil, and tamsulosin arms. After 12 weeks, IPSS improvement between tamsulosin and tadalafil was similar and greater in both than the placebo arm. Only the tadalafil arm saw any improvement in the IIEF score [21]. Another study found the combination of PDE5Is and 5ARIs to be associated with improvement of BPH-LUTS, regardless of preexisting ED symptoms [22]. Meta-analysis of the use of PDE5Is alone was associated with a significant improvement of IPSS compared with placebo [23]. The AUA BPH guidelines do not mention PDE5I but the European Association of Urology guidelines from 2014 recommend PDE5I with or without an alpha-blocker for the management of non-neurogenic LUTS regardless of the presence of ED [24]. Common side effects of PDE5Is include headache, back pain, facial flushing, and dyspepsia. These medications are contraindicated in patients who are on nitrates for angina or hypertension due to risk of subsequent hypotension.

Minimally Invasive Surgical Therapies

Transurethral resection of the prostate (TURP) remains the gold standard for definitive BPH treatment. However, as the mean age, comorbidities, and complexity of the treatment population all continue to rise, there is a growing need for definitive treatments which can be performed in an office setting or in patients who cannot stop anticoagulation therapies. Patients are also looking for treatments that can prevent disease progression without the sexual side effects and incontinence risk of more invasive surgery.

High-Energy Transurethral Microwave Treatment

High-energy transurethral microwave treatment (HE-TUMT) was first proposed in the 1990s as a method to induce tissue necrosis in a specifically targeted region of the prostate. This technology was not initially embraced because the high-intensity energy required to achieve the desired tissue loss was liable to cause urethral and rectal injuries. Lower intensity models required multiple treatments for symptomatic improvements that were worse than TURP. Newer technological developments allow the safe delivery of high-intensity treatment. A 2008 meta-analysis of studies comparing TUMT to TURP found that TURP produced greater changes in Qmax, PVR, and IPSS, but stratified data showed newer models came close to approximating objective TURP results [25]. Wagrell et al. found no significant difference in QoL score or Qmax between patients treated with TURP and TUMT after 3 years, though the TURP group did have significant improvement in IPSS [26]. In the 5-year follow-up, the TUMT group had a 10% retreatment rate, compared with a 4.3% retreatment rate in the TURP group [27]. Dajvan et al. compared patients treated with TUMT and alpha-blockers. That trial found the TUMT arm demonstrated better improvements in objective outcomes. After 6 months, 78.4%, 64.7%, and 84.3% of patients in the TUMT arm reported greater than 50% improvement in IPSS, Qmax, and QoL, compared with 32.7%, 9.6%, and 40% of the alpha-blocker arm [28]. Since its introduction, TUMT has fallen out of favor due to high retreatment rates but remains a viable option in very select patients.

Prostatic Urethral Lift

Prostatic urethral lift (Urolift) is a MIST that reshapes the prostate by physically retracting the lateral lobes and expanding the urethral diameter, thereby decreasing the outflow resistance. To achieve this goal, a cystoscopy is performed with a customized handpiece that allows prostatic placement of monofilament

sutures with anchors on either end to tent open the lateral aspects of the prostatic urethra. Several studies have reported IPSS improvements over 50%, and in a prospective, sham-controlled trial, the mean decrease in IPSS was 11 points [29]. The L.I.F.T. study is a multi-center randomized blinded trial, where patients were randomized 2:1 to undergo Urolift or a sham operation. At 3 months, patients in the experimental arm were reporting reductions in IPSS 90% greater than the sham procedure. After 3 years, average improvements were statistically significant for total IPSS reduction (41%), QoL improvement (49%), and Qmax (51%) [30]. However, the improvement is less than that reported in the literature with conventional TURP and laser debulking technologies. The 5-year data show a 13.6% surgical retreatment rate with an additional 10.7% of subjects taking alpha-blockers or 5ARIs [31•]. One advantage of Urolift over traditional interventions is the ability to improve LUTS while preserving erectile and ejaculatory function, though currently a major limitation is the inability to perform the procedure in prostates with an enlarged median lobe [32]. Current ongoing clinical trials are evaluating the possibility of being performed under local anesthesia and efficacy of the procedure in patients with a prostatic median lobe.

Water Vapor Energy

Radiofrequency water vapor thermal ablation of the prostate (Rezum) utilizes a modified cystoscope to administer bursts of steam into the transition zone of the prostate. The high-temperature steam causes convective heating of treated tissue, which rapidly and evenly elevates the tissue temperature throughout the treated area, resulting in cell death and tissue destruction. The Rezum II trial enrolled men 50 years old or older with an International Prostate Symptom Score of 13 or greater, maximum flow rate of 15 ml/s or less, and prostate size of 30 to 80 cc randomized 2:1 between thermal therapy with the Rezum System and sham surgery control arm. The trial showed a decreased IPSS of 11.2 after 3 months compared with a decrease of 4.4 in the control group—an improvement that was sustained at 1 year [33]. Adverse events were mild to moderate and resolved quickly. A total of 32% of patients at 3 months and 27% at 1 year, including those with moderate to severe erectile dysfunction, reported clinically significant improvement in erectile function [34]. MRI studies have confirmed whole prostate volume decreases of 29% and transition zone volume decreases of 38% 3 months after treatment [35, 36]. These improvements in IPSS, QoL, and Qmax were sustained through a 3-year follow-up without any incidence of late adverse events or de novo ED [37].

Intraprostatic Injections

Currently, there are several prostate injection therapies that are under development and initial clinical testing. So far, the only agent which has yielded positive results is PRX302, topsalysin, which is a protein that induces apoptosis by creating a pore in the cellular membrane. This protein is specifically modified so that it is only enzymatically activated by PSA, ensuring the apoptotic effect is confined to the prostate. The protein is delivered via transperineal injection to sites within the transition zone. Results of a phase 3 "PLUS-1" study (clinicaltrials.gov identifier: NCT01966614) demonstrated a statistically significant IPSS improvement over 12 months after a single dose. Patients reported an improvement of 7.6 compared to 6.58 ($P = 0.04$) in the vehicle-only arm. Adverse events were the same between the two groups and all resolved without consequences. Treatment demonstrated significant symptomatic improvement, average IPSS reduction was 9, and increase in Qmax was 3 mL/s [38, 39]. Both measures are better than typical improvement seen with a single oral agent with the added benefit of no sexual side effects.

Comparing MIST and Medication

To date, there are no studies directly comparing the efficacy or economic impact of medical management of BPH and minimally invasive non-surgical treatments. Nickel et al. explained that a cost/QALY (quality-adjusted life year) less than $20,000 was strong evidence to adopt a therapy, cost/QALY between $20,000 and $100,000 was provided moderate support for a therapy, and anything greater than $100,000 was weak support for the therapy [40]. The cost utility of pharmacologic monotherapy ranged from ~$35,000/QALY to ~$45,000/QALY, while the cost utility of a combined pharmacologic therapy ranged from ~$28,000/QALY to ~$34,000/QALY. A combination therapy is more expensive but also provides a greater clinical efficacy [41, 42]. The estimated direct cost of pharmacologic monotherapy to treat BPH ranges from $1333 to $1566 annually. If the patient needed a combination pharmaceutical regimen, the annual cost could be as much as $2843 [43]. This does not include any ancillary costs of complications of medical management or hospital costs incurred after failed medical management. To our knowledge, no such analysis has been performed for any MIST.

While no study has directly compared MIST to medical management, mathematical modeling can give comparisons across numerous studies. Ulchaker et al. examined 40 peer-reviewed publications from 2000 to 2017 to determine average IPSS improvement and cost effectiveness of medical and surgical therapy for LUTS/BPH over 2 years. Cost effectiveness was defined as the difference in average treatment cost divided by the difference in IPSS improvement; in other words, the cost of each additional point decreases in the IPSS. A treatment that is both more effective and less costly than another is defined as dominant [44•]. The study found the generic combination medical therapy the least expensive and

least effective treatment, with patients only reporting a 3-point IPSS improvement. TUNA and water vapor energy (WaVE) treatments were similar in overall cost and both reduced IPSS by 11 or 12 points. Urolift was shown to provide similar reductions in IPSS but with a cost that is $3500 higher than Rezum over 2 years. Photovaporization of the prostate (PVP) and TURP offered the largest improvement, an average IPSS reduction of 16 points, for the highest cost. Compared to Rezum, patients undergoing TURP or PVP pay an extra $686 for each additional point reduction in IPSS [44•].

Another method that has been used to compare medical and minimally invasive therapies is to compare published long-term outcomes. The MTOPS trial has been used as a benchmark for HE-TUMT and Rezum. Lerner et al. pooled outcomes and costs data on HE-TUMT from seven studies across 25 treatment centers. HE-TUMT had significant improvement in voiding symptoms and QoL compared to all MTOPS arms at 2 years [45]. At 4 years, all therapies had similar IPSS improvements, but the 4-year cost of HE-TUMT was $3620, compared with $7200 for 4 years of medical therapy [45]. Gupta et al. used a similar method to compare Rezum to medical treatments. Evaluation was restricted to patients in the MTOPS trial with a prostate volume 30–80 g, which was 37.4% of the original cohort. Outcomes were compared at 3 and 6 months, and 1, 2, and 3 years for symptomatic changes and rates of clinical progression. Rezum was far superior with respect to preventing clinical progression. Rate of progression among patients treated pharmacologically was 1.5 to 1.7 per 100 person-years compared with 0.3 for Rezum [46•]. A single treatment with Rezum has better symptomatic improvement after 12 months with durable improvement through 36 months, is superior to medical monotherapy with either alpha-blockers or 5ARIs, and has similar 36-month symptom improvement compared to combination medical therapy [46•].

A major consideration when comparing medical therapy with MIST for LUTS/BPH is adverse effects, especially sexual side effects. To date, there is no published direct comparison of sexual side effects between medical therapy and MISTs, though generally medical therapy seems to have a small risk of erectile and ejaculatory dysfunction while MISTs largely preserve these functions.

Conclusion

Despite its name, BPH is not a benign disease and does have serious long-term sequela for patients who are not treated or those who are improperly treated. Lifelong medical management is the accepted first-line therapy for patients with LUTS/BPH. However, several MISTs have been shown to have symptomatic improvement equal to if not better than medical management without some of the negative side effects associated with medical management, TURP, or PVP, though long-term durability of MISTs remains to be proven. These treatments have a greater initial cost compared to medical therapy but when compared to the cost of several years of medical therapy these MISTs are more cost effective. Thus, MISTs may be an appropriate first-line treatment for many properly selected men with bothersome LUTS/BPH.

Compliance with Ethical Standards

Conflict of Interest Joshua Sterling and Nicholas Farber each declare no potential conflicts of interest.

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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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