

Impact of Treatment of Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia in Ageing Men

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ABSTRACT

Lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) are common and significant causes of morbidity in ageing men. Historically, transurethral resection of the prostate has been the standard treatment and provided the most effective solution for LUTS/BPH. The α -adrenoceptor antagonists are documented to be beneficial for treatment of benign prostatic obstruction, to improve quality of life and to reduce the necessity for surgical intervention. 5α -reductase inhibitors are also well-established effective agents to relieve LUTS/BPH, to shrink the prostate volume and to resolve prostate-related bleeding. However, an overactive bladder, which is characterized by urge, frequency, urge incontinence and nocturia, might persist even after the surgical removal of the obstruction. Many studies have confirmed the effectiveness of antimuscarinic agents on an overactive bladder. The link between LUTS and erectile dysfunction has been emphasized by epidemiology and pathophysiology in recent years. Successful treatment of BPH/LUTS is suggested to have advantages for improving quality of life and sexual function. On the other hand, some evidence indicates that phosphodiesterase-5 inhibitors have beneficial effect on LUTS. In this review, we discuss the influence of these treatment modalities on LUTS/BPH in ageing men.

Key words: benign prostatic hyperplasia, lower urinary tract symptoms, overactive bladder, antimuscarinics, quality of life

INTRODUCTION

Lower urinary tract symptoms suggestive of benign prostatic hyperplasia (BPH/LUTS) are common in older man and the prevalence increases with age. Enlargement of the prostate may lead to bladder neck obstruction, which could produce LUTS or complications such as urinary tract infection, bladder calculi, acute urinary retention and renal failure. Transurethral resection of the prostate was the treatment choice before the 1990s but several adverse events, such as retrograde ejaculation and so on, may cause complications. Over the past decade, investigations into medical therapy have documented the benefits of α -blockers and 5α -reductase inhibitors for men with BPH [1,2]. In recent years, many studies have focused on the detrusor overactivity (DO) related to BPH, which results in urinary frequency, urgency and incontinence. The mechanism and efficacy of antimuscarinic agents have also been extensively studied [3,4]. Ad-

verse effects from medical therapy for BPH have been well described, and include dizziness, hypotension, and ejaculatory and sexual dysfunction. Quality of life (QOL) was significantly influenced by the medications.

The correlation between sexual function and BPH/LUTS has been demonstrated by several studies [5,6]. Increasingly, evidence suggests that treatment of BPH/LUTS also has therapeutic effects on sexual function [7,8]. We reviewed a number of contemporary issues that relate to the management of BPH/LUTS to discuss the beneficial effects and side effects of these treatments.

DEFINITION OF LUTS/BPH

Symptoms of LUTS can be divided into obstructive (voiding) and irritative (storage) components. Voiding symptoms include slow stream, intermittency, hesitancy and straining. Increased daytime frequency of urination, nocturia, urgency and urge urinary incontinence are all storage manifestations. BPH can lead to bladder outlet obstruction (BOO) and DO, which result in overactive bladder symptoms clinically. However, the diagnosis of BOO or DO requires urodynamic study.

TREATMENT OF LUTS/BPH

Transurethral resection of the prostate (TURP)

Despite the introduction of alternative techniques, TURP still represents the gold standard in the operative management of LUTS/BPH [9]. Over the past decade, medical therapy has been the mainstay of treatment for BPH. According to the American Urological Association (AUA) guidelines, absolute indications for TURP include recurrent urinary tract infection, renal impairment, bladder stones and urinary retention [9]. TURP provides satisfactory improvements in LUTS and QOL but the incidence of TUR-syndrome is about 1%. Regarding late complications, urethral stricture, bladder neck stenosis, retrograde ejaculation and impotence might occur [10].

Photoselective vaporization of the prostate (PVP) is a new procedure for relieving BOO due to prostate enlargement. PVP uses a high-powered laser (green light laser) to vaporize and remove the obstructing prostate adenoma without destroying other tissue. Significant clinical improvements in increased peak flow rate, post-voiding residual urine, International Prostate Symptom Score (IPSS) and QOL score have been observed within one month of the treatment. Advantages of PVP include less blood loss, shorter duration of catheterization, short hospital stay and lower incidence of retrograde ejaculation in sexually active men [11]. PVP is a less invasive procedure and provides a safe alternative in high-risk patients receiving anticoagulant agents.

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α -Adrenoceptor antagonists

In the early 1990s, prostate surgery, mainly TURP, was the standard management for patients with LUTS/BPH. With the large number of randomized controlled studies published, pharmacological therapies have been the most common modalities prescribed by urologists [2]. The prostate contains glandular and stromal tissue, which consists of smooth muscle, and is the dynamic component of BOO. Blockade of the α -receptors in the bladder neck cause muscle relaxation and relieve BOO by inhibiting the sympathetic nervous system-mediated contraction of smooth muscles in the prostatic tissues [12]. At present, there are four α -blockers available, including doxazosin, terazosin, tamsulosin and alfuzosin. The AUA Guideline Committee described all four as being equally effective, causing an average 4 to 6 point improvement in the IPSS [9]. Reduction of outlet resistance leads to changes in bladder function, thus α -blockers increase maximal urinary flow (Qmax), and improve both voiding and storage symptoms. When patients have moderate to severe symptoms (IPSS \geq 8), all four abovementioned α -blockers are recommended. The common primary adverse events reported with α -blocker therapy are orthostatic hypotension, dizziness, ejaculatory problems and nasal congestion.

5-Alpha-reductase inhibitor (5ARI)

The 5ARI drugs (finasteride and the dual inhibitor dutasteride) can ablate the accumulation of intraprostatic dihydrotestosterone (DHT), the hormone most responsible for prostate growth and maintenance. Not only can the two drugs relieve symptoms but they can also reduce the progression of BPH. A prostate cancer prevention trial (PCPT) demonstrated that finasteride has a chemoprevention effect on prostate cancer [13]. With regards to prophylaxis of BPH-related complications, McConnell and his co-workers showed the advantage of finasteride on reducing subsequent urinary retention and the need for surgery related to BPH [2]. However, it is emphasized that 5ARI therapy will result in a reduction of serum total prostate specific antigen (PSA) level of nearly 50% in men with BPH; hence, multiplying the PSA level by a factor of 2 is necessary and allows physicians to continue using PSA as a screening marker for detection of prostate cancer. In the PCPT study, an increased percentage of high grade prostate cancer was also observed [13]. In addition, finasteride has been reported to be effective against BPH-related bleeding via inhibition of angiogenesis with a reduction in microvessel density of the suburethral prostate tissue [14].

According to the 2003 AUA guidelines, the combination of an α -blocker and a 5ARI for management of BPH/LUTS is an appropriate and well-adapted treatment option for patients with high IPSS, high PSA levels and large prostate volume, who are thought to be at higher risk of progression [9,15,16]. The Medical Therapy of Prostatic Symptoms (MTOPS) study demonstrated that the combination of finasteride and doxazosin reduces the risk of overall BPH progression, which consists of increase in IPSS \geq 4 points, acute urinary retention, urinary incontinence, renal insufficiency or recurrent urinary tract infection [2].

Antimuscarinics

Overactive bladder (OAB) can arise in men with BOO caused by BPH, and OAB symptoms are components of LUTS. The application of antimuscarinics is one of the treatment options for patients with OAB symptoms. Antimuscarinics selectively block muscarinic receptors on the detrusor muscle that are stimulated by acetylcholine, released from

activated parasympathetic nerves. Consequently, these agents reduce bladder contraction. There are several antimuscarinics available for treating OAB symptoms. However, tolterodine has a well-documented effect on storage symptom components of LUTS/BPH. It is well tolerated and is the first-line therapy currently. Kaplan et al recently conducted a randomized, double-blind, placebo-controlled trial and reported that the men who received a combination of tolterodine and tamsulosin had better symptom control and QOL than men treated with either one of the medications or the placebo [17]. The investigators suggest that in men who have very bothersome frequency, urgency or urge incontinence bladder symptoms, urologists should consider using a combination of medications for the bladder and prostate.

Desmopressin

Nocturia is one of the most bothersome LUTS and also most difficult to be eliminated in ageing men. Nocturnal polyuria associated with circadian change of arginine vasopressin and atrial natriuretic peptide in the elderly has been suggested as the most dominant type of nocturia. Kuo HC demonstrated that desmopressin is effective in treating nocturia to improve the patients' QOL, although a few adverse events such as hyponatremia might occur [18].

IMPACTS OF MEDICAL TREATMENT

Prevention of progression and improvement of QOL

The rationale for use of α -adrenoceptor antagonists and 5ARI to alleviate LUTS has been well established. Whether or not LUTS and/or OAB symptoms are secondary to BPH and/or BOO, the goal of treatment of symptoms should be to improve QOL and to prevent clinical deterioration. The MTOPS trial indicated both finasteride and doxazosin targeting the prostate significantly reduced the risk of overall clinical progression and necessity of BPH-related surgery afterwards when compared to the placebo [2]. Combination therapy was more effective than monotherapy.

The impact of LUTS/BPH on QOL has been addressed over the past decades [19,20]. Management of bothersome symptoms and improvement in the patient's QOL are important treatment goals in LUTS/BPH. Although voiding symptoms are most common, storage symptoms are most bothersome, interfering with daily life activities the most, and have a major effect on QOL. The beneficial effects of α -blockers have been well-established [12,21].

Results of 5ARI on QOL in patients with LUTS/BPH were reported in the Proscar Long-term Efficacy and Safety Study (PLESS), in which patients receiving finasteride had significant improvements in health-related QOL when compared with those receiving the placebo [22]. Desgrandchamps and colleagues recently reported that dutasteride treatment for 24 weeks also significantly improved BPH symptoms, QOL, patient discomfort and satisfaction [23].

Effect on sexual function

LUTS and erectile dysfunction (ED) have a negative impact on sexual function, and when comorbid they result in reduced QOL; many epidemiology data have shown that sexual dysfunction is significantly more prevalent in men with LUTS/BPH than in those without [6,24]. It is also recognized that the severity of LUTS is a risk factor for sexual dysfunction independent of age and cardiovascular comorbidities [25]. From a Spanish cross-sectional study (the EDEM study), the preva-

lence of ED, evaluated by the ED domain of the International Index of Erectile Function, increased with age. Of note, the presence of LUTS was the strongest risk factor for ED [26].

The four α -blockers mentioned previously are suggested to be equally effective in LUTS/BPH and no evidence indicates that they affect libido or erectile function. Kirby et al reported that doxazosin has advantages for sexual function in patients with LUTS/BPH [27]. Similarly, another study on alfuzosin treatment for men with LUTS/BPH also demonstrated that ED is significantly improved after administration of alfuzosin for one year. The improvement was particularly significant in men with severe LUTS [28].

Decrease of libido is a common adverse effect during treatment with finasteride or dutasteride; the estimated incidence of ED was 8% with finasteride treatment and 7% with dutasteride administration [29].

The role of phosphodiesterase-5 (PDE-5) inhibitors for managing patients with co-existing ED and LUTS/BPH has also received attention recently, and several studies have indicated that sildenafil or tadalafil have beneficial effects on LUTS [30,31]. A placebo-controlled randomized study is needed to confirm the significance of PDE-5 inhibitors for the treatment of LUTS/BPH.

Adverse effects

It is well-recognized that α -blockers might lead to dizziness, sedation and orthostatic hypotension. In addition, ejaculation disorders have been reported in as many as 6% of patients receiving α -blockers [32].

5ARI finasteride or dutasteride act by inhibiting DHT and result in decreased libido, ED and ejaculation disorders [33]. The MTOPS study also confirmed that sexual dysfunction is the most prevalent side effect in patients prescribed finasteride [2].

CONCLUSION

In ageing men, treatment of LUTS/BPH improves QOL and reduces the probability of clinical progression. Regarding the surgical modality, TURP is the standard procedure but evolving laser photoselective vaporization of the prostate is a less invasive procedure, which has an equivalent efficacy. Combination therapy, including α -blockers and 5 α -reductase inhibitors or antimuscarinic agents, has been documented as more beneficial for men with LUTS/BPH than monotherapy with α -blockers. Desmopressin also has been recognized as an effective agent for nocturia. Sexual dysfunction might be altered after men receive management of LUTS/BPH; the clinical significance of PDE-5 inhibitors in LUTS/BPH is under investigated.

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