Strategy Planning in Managing Benign Prostatic Hyperplasia and Male Lower Urinary Tract Symptoms

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INTRODUCTION

The treatment goals for lower urinary tract symptoms (LUTS) that are suggestive of benign prostatic hyperplasia (BPH) should aim to relieve symptoms and improve quality of life, as well as prevent clinical progression and complications. However, these benefits need to be balanced against potential side effects of treatments [1]. The treatment options for LUTS/BPH include: watchful waiting, medical treatments, surgery, minimally invasive treatments and alternative treatments. Currently, non-surgical treatments have replaced surgery as the mainstay therapeutic approach. In the Taiwanese Continence Society (TCS) Symposium for LUTS/BPH held in Taipei on June 23, state-of-the-art advances in non-surgical treatments were presented by Drs. Hann-Chorng Kuo, Chieh-Lung Chou and Yao-Chi Chuang.

WATCHFUL WAITING

Patients with mild LUTS that have little impact on quality of life and cause minimal bother can be managed expectantly. The 2003 American Urological Association (AUA) guidelines on management of BPH recommended that patients with mild symptoms of BPH (AUA Symptom Score ≤ 7) and patients with moderate or severe symptoms (AUA Symptom Score ≥ 8) who are not bothered by their symptoms (i.e., they do not interfere with the daily activities of living) should be managed using a strategy of watchful waiting [2].

Watchful waiting is by no means passive. Life style modification should be advised to moderate fluid intake and avoid caffeinated drinks as well as alcohol. In frail elderly patients, it is important to review their drug history. Diuretics and any prescriptions that may cause impairment of mental state, dexterity or mobility may be the culprit for LUTS [3]. LUTS may be alleviated by mere termination or dose reduction of these drugs. Lastly, it is important to caution patients on watchful waiting to seek medical help promptly if their LUTS deteriorate.

MEDICAL TREATMENTS

Currently, standard medical treatments for LUTS/BPH include: (1) α_1-antagonists; (2) 5 α-reductase inhibitors (5-ARIs); (3) combination therapy with α_1-antagonist and 5-ARI.

α_1-Antagonists

Received: July 9, 2007 Accepted: July 24, 2007
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Since the pivotal reports by Caine et al [4], alpha-blockers have become the first-line medical treatment for LUTS/BPH. Activation of the α_1 adrenoceptors causes contraction of the prostatic smooth muscle. Inhibition of the receptors relaxes the prostate, which decreases urinary outflow resistance and helps improve LUTS. Review of randomized controlled trials has demonstrated that all current on-market α_1-antagonists have similar efficacies [5]. The drugs improve symptom scores by 30%-40% and maximum flow rate by 15%-30% [6]. On the other hand, the prostatic size and disease progression are not significantly altered. The benefit of using α_1-antagonists is that the drugs act rapidly within 2 to 3 days. About 70% of men will respond to this treatment, and non-responders can be identified rapidly and other treatments initiated [1]. This class of drugs is suitable for patients with moderate to severe LUTS and a low or intermediate risk of disease progression. Non-selective alpha-blockers such as prazosin and phenoxybenzamine are no longer recommended.

Adverse reactions are common among users of α_1-antagonists. The main side effects include: postural hypotension, dizziness, asthenia, somnolence, headache and ejaculatory difficulty. The adverse event profile varies with different drugs. Ejaculatory dysfunction is most frequently caused by tamsulosin. At a daily dose of 0.8 mg, tamsulosin decreased ejaculate volume in almost 90% of normal volunteers and caused anejaculation in approximately 35% [7]. Based on systematic reviews, on the other hand, tamsulosin and once daily preparations of extended release alfuzosin have the lowest risk of cardiovascular adverse events, and are suitable agents in high risk and elderly patients [8]. Recently, floppy iris syndrome, which may cause technical problems during cataract surgery, has been reported as a side effect of alpha-blockers. The problem occurs most often with tamsulosin: ophthalmologists undertaking cataract surgery should identify patients who are using these medications [9].

5-ARIs

Testosterone is converted to dihydrotestosterone (DHT) by the enzyme 5α reductase. DHT acts on the prostate to induce BPH. 5-ARIs decrease the production of DHT, thus arresting prostate growth and reducing its volume. However, prostate size shrinkage is slow and LUTS improvement takes three to six months to achieve. Evidence has suggested that 5-ARIs decrease BPH clinical progression and the development of acute urinary retention. As such, this class of treatment is especially beneficial for patients with risk factors for disease progression: age >70 years, International Prostate Symptom Score (IPSS) >7, prostate volume >30 mL, prostate specific antigen (PSA) > 1.4 ng/mL and post-void residual urine volume >100 mL [10]. Common side effects of 5-ARIs include: erectile dysfunction, reduced libido, ejaculatory disorders and breast tenderness.

Two 5-ARIs are currently available, finasteride and dutasteride. A systematic review of 19 finasteride randomized placebo controlled trials showed that symptom scores and flow rates consistently improved, and prostate volume decreased by 25% in patients on this drug [11]. For dutasteride, a four-year multi-center randomized placebo controlled trials was reported [12]. The results showed improved symptom scores, a 26% decrease in prostatic volume and improved urinary flow rates. There was also a 57% reduction in relative risk of acute urinary retention and a 48% reduction in relative risk of surgical treatment. Head to head comparison of clinical effectiveness of the two 5-ARIs was performed. A randomized multi-center comparison trial between finasteride and dutasteride found no significant difference between these drugs with respect to their safety profiles or changes in prostate volume, symptom score and peak flow rate [13]. By and large, this class of drugs is suitable for patients with moderate or severe LUTS and prostate volume >30 mL or serum PSA >1.4 ng/mL [14]. Patients should be educated that there may be no apparent improvement in LUTS for six months and that treatment will need to continue long-term. Additionally, since 5-ARIs decrease PSA serum concentrations by about 50%, reference values need to be adjusted for following up the possibility of prostate cancer.

AUA guidelines recommend that patients with symptomatic prostatic enlargement but without signs of bother may be offered a 5-ARI to prevent progression of the disease. However, the disadvantages of this therapeutic approach (e.g., side effects such as sexual dysfunction) and the need for long-term daily therapy should be presented to the patient in comparison to a reasonable estimate of his baseline risk of progression (i.e., retention and the risks associated with BPH-related surgery) so that an informed decision can be made. 5-ARIs are not appropriate treatments for men with LUTS who do not have evidence of prostatic enlargement [2].

Combination therapy with α_1-antagonist and 5-ARI

The National Institute of Health (NIH)-sponsored Medical Therapy of Prostatic Symptoms Study (MTOPS) was a long-term multi-center randomized controlled trial comparing the clinical progression of patients receiving placebo, finasteride, doxazosin or a combination of both drugs [15]. Clinical progression was defined by any one of five conditions: acute urinary retention, recurrent urinary tract infections or urosepsis, incontinence, renal function deterioration (50% rise from baseline serum creatinine) or a >4 point IPSS increase. The results showed that combination therapy of both drugs was more effective in preventing disease progression than either drug alone or placebo. The risks of progression to acute urinary retention or surgery were significantly reduced by both finasteride and combination therapy. Thus, combination therapy may be recommended for patients at high risk of progression. Large prostate volume, high serum PSA level, large post-void residual urine volume, high IPSS and bother scores are probable risk factors for BPH progression. On the other hand, more side effects were reported in patients on combination therapy. A population-based cost-benefit analysis is mandatory to endorse this approach to treatment, and any therapeutic advantage of combination therapy needs to be balanced against the increased side effects and costs [1].

SURGICAL MANAGEMENT

Since effective pharmacological therapy has taken center stage, the number of surgical procedures for BPH has been declining. However, surgical treatment for BPH is still an effective option for improving LUTS and decreasing clinical progression in patients who have inadequately controlled diseases. The AUA guidelines recommend that patients who have developed complications of BPH are best treated surgically. The choices of surgical approach (open or endoscopic and energy source - electrocautery versus laser) are technical decisions based on the patient's prostate size, the individual surgeon's judgment and the patient's co-morbidities.

The gold standard treatment, transurethral resection of the prostate (TURP), significantly improves urinary symptoms and urinary flow. However, TURP may carry multiple morbidities. The Veterans Affairs Cooperative Study demonstrated a 1% risk of urinary incontinence and an overall decline in sexual function. However, no significant differences in these incidences were observed when compared to the watchful waiting group [16]. One unique complication of TURP is TURP syndrome, a dilutional hyponatremia that occurs when hypotonic irrigation fluid, most commonly distilled water, is absorbed into the bloodstream. Other complications that have been reported in more than 5% of patients include: sexual dysfunction, irritative voiding symptoms, bladder neck contracture, blood transfusion, infection and hematuria [2].

MINIMALLY INVASIVE THERAPY

For patients with poor surgical risk but who have not been effectively treated pharmacologically, there are a number of minimally invasive procedures that may be safe alternatives to TURP. The 2003 AUA guidelines include the following technologies as treatment options: Prostatron® (Prostasoft® 2.0 and 2.5; Urologix, Minneapolis, Minnesota, USA), the Targis® device (Urologix, Minneapolis, Minnesota, USA), the TUNA® System (Medtronics, Minneapolis, Minnesota, USA) and the UroLume® Endoprosthesis Stent (American Medical Systems, Minnetonka, Minnesota, USA). The available evidence was inadequate to support inclusion of the following technologies as treatment options at this time: HIFU (Ablatherm®, EDAP Technomed, France) and interstitial laser coagulation (ILC; Indigo Optima Laser System, Ethicon Endo-Surgery, Cincinnati, Ohio, USA). These treatments have not been subjected to rigorous prospective, multi-center, controlled trials [2].

To assess the therapeutic efficacy and safety of laser prostatectomy techniques for treating men with symptomatic benign prostatic obstruction (BPO), randomized controlled trials were reviewed by the Cochrane Collaboration Library [17]. Trials were eligible if they: (1) were randomized comparisons of a laser technique with TURP, (2) included at least 10 men with BPO in each treatment arm, (3) provided at least 6 months follow-up, and (4) included clinical outcomes such as urologic symptom scales or urodynamic measurements. Twenty studies involving 1,898 subjects were evaluated. The pooled percentage improvements for mean urinary symptoms ranged from 59% to 68% with lasers and 63% to 77% with TURP. The improvements for mean peak urinary flow ranged from 56% to 119% with lasers and 96% to 127% with TURP. Overall, laser subjects were less likely to receive transfusions or develop strictures and their hospitalizations were shorter. Re-operation occurred more often following laser procedures. The Cochrane report concluded that laser techniques are a useful alternative to TURP for treating BPO. Small sample sizes and differences in

study design limit any definitive conclusions regarding the preferred type of laser technique. Data were insufficient to compare laser techniques with other minimally invasive procedures.

ALTERNATIVE TREATMENTS

Symptomatic improvement of LUTS/BPH by phytotherapy with a number of plant extracts have been reported [18]. These include: Serenoa repens (saw palmetto) berry, Cucurbita pepo (pumpkin) seed, Urtica dioica (stinging nettle) root, Opuntia (cactus) flower, Hypoxis rooperi (South African star grass), Pygeum africanum (African plum). However evidence levels are still low for treatment recommendation.

Among the phytotherapeutic agents, Serenoa repens is a popular remedy for LUTS/BPH. According to the Cochrane review, evidence suggests that Serenoa repens provides mild to moderate improvement in urinary symptoms and flow measures. Serenoa repens produced similar improvement in urinary symptoms and flow compared to finasteride and is associated with fewer adverse treatment events. The long-term effectiveness, safety and ability to prevent BPH complications are not known. Research into long-term effects of Serenoa repens and other phytotherapeutic agents on LUTS/BPH are needed [19].

AN OUTLINE OF TREATMENT STRATEGIES FOR LUTS/BPH

1. Treatment objectives for LUTS/BPH include: relief of symptoms and improvement of quality of life, as well as prevention of disease progression and complications.
2. Watchful waiting is safe for informed patients not bothered by their symptoms.
3. For patients with bothersome LUTS, the first-line medication is the α_1-antagonist. The treatment rapidly improves LUTS in about three quarters of patients. The choice of drugs may depend on side-effect profiles.
4. 5-ARIs may be beneficial for patients with risk factors for disease progression, such as large prostate volume and high PSA. The possible side effects on sexual function should be discussed with patients.
5. Evidence has demonstrated that combination therapy is the most effective drug treatment to prevent clinical progression of BPH. However, the benefits need to be balanced against the increased side effects and costs.
6. Surgical treatment is effective for improving symptoms and decreasing progression. TURP is still the gold standard. Possible surgical morbidities should be explained to the patients.
7. Minimally invasive treatments may be useful in patients with poor surgical risk but unsatisfactory pharmacological outcomes. However, the re-treatment rates are high and evidence for long-term results is insufficient.
8. Evidence for recommendations of phytotherapies and other alternative therapies is currently insufficient.

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