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TEACHING ARTICLE

NON-SURGICAL TREATMENT OF BENIGN PROSTATIC HYPERPLASIA: WHERE DO WE STAND IN 2005?

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INTRODUCTION

In the last decade the management of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) has dramatically changed. The standard therapy for men with uncomplicated LUTS/BPH involves a cascade of noninvasive treatment, minimally invasive procedures and invasive endoscopic or open surgical techniques. The choice depends on balancing symptom severity and bother with benefits, risks and side-effects[1,2]. The aim of the present article is to shed light on the most recent advances in non-surgical treatment of LUTS/BPH including self-management and medical treatment.

SELF-MANAGEMENT

Self-management should be the primary strategy for all men with uncomplicated LUTS/BPH. It is also termed watchful waiting or active monitoring. It does not mean doing nothing. It varies from an annual review of symptoms with simple investigations (symptom score, flow rate) to an intensive program of education, reassurance and advice delivered in a multidisciplinary setting[2,3]. It consists of three elements namely: education and reassurance, lifestyle modification of fluid intake and concurrent medical therapy and finally behavioral interventions including the management of post-void dribbling and bladder retraining.

Education and reassurance

Most patients want to be informed about their condition. The patient must be advised about the natural history and the different treatment options of LUTS/BPH as well as about the pros and cons of each treatment option. It is also important to know the patient's perspectives and his sexual ability. Anxiety regarding prostate cancer can be the principal reason why a man consults his doctor about his LUTS; in this situation reassurance is the only intervention required.

Life-style modification

Life-style modification useful for the self-management of LUTS/BPH includes: fluid management and concurrent medical therapy.

Fluid management

Recommending changes is only possible if detailed information about fluid intake and how this relates to voiding is known. Frequency volume charts (voiding diaries) are the easiest way to achieve this. Patients document the type and volume of fluids consumed, and the time and volumes of urine passed[4]. From these charts, the fluid intake, its relationship to voiding patterns, the voided volume (bladder capacity) and the frequency both by day and night can be estimated. This information would be difficult to obtain through questioning alone[2].

There are a few basic components to fluid management:

- The overall fluid intake should be approximately 1500-2000 ml/day (with minor modifications made according to climate and activity). There is a belief promoted by the

mineral water industry, and now held by many, that drinking three liters of water every day affords some health benefit. While dehydration should always be avoided, there is no evidence to support the belief that drinking more water is better[5].

- A patient should reduce or avoid fluid intake at specific times when urinary frequency is inconvenient (but the overall daily fluid intake should not be reduced).

- The patient should avoid fluid intake two hours prior to sleep if nocturia is a symptom (but, again, the overall daily fluid intake should not be reduced).

- The patient should avoid or moderate intake of caffeine and alcohol which may have a diuretic and irritant effect on the bladder, thereby increasing fluid output and enhancing frequency, urgency and nocturia[2].

Concurrent medical therapy

Medication with an effect on the urinary tract can both cause and exacerbate LUTS. Diuretics may cause diuresis. Tricyclic antidepressants, antispasmodics and anti-histamines have anticholinergic effects that may reduce bladder emptying. Anti-parkinsonian drugs and calcium channel blockers cause smooth muscle relaxation that may also reduce bladder emptying. Where a suitable alternative exists with less effect on the urinary tract, changes can be made such as substituting a thiazide diuretic used for hypertension for a beta-blocker or ACE inhibitor. Where substitution is not possible, such as with loop diuretics for heart failure, patients can be advised to alter the time at which drugs are taken. Taking a loop diuretic early in the evening rather than first thing in the morning will reduce daytime frequency and nocturia[2].

Behavioral interventions

These include: management of post-void dribbling and bladder retraining.

Management of post-void dribbling

Post-micturition dribble is a very common and bothersome symptom. It is underreported by patients and does not feature in the international prostate symptoms score (IPSS)[6]. By milking the urethra with a combination of leaning forwards, perineal pressure and contracting the pelvic floor muscles, urine that collects in the "U-bend" of the urethra after voiding can be expelled[2]. Randomized studies have shown urethral milking and pelvic floor contractions to be more effective than counseling alone in reducing post-micturition dribble[7].

Bladder retraining

Bladder retraining involves the patient's resisting the sensation of urinary urgency with distraction techniques and pelvic floor squeezes to postpone voiding, thereby overcoming abnormal voiding patterns. Initially voiding should be postponed only for a short period of time, such as a minute. Once this is achieved with ease, patients can progress and postpone voiding for longer and longer aiming at an increase of their bladder capacity to 300-400 ml and of their inter-void time to 3-4 h.

The success rate of self-management is only subjective and is based upon the reduction of symptoms. If self-management fails, medical or surgical intervention is required. Many of the self-management interventions discussed in this article have little or no scientific evidence to support them because effectiveness studies have not been performed. However, in the UK secondary-care setting approximately one third of men with LUTS/BPH are managed by self-management[3]. The widespread use of self-management suggests its effectiveness. Further research is, therefore, required to define and test the effectiveness of self-management either as a primary intervention or to augment existing medical therapies.

MEDICAL TREATMENT

Medical treatment of LUTS/BPH aims at fighting against the causative factors. The static component of prostatic obstruction can be targeted with 5-α-reductase inhibitors (5 ARIs) or phytotherapy. The dynamic component of pro-static obstruction can be treated with α-blockers. Irritative or storage bladder symptoms can be treated with anticholinergics and partially with α-blockers, and finally α-blockers may also have an impact on the spinal cord level[8].

Medical treatment is indicated in patients with uncomplicated LUTS/BPH and mild to moderate symptoms (IPSS < 8-20) and those

waiting, unwilling or unsuitable for surgery. Medical treatment must be stopped in cases of complicated LUTS/BPH. This includes patients with refractory hematuria, repeated episodes of acute urinary retention (AUR), repeated attacks of urinary tract infection (UTI) and renal insufficiently secondary to BPH.

α -blockers

Short- and long-acting α_1-selective antagonists treat the dynamic component of BPH through relaxation of the smooth muscle in the prostate, by blockade of α_1-receptor-mediated sympathetic stimulation. A number of double-blind, placebo-controlled studies evaluating the efficacy of α_1-blockers have been conducted in patients with symptomatic BPH[9,10]. α_1-blocker studies have recently undergone meta-analysis by the American Urological Association (AUA)[11]. The α_1-blockers alfuzosin, doxazosin, tamsulosin and terazosin demonstrate a statistically significant improvement, compared with placebo, in symptom scores, maximum flow rate (Q_{max}) and quality of life. Following the meta-analysis of α_1-blocker studies conducted in 1999, the AUA guidelines conclude that the four α_1-blockers examined provide equivalent benefit in improving symptoms and flow[11,12]. Discontinuation due to adverse events ranges between 4 and 10% for alfuzosin and tamsulosion, rates that are comparable with placebo. However, for terazosin and doxazosin, an additional 4-10% of patients withdraw due to adverse events[12]. The most common adverse events observed with α_1-blockers at a significantly higher frequency than with placebo are dizziness and postural hypotension, although there may be differences between individual agents within the class[12].

In general, α_1-blockers are associated with a similar incidence of sexual adverse events as placebo, except for tamsulosin which has an incidence of retrograde or delayed ejaculation of 4.5-10% versus 0-1% for placebo[13].

5 α –reductase inhibitors (5 ARIs)

5 ARIs inhibit the conversion of testosterone to dihydrotestosterone (DHT), the primary androgen involved in both normal and abnormal prostate development. By reducing the production of DHT, 5 ARIs significantly reduce prostate volume in men with BPH. Two 5 ARIs are currently available for the treatment of BPH: finasteride and dutasteride, which differ in their profile of 5 α –reductase (5 AR) binding and inhibition of the type 1 and type 2 isoenzymes of 5 AR. Finasteride is a mono-inhibitor of 5 AR type 2, whilst dutasteride is a dual inhibitor of both 5 AR type 1 and type 2[14]. Dutasteride treatment results in an increased and more consistent level of serum DHT suppression, namely $\geq$ 90% DHT suppression in over 85% of subjects receiving dutasteride, compared with > 90% in 2.2% of subjects receiving finasteride[15].

The effects of finasteride on the symptoms and progression of BPH have been evaluated in the Proscar Long-term Efficacy and Safety Study (PLESS), a large-scale, long-term, double-blind, placebo-controlled trial[16]. Finasteride reduced the prostate volume by 18%, improved the symptom score by 2.6 points, increased the Q_{max} by 1.9 ml/s and reduced the risk of AUR by 57% and surgery by 55%. Although the 7-year Prostate Cancer Prevention Trial (PCPT) recruited men with a normal digital rectal examination, a PSA$\leq$ 3.0 ng/ml and AUA symptom score < 20, and was designed to examine the effect of finasteride versus placebo on the risk of prostate cancer, it also confirmed that finasteride treatment was associated with a lower risk of AUR and need for transurethral resection of the prostate (TURP)[17].

The efficacy of dutasteride has been examined in double-blind, placebo-controlled phase-III studies[18]. Dutasteride reduced the symptom score by 4.5 points, increased the Q_{max} by 2.2 ml/s and reduced the risk of AUR and surgery by 57% and 48%, respectively.

Both finasteride and dutasteride are generally well-tolerated. Withdrawals due to adverse events were similar to placebo except for sexual adverse events. Compared to placebo, 5 ARIs have a significantly higher incidence of sexual side-effects in terms of decreased libido, impotence, ejaculation disorders, reduced ejaculate volume and gynecomastia.

Phytotherapy

Phytotherapeutic agents have become a popular treatment for LUTS/BPH. These agents are employed extensively in Europe, where their use is more prevalent than α–blockers and finasteride together[19]. In the USA, consumers often purchase herbal medication

over the counter to supplement traditional treatment or as a substitute[19]. Herbal treatment for BPH has been extensively reviewed[19-23] and a detailed discussion of this topic is beyond the scope of the present article.

The mechanism of action of phytotherapeutic agents is poorly understood and difficult to ascertain because plant extracts are of variable contents. Nevertheless, the same studies suggest that intracellular inhibition of 5 AR is a mechanism of action[19].

A recent study has demonstrated that phytotherapy with permixon improves LUTS due to BPH with no negative impact on sexual function[24].

Several recent studies have suggested a potential benefit of phytotherapy for BPH. In addition, few-side effects have been reported. These agents may have a role in the treatment of BPH in patients seeking alternative medication; but these patients should have minor symptoms only and no absolute indication for medical or surgical management[19, 20].

Anticholinergics

Bladder outlet obstruction (BOO) caused by BPH will result in detrusor instability and overactive bladder. A substantial proportion of men with LUTS/BPH will have irritative bladder symptoms due to an overactive bladder commonly associated with BPH. There is, therefore, a rational basis for treating such symptoms with anticholinergic drugs[25].

It is a common perception that using an anticholinergic in men with BOO runs the risk of AUR, because of the inhibitory effect of anticholinergics on bladder contraction in the presence of BOO, and so these drugs tend not to be used. Nevertheless, some recent studies have specifically determined the safety of anticholinergic drugs in this situation[26]. Large tolerability and safety studies of anticholinergic drug treatment which included a large number of men (many of whom are likely to have BOO) suggest that anticholinergic medication is likely to be safe in men with LUTS /BPH[27]. Preliminary recent data from men with urodynamically proven BOO support this assertion[28]. Larger studies are required to determine the safety and therapeutic role of anticholinergic medication in men with LUTS/BPH.

Combination of α–blockers plus 5 ARIs

The rationale for combining α–blockers with 5 ARIs is the fact that this combination theoretically should have a dual synergetic effect against both the dynamic and the static components of obstruction in patients with LUTS/BPH. In the following, the most important prospective randomized trials that studied this issue are summarized.

The ALPHIN Study

The most relevant among the non-controlled trials is the Alphin Study involving more than 1000 patients. In this study alfuzosin or finasteride alone was compared to a combination of alfuzosin and finasteride over a period of 6 months. The results revealed that alfuzosin and the combination did significantly better on IPSS improvement, however, the combination did not provide any additional benefit over alfuzosin alone[29].

The Veterans Affairs Study

The oldest placebo-controlled study is the Veterans Affairs Study comparing terazosin or finasteride alone with placebo or a combination of both drugs[30]. The outcome showed that terazosin and the combination did better than finasteride alone or placebo and there was no additional benefit in administering the combination over terazosin alone. One of the drawbacks of this study was the small volume of the prostate included, which did not allow finasteride to act optimally.

The PREDICT Study

The second placebo-controlled study was recently published[31]: the Prospective European Doxazosin and Combination Therapy (PREDICT) Study. This one-year trial compared doxazosin or finasteride alone with placebo or a combination of both drugs on more than 1000 patients. The results are quite similar to the Veterans Affairs Study. Doxazosin and the combination did better on IPSS improvement than finasteride alone or placebo. There was no additional benefit in administering the combination over doxazosin alone.

The MTOPS Study

The design of the Medical Therapy Of Prostatic Symptoms (MTOPS) was recently

published[32] and preliminary results have been reported[30,31]. A total of 3047 BPH patients were randomized into four arms to receive doxazosin (4 or 8 mg) alone, finasteride (5 mg) alone, placebo or a combination of both drugs. The primary goal of this prospective study was to determine if medical treatment could prevent or delay the clinical progression of BPH, defined as AUR, renal insufficiency due to BPH, recurrent UTIs or urosepsis, incontinence or a rise of more than 4 points on the IPSS. In contrast to the previous combination therapy studies, many of the patients enrolled in the MTOPS study fulfilled the conditions for maximal efficacy of finasteride: 31% had a PSA above 1.4 mg/ml. At 4 years, the change in symptom score was 7 points for the combination, 6 points for doxazosin, 5 points for finasteride and 4 points for placebo, the median baseline symptom score being 17. These improvements were paralleled by changes in the Q_{max}: 3.7 ml/s for the combination, 2.5 ml/s for doxazosin, 2.2 ml/s for finasteride and 1.4 ml/s for placebo, the median baseline Q_{max} being 10.6 ml/s. The combination therapy was more effective in relieving and preventing the progression of symptoms than either of the two drugs alone. The addition of finasteride to doxazosin significantly reduced the risk of AUR and the need for BPH-related surgery. The overall risk of progression was reduced by 39% for doxazosin, 34% for finasteride and 67% for the combination therapy. The risk of retention was reduced by 31% for doxazosin, 67% for finasteride and 79% for the combination therapy, while the risk of surgery was reduced by 64% and 67% for finasteride and the combination therapy, respectively, with no significant change in the risk for the doxazosin group compared with placebo[33].

Should all BPH patients receive combined therapy?

Certainly not, and for many reasons. The daily cost of treatment is a matter for concern, but more important is the risk of adverse effects: patients receiving combination therapy experience the adverse effects due to both agents[8]. Patient selection has to be defined so that combination therapy is administered only to those patients who can expect maximal clinical benefit. Patients most likely to benefit from combination therapy are those in whom the baseline risk of progression is significantly higher, generally patients with larger glands (> 30g) and a higher PSA (> 1.6 mg/ml)[11].

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