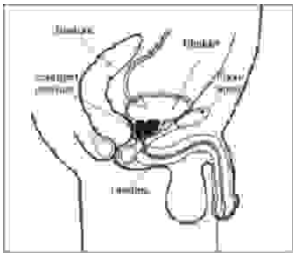
REVIEW PROF- 795

CURRENT TRENDS IN THE MEDICAL MANAGEMENT OF BENIGN PROSTATIC HYPERPLASIA



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ABSTRACT... rafiqanju@hotmail.com Symptomatic benign prostatic hyperplasia (BPH) is a common condition in older men and has a significant effect on their daily lives. Medical treatment of BPH has undergone many changes in the last decade. For patients presenting with minimal bothersome symptoms watchful waiting is an acceptable first line strategy. Many placebo controlled double blind trials have confirmed the efficacy of alpha blockers and 5 alpha reductase inhibitors in the medical management of BPH. The therapeutic efficacy of all contemporary alpha- blockers appear similar both in terms of symptomatic relief and urodynamic improvements in urine flow rate. Alpha blockers have a rapid onset of action and are likely to produce a therapeutic result within weeks, regardless of prostatic volume. There is well documented evidence of reduction in LDL cholesterol and serum triglyceride levels. In addition some patients on alpha blockers experience improvement in sexual function and quality of their erectile response. There is a small risk of hypotension, asthenia and dizziness with alpha blockers therapy. Finesteride, a potent 5-alpha reductase inhibitor, must be given for 6 months before its effectiveness in a given patient can be assessed and for at least 12 months to achieve maximum prostate shrinkage and the full extent of its other beneficial effects. This may be considered as a disadvantage when compared with the rapid relief afforded by surgery or alpha blockers. The efficacy of finesteride is also dependant on the prostate size. Finesteride is more effective in patients with prostate size greater than 40 gram. However on the long term it may reverse the disease progression and reduce the risk of urinary retention or prostate surgery. Side effects associated with finesteride therapy include decrease libido, impotence and interference with PSA estimation. In selected patients combination therapy with alpha adrenergic blocker and finesteride can be offered to relieve urinary symptoms and prevent BPH progression. When medical treatment fails and in those patients presenting with complications surgical treatment should be considered.

Key Words: BPH, Alpha adrenergic blockers, Finesteride

Benign prostatic hyperplasia (BPH) is the most frequent urological problem in ageing men. As many as 1 in 3 men over the age of 50 years experience the moderate to severe lower urinary tract symptoms (LUTS), that are thought to be associated with BPH diagnosis[1].

The pathogenesis of the BPH is incompletely understood. The two essential requirements for the development of BPH are old age and the presence of

functioning testes i.e. source of androgen. Although the hyperplasic changes in the prostate begin as early as 3rd decade of life, symptoms generally appear after the age of 60 years[2].

The urinary symptoms that results from the BPH is termed LUTS (Lower urinary tract symptoms). Most men with BPH experience only mild or moderate symptoms of obstruction. However severe BPH which is more problem in men over 60 years of age can lead to complications namely urinary retention, urinary tract infections(UTI's), renal insufficiency , vesical stones and hematuria[3]. Early diagnosis of BPH and implementation of effective therapy can help relieve symptoms, improve quality of life and prevent complications and morbidity associated with untreated BPH.

The goals of treatment for BPH are outlined in Table-I. Treatment options for BPH include watchful waiting, medical therapy and surgical intervention. Decision regarding the best treatment approach is based on the severity of symptoms and the presence or otherwise of co-morbid conditions.

WATCHFUL WAITING

A significant proportion of patients with mild prostatic symptoms will benefit from simple measures like decreasing intake total fluid intake especially at night, moderating the intake of caffeine containing products (tea or coffee) and by adhering to the timed voiding schedule. They should avoid cold medications & cough suppressants containing sympathomimetic drugs. Patients with large post-void urine volume and troublesome prostatic symptoms are not suitable candidates for watchful waiting [4].

MEDICAL TREATMENT

The medical treatment is currently being considered a preferred option for those patients who are symptomatic but lack absolute indications for surgery

TABLE- I GOALS OF THERAPY FOR BENIGN PROSTATIC HYPERPLASIA
DECREASE SYMPTOMS
IMPROVE QUALITY OF LIFE
DECREASE BLADDER OUTLET OBSTRUCTION
DECREASE POSTVOID RESIDUAL URINE
PREVENT DISEASE PROGRESSION

TABLE-II. ABSOLUTE INDICATIONS FOR SURGERY
RECURRENT ACUTE URINARY RETENTION
RECURRENT URINARY TRACT INFECTIONS
RENAL INSUFFICIENCY
VESICAL CALCULI
RECURRENT GROSS HEMATURIA

The availability of medical treatment has reduced the number of prostatectomy in many countries including France, Germany, Canada and Denmark [5]. In USA alone there has been around 55% reduction in TURP during the period from 1987 to 2000 [6].

ALPHA ADRENERGIC BLOCKERS

The smooth muscles in the prostatic stroma, capsule and bladder neck are rich in alpha adrenergic receptors. It has been suggested that the symptoms of BPH originate from both the static (increased size of prostate) and dynamic component (increased tone in the prostatic stroma and capsule).

In BPH, alpha adrenergic mediated smooth muscle tone may account for up to 40% of the total urethral pressure [7].

Treatment with alpha blockers benefits patients by decreasing the tone in prostatic stroma, capsule and bladder neck with consequent improved urinary flow and symptoms in around 60-70% of patients [8]. Therapeutic efficacy of all contemporary alpha blockers appear similar, both in terms of symptomatic relief and urodynamic improvement. In addition alpha blockers have a rapid onset of action and are likely to produce a therapeutic result within weeks regardless of the prostatic size[9].

A recent study[10] has suggested that treating patients with alpha blockers increases prostatic apoptosis and this has been identified as an additional molecular mechanism for long term effect of these drugs in benign prostatic hyperplasia.

The efficacy of alpha blocker in improving urinary symptoms is balanced against a small, but significant, incidence of side effects that consists of headache, dizziness, asthenia and occasionally postural hypotension[8].

Dizziness and asthenia are mediated by the effects of alpha blockers at the CNS level as there is lack of correlation between these effects and reduction in blood pressure[11]. Long acting alpha blockers doxazocin and terazosin may cause postural hypotension especially in hypertensive patients because of their effect on blood vessels and this may lead to increased episodes of fall in blood pressure in elderly patients.

To avoid such side effects initially patients should receive low dose of alpha blockers and it should be gradually increased to therapeutic dosage.

Molecular cloning studies have identified three subtypes of alpha 1 receptors termed as alpha1a, alpha 1b and alpha 1c[12]. The predominant receptor subtype in the human prostate is the alpha 1 a adrenoceptor[13,14]. The available alpha blockers differ in their receptor selectivity, duration of action and dosing frequency.

Tamsulosin is a new subtype selective alpha blocker that has high affinity for alpha 1a adrenoceptors. Its clinical efficacy appears to be similar to non-subtype selective doxazosin and terazosin but is associated with few cardiovascular side effects[14].

TABLE- III CLASSIFICATION OF ALPHA ADRENERGIC BLOCKERS AND DOSAGE

NON-SELECTIVE	DOSAGE
PHENOXYBENZAMINE	10 mg BID
SELECTIVE ALPHA 1(SHORT ACTING)	
PRAZOSIN	2 mg BID
ALFUZOSIN	5 mg BID
INDRAMIN	20 mg BID
SELECTIVE ALPHA (LONG ACTING)	
TERAZOSIN	5-10mg OD
DOXAZOSIN	4-8mg OD
HIGHLY (ALPHA 1a) SELECTIVE	
TAMSULOSIN	0.4mg OD

Approximately 30% of men treated for BPH have co-existent hypertension[15].The overwhelming clinical evidence demonstrates that terazosin and doxazosin lower blood pressure in hypertensive patients[16,17]. It is reasonable to advocate the use of alpha blockers as the treatment of choice in patients with hypertension and BPH.

There are also some important effects of alpha adrenoceptor blockers. There is well documented evidence of reduction in LDL cholesterol as well as serum triglycerides [8]. In addition it has been observed that patients receiving certain alpha blockers notice improvement in their sexual function and in particular the quality of their erectile response [18]. This effect has been attributed to decreased sympathetic vasoconstrictive tone to helicine arteries supplying the lacunar spaces of the corpora cavernosa[8]. However ejaculatory dysfunction with one of these agents namely tamsulosin occurs at a rate of 4-18%, rising to 30% with long term use [19].

5 ALPHA REDUCTASE INHIBITORS

Although the testosterone is the primary plasma androgen inducing the growth of prostate gland and other accessory tissues, it appears to function as a prohormone in that the active form of the androgen in the prostate is not testosterone but a more potent androgenic metabolite diydrotestosterone (DHT). In the prostate, the testosterone in converted into DHT under the influence of enzyme called 5 alpha reducatse. Two types of 5 alpha reductase enzymes

have been identified i.e. type I and type II. Type I enzyme predominates in the skin and liver while type II enzyme is present in the prostate stromal compartment[20]. After the free testosterone in the plasma has entered the prostatic cells through diffusion over 90% of it is rapidly converted to DHT. Finasteride is 5 alpha reducatase inhibitor that blocks/ inhibits the conversion of testosterone into DHT by acting upon type II isoenzyme of 5 alpha redutase. Numerous short term and long term studies comparing finasteride with placebo have been presented. The results suggest that physiologically , treatment with finasteride significantly decreased level of both serum and intraprostatic DHT about 70-80% from base line. In addition total gland size decreased significantly about 15-25% from base line- particularly in the area of periurethral zone of prostate[21].

Baseline prostate size has been found to have a relation to efficacy of finasteride treatment. The larger the prostate at baseline, the greater the urinary flow increased and symptoms score decreased compared with placebo. [22,23,24]. Some authors are of the opinion that men with small prostate are not suitable candidates for finasteride therapy [25,26].
Finasteride therapy must be given for 6 months before its effect on a given patient can be assessed and for at least 12 months to achieve maximum prostate shrinkage and the full extent of its beneficial effect. This may be considered as a disadvantage, when compared with the rapid results offered by surgery or alpha blockers [26].

Finasteride is associated with problems of ejaculation (2.1-7.7%), erection (4.9-15.8%) and libido (3.1-5.4%)[19]. Such significant and undesirable complication in relation to sexual function produces a well documented negative effect on the quality of life of patient.

Recently, a second 5 alpha reductase inhibitor, Dutasteride, has been approved by FDA for medical treatment of symptomatic BPH. It has been claimed that dutasteride can inhibit both types of 5 alpha reductase enzymes. Biochemically it achieves greater and more rapid DHT suppression compared with finasteride. Clinically it appears to be at least as good in terms of improving symptoms and flow rate and reducing the risk or the requirement for BPH related surgery [27].

COMBINATION THERAPY

(ALPHA ADRENERGIC BLOCKERS & 5 ALPHA REDUCTASE INHIBOTRS)
To address both the dynamic (smooth muscle tone) and static (tissue mass) components of BPH , numerous researchers have tested the combination therapy of alpha blockers and 5 alpha reductase inhibitors. One placebo controlled study by Veteran Affairs Co-operation[28] compared the effectiveness of finasteride plus terazosin therapy with monotherapy. Study period was around 1 year. Patients who received either terazosin monotherapy or finasteride plus terazosin experienced the greatest relief of symptoms and greatest improvement in peak flow rates. The finasteride monotherapy was not effective. However the long term results of the doxazosin, finasteride or combination therapy on the clinical progression of BPH have recently been published [29]. In this multicentre, placebo controlled study over 3000 patients were enrolled and this lasted for 4.5 years. The study concluded that combination therapy with 5 alpha reducatse inhibitor finasterile plus the alpha blocker doxazosin reduced the BPH progression by 67%. The risk of BPH progression was reduced by 39% with doxazosin alone and by 34% by finasteride alone. Combination therapy and finasteride alone reduced the long term risk of acute urinary retention and the need for invasive therapy.

CONCLUSION

For patients presenting with minimal bothersome symptoms watchful waiting is an acceptable first line strategy. However, patients on watchful waiting should be closely observed and followed-up at intervals to assess whether symptoms have worsened and whether intervention is necessary.

For patients with bothersome symptoms of BPH, medical therapy with alpha adrenergic blockers is the

preferred first line treatment that gives rapid improvement in symptoms in around 70% patients regardless of the prostate size. 5 alpha reductase inhibitor finesteride is slow to offer improvement in urinary symptoms but also reverses disease progression in selected patients with long term use. Men with small prostate are not suitable candidates for finesteride therapy.

Recent studies support the beneficial effects of combination therapy using alpha adrenergic blocker and 5 alpha reducatase inhibitor to prevent BPH progression in selected patients.

In those patients in whom a reasonable course of medical treatment fails to resolve symptoms of BPH or those patients presenting with absolute indications of surgery, surgical treatment should be considered.

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