General Urology / Genel Üroloji Review / Derleme

Medical management of benign prostatic hyperplasia in the light of available evidence

Mevcut kanıtlar ışığında benign prostat hiperplazisinin tıbbi tedavisi

Zahoor Ahmed Naikoo, Mohammed Saleem Wani, Arif Hamid Bhat

Sher E. Kashmir Institute of Medical Sciences, Srinagar, India

Abstract

Benign prostatic hyperplasia (BPH) is an age-related androgen dependent progressive disease. It is associated with bothersome lower urinary tract symptoms which prove detrimental to the quality of life for both the effected men and their partners. With an aging population elderly people constituting greater proportion of population, the prevalence of BPH is on the rise with a significant impact on medical sector. Initial investigations using simple diagnostic tools can be offered to the patient suspected of having BPH as first diagnostic step in primary care setting and can help in minimizing the delay in diagnosis and management. Due to extensive work done recently in understanding the natural history of BPH and the knowledge of physiological effects of various medical interventions has greatly helped us in choosing therapeutic options for individualized treatment. This has resulted inconsiderable reduction in the rate of transurethral prostatectomy seen during the last couple of decades. Development of adrenoceptor blockade and hormonal manipulation has moved increasing number of men away from surgery towards pure medical management of BPH. We reviewed the current status of medical management in light of the evidence in support of each agent, and the correct selection of treatment.

Key words: Benign prostatic hyperplasia; bladder outlet obstruction; prostate.

Özet

Benign prostat hiperplazisi (BPH) yaşla ilişkili ve androjen bağımlı ilerleyici bir hastalıktır. Hastalar ve eşleri için yaşam kalitesinde bozulmalara yol açtığı gösterilen rahatsız edici alt üriner semptomlara neden olur. İleri yaştaki bireylerin toplumun çoğunluğunu oluşturduğu yaşlanan bir toplumda, BPH prevelansı artmakta, bu da tıp sektörü üzerinde önemli etkiler oluşturmaktadır. Birinci basamakta BPH şüphesi olan hastalarda ilk değerlendirme basit tanısal yöntemler ile yapılarak tanı ve tedavide gecikme en aza indirilebilir. BPH'nın doğasına yönelik son yıllarda yapılan yoğun çalışmalara bağlı olarak, çeşitli tıbbi tedavilerin fizyolojik etkileri üzerine elde edilen bilgiler, bireyselleştirilmiş tedavi uygulamalarının seçiminde büyük ölçüde yardımcı olmaktadır. Bu durum geçtiğimiz birkaç on yılda transüretral prostatektomi oranın yadsınamaz düşüşe neden olmuştur. Adrenoreseptör blokajı ve hormonal tedavilerin gelişmesi ile artan sayıda hasta cerrahi yerine sadece tıbbi yaklaşımla tedavi edilmektedir. Her ajan için mevcut kanıtlar ışığında benign prostat hyperplazisinin tıbbi tedavisinin güncel durumunu ve doğru tedavi seçim yaklaşımlarını gözden geçirdik.

Anahtar sözcükler: Benign prostat hiperplazisi; mesane çıkım obstrüksiyonu; prostat.

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Benign prostatic hyperplasia (BPH) is an age-related, androgen dependent progressive disease with an increasing incidence within an aging population (occurring in 70% of men older than 60 years).[1] The term BPH actually refers to a histological condition characterized by stromal-glandular hyperplasia within the prostate gland[2] and when it is associated with bothersome lower urinary tract symptoms (LUTS) it attains clinical relevance. These LUTS (Table 1) prove detrimental to the quality of life for both the effected men and their partners.[3,4] Beyond symptomatology, health and economic implications of BPH are indisputable. However, the relationship between BPH and LUTS is very complex. Not all men with histological BPH will develop significant LUTS while LUTS can be present in patients without BPH. Benign prostatic enlargement (BPE) is a related entity but different from BPH. Not all men with his-

tological BPH develop BPE; neither do all men with LUTS have concomitant BPE. Similarly, not all men with BPE will have bothersome LUTS.[2] Bladder outlet obstruction (BOO) results from pressure gradient at the bladder neck/prostatic urethra. BOO may cause compression of urethra leading to compromised urine flow and subsequent back flow changes in upper urinary tract with renal failure. Men with BPH/BPE and LUTS do not necessarily have BOO; meanwhile there can be causes of bladder outlet obstruction other than BPH/BPE, though these are commoner. It is important to remember when treating patients with LUTS or BOO, to exclude other conditions (Table 2) before initiating treatment for BPH. The prevalence of LUTS varies with age, in European countries it ranges from 14% for men in fourth decade of life to greater than 40% for men in their sixth decade.[5] There is little cultural variation seen in prevalence of LUTS in these countries. Furthermore, with an ageing population and elderly people constituting greater proportion of population the prevalence of BPH is on the rise with a significant impact on medical sector. In clinical practice LUTS are the common determinants in diagnosis of BPH. There are simple yet effective

Table 1. Lower urinary tract symptoms

Obstructive Symptoms	Irritative Symptoms
Hesitancy	Frequency
Straining	Nocturia
Weak stream	Urgency
Narrow stream	Urge incontinence
Terminal dribbling	Small voided urine volume
Prolonged voiding	
Overflow incontinence	
Suprapubic pressure/pain	
Initial hematuria	

Table 2. Differential diagnosis of benign prostate hyperplasia

Symptoms	Conditions
Frequency, normal urine flow and volume	Diabetes mellitus
Irritative voiding symptoms	Cystitis (infectious, radiation, interstitial)
	Bladder cancer (adenocarcinoma, squamous cell carcinoma, transitional cell carcinoma, carcinoma in situ)
	Bladder stone
Irritative and obstructive voiding symptoms	Prostatitis (acute, subacute, chronic)
	Large bladder diverticulum
	Neurological conditions (congenital spina bifida, myelomeningocele, spinal cord injury, multiple cerebrovascular accidents, followig radical pelvic surgery)
	History of ingestion of medicine (nticholinergic, antidepressants, tranquilisers, decongestants)
Obstructive voiding symptoms	Prostate cancer
	Urethral stricture (post-instrumentation: catheterization/cystoscopy, post infection: non-specific/gonococcal)
	Bladder neck stricture or contracture

investigations, which can accurately diagnose LUTS because of BPH. According to European Association of Urology (EAU) guidelines, evaluation in men with LUTS suggestive of bladder obstruction should initially include conducting a physical examination, creatinine measurement, urinalysis, flow rates, measurement of post void residual urine (PVRU) and serum prostate specific antigen (PSA) in addition to clinical history using a validated questionnaire to assess symptoms.[6] American Urological Association (AUA) does not include measurement of creatinine, PVRU or flow rates in initial evaluation.[7] High correlation between diagnosis based on medical history, serum PSA, digital rectal examination (DRE) and International Prostate Symptom Score (IPSS) and those based on various investigations including ultrasonography and uroflowmetry has been demonstrated.[8] Initial investigations using simple diagnostic tools can be offered to the patient suspected of having BPH as first diagnostic step in primary care setting and can help in minimizing the delay in diagnosis and management with appropriate referral for specialized care.[8] Extensive work done recently has helped us to better understand the natural history of BPH. The knowledge of physiological effects of various medical interventions guides us in choosing therapeutic options for individualized treatment in each clinical setting. Rate of transurethral prostatectomy has considerably reduced from the level reported by American national survey of urologists in 1989, facilitated largely by the development of non operative management of BPH.[9,10] Development of adrenoceptor blockade and hormonal manipulation has moved increasing number of men away from surgery and towards pure medical management of BPH. We analyse the current status of medical management in light of the evidence in support of each agent, and the correct selection of treatment.

BPH: natural history and progression

Progression according to expert review of evidence is defined as worsening of symptoms, increase in prostate volume (PV), deterioration of urinary flow rate, acute urinary retention and need for surgery either for symptoms or acute urinary retention (AUR).[11] Although rarely encountered, renal insufficiency and recurrent urinary tract infection have been included as additional events as measure of BPH progression in clinical trials.[12] Most of the clinical evidence on natural history and progression of BPH we have is from placebo arms of clinical trials. Until recently we had little data about natural history of BPH defined by urodynamic criteria of bladder outlet obstruction. Thomas et al.[13] reported little urodynamic or symptomatic deterioration in men who initially opted for no treatment. In that series, 83% men did not need treatment after a minimum of 10 years follow up after urodynamic diagnosis of obstructive BPH.[13]

Olmsted County study, a large longitudinal study conducted in USA on a sample of 2,115 men aged 40-79 years reported a ≥3-point increase in AUA symptom index (AUA-SI) in 31% of participants at 92 months follow-up.[14] The mean annual increase in the AUA-SI was 0.34 points.[14] The AUA-SI is identical to the seven symptom questions of the IPSS. The Medical Therapy of Prostate Symptoms (MTOPS) study allowed placebo observation of 737 men.[12] Clinical progression of BPH in the placebo arm was defined as an increase in AUA-SI of ≥4 points, AUR, urinary incontinence, recurrent urinary tract infection or renal insufficiency. The rate of overall clinical progression in MTOPS study over a period of 4.5 years was 17.4%.[12] Deterioration of symptoms was the most common (78%) of progression event seen in the study.[12] In comparison, AUR (12%) and invasive treatment due to BPH (5%) were less common but none the less important in view of their financial and emotional consequences.

Relationship between age and markers of progression of BPH has been demonstrated by several studies. In one study, 0.1% of men aged 40-49 years required prostatectomy in contrast to 9.5% of men in eighth decade.[15] In Olmsted County study the percentage of men with moderate to severe urinary symptoms increased from 13% in men aged 40-49 to 28% in men aged >70 years.[16] Similar increase in symptom severity has been observed in Asian men as well. The incidence of AUR in Olmsted County study in those with moderate to severe LUTS increased from 3.0/1,000 person years in those aged 40-49 years to 34.7/1,000 person years in those aged 70-79 years.[16] The overall risk of AUR was estimated to be 23% for an average 60 year old man if he survives for another 20 years.[16] In a recent study on 1,859 men with symptomatic BPH, PV was shown to increase

with age from a mean of 27.7 mL in men aged 40-49 years to 52.3 mL in those aged 70-80 years.[17] Men with PV of ≥30 mL are more likely to suffer moderate to severe symptoms, decreased flow rates and AUR compared to men with PV <30 mL.[18] Enlarged prostate also predicts the need for BPH related surgery but PV is underestimated by DRE by as much as 55%.[19] Transabdomenal ultrasound can assess PV but with limitations in imaging prostate compared to the more invasive transrectal ultrasound.[20] Proscar Longterm Efficacy and Safety Study (PLESS) was placebo controlled observation of 1,500 men with BPH. Data from the placebo arm of PLESS has demonstrated PSA to be a strong predictor of enlarged prostate or the one likely to increase, as well as the risk of developing LUTS, poor urinary flow, AUR and BPH related surgery.[21] Relationship between PSA and prostate growth may show individual variation.[17,22] Data from PLESS showed PSA threshold for detecting PV ≥30 mL as ≥1.3 ng/mL, ≥1.5 ng/mL, and ≥1.7 ng/mL in men with BPH aged 50-59, 60-69 and 70-79 years respectively.[23] Study on Dutch patients showed 89% of the patients with PSA ≥1.5 ng/mL had a PV >30 mL.[17] Correlation between serum PSA and PV is also seen in Asian men.[24,25] Analysis of data suggest that PSA can be used to estimate degree of prostatic enlargement and it showed a sensitivity in predicting prognosis of BPH comparable to the five variable model (comprising of serum PSA, symptoms, peak flow rate, urinary frequency and hesitancy).[26] For this reason, current EAU guidelines use PSA instead of PV in evaluation of risk of developing AUR or requiring surgery in management of BPH.[6] Serum PSA has the advantage of being easily measured and helps in identification of those men most likely to suffer disease progression in BPH. Recently, symptom score and PVR volume worsening have been shown to be good predictors of AUR in men with LUTS suggestive of BPH.[27]

Inflammatory infilterate within prostate biopsies is another variable predictive of poor outcome. Progression increased from 13% to 21% and incidence of AUR increased from 0 to 5.6% in those with inflammatory infilterate.[12]

In a study to evaluate alfuzosin in real life setting with no IPSS or peak flow restriction, history of an episode of urinary retention managed non-operatively was by far the most powerful predictor for future retention.[28] An IPSS bother score of >3 and deterioration while on treatment further increased the risk of AUR.[28]

In the UK and USA, AUR resulted in prostatectomy in 24-42% of men and those patients who avoided surgery through a successful trial without catheter are still at a higher risk of requiring surgery within a year.[29] Furthermore, in the Veteran Affairs study in USA, 36% of men with BPH randomized to watchful waiting required invasive therapy within 5 years of enrolment.[30]

As has been previously mentioned BPH progression can take a variety of forms. LUTS is the most common complaint but patient surveys suggest that risk of surgery is a far greater concern for patients than factors such as symptoms or quality of life.[31,32] In a study, men treated with finasteride, 88% respondents rated reducing the risk of major urological complications as very or extremely important and 93% regarded reducing the need for surgery as very or extremely important.[32] In a survey of men with BPH in European Countries (PROBE), 58% of patients were concerned about risk of developing AUR 56% of requiring prostate related surgery.[33] Reducing the risk of surgery by half was considered more important outcome of drug treatment than rapid symptom relief by more than three quarter of the men in this study.

Over the past decade, medical therapy has become the most frequently used treatment option for management of symptoms associated with BPH with a decline in popularity of surgery. Moreover, patients with mild to moderate symptoms can be managed primarily in primary case setting with referral to urologist required for evaluation and management of complicated cases.

Adrenoceptor blockade

BPH causes obstruction due to a dynamic component of stromal mesenchyme (mainly smooth muscle) and a static component of epithelial glandular tissue.[34] Smooth muscle cells comprise about 40% of the total prostate volume.[35] The adrenoceptors are found in high concentration with in the dynamic component of the prostate gland and influence the resting tone of the smooth muscle with in the prostate and bladder neck.[36] Since the first reports of alpha adrenoceptor influence on benign prostatic obstruction in 1970

based on the non specific α blockade of phenoxybenzamine,[37] much research has allowed description of four subtypes of α_1 adrenoceptors with highest affinity for prostate stromal tissue in the α_{1A} receptor.[38] The alpha blockers work by inhibiting α_1 mediated sympathetic stimulation and thereby promote relaxation of bladder neck and prostatic smooth muscle. These also act on bladder and central nervous system.[39] Alpha-blockers as a treatment option are included in EUA guidelines in case of BPH with bothersome LUTS with no absolute indication for surgery. Alpha-blockers have a rapid onset of action with a 30-45% improvement in symptom scores after 3-month treatment.[40] However, the overall long-term risk of AUR or BPH related surgery is not reduced after treatment with alpha-blockers.[12,41] There are certain collateral benefits of adrenoceptor antagonism such as lowering blood pressure and lipid profile and enhancing erectile function.[42-44]

Terazosin is selective for α_1 receptors, has no specificity for any 4 subtypes.[45] It shows durable efficacy compared to placebo.[46] Tachyphylaxis is not seen with this drug and it is probably due to stromal apoptotic effect or more central mediated effects.[47,48] Doxazocin has similar profile as terazosin,[49] a 45% reduction in the risk of symptom progression (defined as four point increase in AUA-SI) was noted with doxazosin as compared to placebo in MTOPS study.[12] Symptom relief and improvement in urinary flow rates occur irrespective of prostate volume.[50] Doxazosin delayed the time to AUR in the MTOPS study, but the cumulative incidence at 4 years remained similar to placebo, nor did it significantly reduce the incidence of invasive therapy.[12] Alfuzosin also is not a sub selective agent.[51] In Alfuzosin Long Term Efficacy and Safety Study (ALTESS) study over 1,500 men were randomized to placebo or treatment with 10 mg alfuzosin once daily and analysis done after 2 years.[41] There was reduction in symptom deterioration (IPSS points $\geq$ 4) from 16.8 % to 11.7%, but alfuzosin too did not reduce the risk of AUR as compared to placebo (2.1% vs. 1.8%).[41] A lower incidence of BPH related surgery was seen in alfuzosin arm compared to placebo but it was statistically not significant (6.5% vs. 5.1%, p=0.18).[41] These observations can be due to the fact that alpha blockers have no significant effect on PV. Indeed in MTOPS study there was a 24% increase in PV after follow-up of 4.5 years in patients receiving doxazosin which was similar to that seen in placebo group.[12] ALTESS is a relatively young study and long-term studies need to be done to confer the effects of alfuzosin on BPH progression over a longer period of time. There is evidence to suggest that men not responding to alfuzosin treatment (IPSS stable or worsening, and bother score >3 under treatment) are at a greater risk of AUR or BPH related surgery.[27] Alfuzosin can thus be tried as a first line treatment and help in selecting patients at high risk of BPH progression and optimizing management. Alfuzosin for Acute Urinary Retention study for men with acute urinary retention undergoing trial without catheter examined 360 men with first episode of spontaneous AUR randomized to placebo or alfuzosin 10 mg once daily.[52] Successful trial without catheter was observed in 61.9% of men receiving alfuzosin versus 47.9% receiving placebo (p=0.012).[52] Sustained treatment over 6 month period resulted in reduction in BPH related surgery from 24.1% to 17.1%.[53] A residual volume of >1 L and age >65 years increased the risk of failed trial without catheter.[52] No other alpha-blocker had shown any effect in the setting of AUR. Tamsulosin currently is the only α_{1A} selective adrenoceptor antagonist available.[54,55] Since tamsulosin reached the market in 1995 its efficacy in improving symptoms and urodynamic parameters has been demonstrated by several trials.[56-58] Side effects like dizziness and postural hypotension are observed with alpha blockers, with alfuzosin and tamsulosin better tolerated than terazosin and doxazosin.[40] Overall incidence of treatment discontinuation due to adverse effects was low and comparable to placebo. The vascular mediated side effects can be minimized by new gastrointestinal therapeutic system and makes dose titration unnecessary.[59] A higher incidence of abnormal ejaculation compared to placebo has been seen with tamsulosin.[57,60,61]

5α reductase inhibitor

Epithelial component of prostate depends on androgen stimulation for growth. Intracellular conversion of testosterone to much more active dihydrotestosterone (DHT) is catalyzed by 5α reductase.[62] Research into this enzyme as a therapeutic target was led by the observation in 1974 that men deficient in 5α reductase had hypoplastic prostate gland.[63,64] Finasteride

was first described to reduce DHT levels in canine prostate in 1986 and has since become an established 5α reductase inhibitor (5ARI) in clinical use.[65] The two forms of 5ARI, type I and type II are encoded by different genes located on chromosome 5 and 2, respectively.[66] Distribution of each enzyme differs, type II is found in prostatic tissue exclusively, whereas type I is also present in skin, liver and other organs.[67] Selective type II 5α reductase inhibition by finasteride can only reduce circulating DHT levels to 20-40% of normal.[68] The search for an alternative to finasteride lead to the production of combined type I and type II 5ARI dutasteride. Therefore, dutasteride treatment results in a greater degree and consistency of DHT suppression compared to finasteride.[69,70] In a study of men with BPH, mean decrease in DHT was 94.7% with 0.5 mg dutasteride as compared to 70.8% suppression observed with 5 mg finasteride ($p<0.001$).[69] Current EUA guidelines recommend 5ARI for the treatment of bothersome LUTS in men with a PV >30-40 mL with no absolute indications for surgery.[6] Others include PSA ≥1.5 ng/mL in addition to PV >30 mL as indication for use of 5ARI as first line treatment.[71] Significant improvement in symptom scores (2.6 vs. 1.0 points) was seen with finasteride compared to placebo in 4 year PLESS study ($p<0.001$).[23] The risk of symptom progression was reduced by 30% with finasteride as compared to placebo ($p=0.016$) in MTOPS study. Finasteride reduced the overall clinical progression (an increase in AUA-SI ≥4 points, AUR, urinary incontinence, renal insufficiency or recurrent urinary tract infection) risk by 34% relative to placebo.[12] Dutasteride showed a 4.5 point improvement in symptoms at 2 years as compared with 2.3 points with placebo ($p<0.001$). Significant improvement in symptoms occurred after three months in some and six months in majority of patients.[70] Continuous improvement was seen in symptoms; after the end of further two years, improvement in symptom score increased to 6.5 points. ($p<0.001$ vs. 2 years of dutasteride treatment).[72]

Finasteride reduced the risk of AUR by 57% compared to placebo (7% for men receiving placebo and 3% for men receiving finasteride) and surgery by 55% (10% of men receiving placebo and 5% of those receiving finasteride) after 4 years in PLESS study.[23] The MTOPS study also showed significant reduction in AUR and need for surgery in patients receiving finasteride monotherapy as compared to placebo after 4.5 years ($p<0.001$).[12] Similar results have been demonstrated in studies with dutasteride, with a reduction in relative risk of AUR (57%) and surgical intervention (48%) as compared to placebo ($p<0.001$) after 2 years of treatment which was maintained at 4 years of treatment.[70,72] The reduction in risk of AUR and BPH related surgery with 5ARIs is probably due to the effect on PV. Finasteride reduced PV by 18% compared to 14% increase seen with placebo in PLESS study ($p<0.001$)[23] and in MTOPS study PV was seen to be reduced by 19% in patients receiving finasteride compared to 24% increase in those receiving placebo.[12] Dutasteride caused a 26% reduction in PV relative to placebo with significant reduction observed from 1 month after initiation of treatment.[70,72] The 5ARIs are generally well tolerated. The most commonly reported side effects are sexual adverse events,[73] but the incidence of these decreases during prolonged treatment.[23,74] The rates of decreased libido and impotence were identical in finasteride and placebo group after 2 years in PLESS study.[23] Similarly, there was a trend towards reduction in the rate of sexual adverse events over time observed with treatment with dutasteride over a 4-year period.[74] 5ARI therapy reduces serum PSA in a predictable manner and does not effect the diagnostic performance of PSA for detecting prostate cancer. Serum PSA is reduced by approximately 50-60% after 6 months of 5ARI treatment. So, by either establishing a new baseline PSA level or by doubling the PSA values from 6 months onwards in men treated with 5ARI, the clinical utility of PSA in detection of prostate cancer can be preserved irrespective of the PSA level.[75,76] Finasteride treatment may even enhance the sensitivity of PSA for detecting all prostate cancers and high grade disease in particular, because of preferential suppression of PSA related to BPH as shown by the data from Prostrate Cancer Prevention trial.[77]

The additional effects of finasteride, such as the successful treatment of BPH related hematuria have been shown in various small randomized studies.[78,79] This effect on vascularity of the prostate is thought to be mediated through vascular growth factors[80] and can be used to explore the possibility of reduction of intra operative blood loss in patients undergoing transurethral prostatectomy.[81]

Combination therapy

Alpha-blockers offer a rapid symptomatic relief without any effect on underlying disease process, while 5ARIs provide mid and long-term symptom relief as well as a reduction in the risk of disease progression. This complimentary effect provides the rationale for the use of 5ARI/alpha-blocker combination therapy to provide greater and durable benefits than either monotherapy and is a recommended treatment option.[6] Initial studies for the assessment of finasteride in combination with terazosin, doxazosin or alfuzosin were of short duration (6 months to 1 year) and failed to establish a benefit for combination therapy over placebo or alpha blocker monotherapy in terms of symptom improvement.[82-84] During this short duration significant response to finasteride was unlikely to occur. In contrast, MTOPS study demonstrated risk reduction of long term clinical progression by 66% with combination therapy ($p<0.001$ vs. placebo) and this reduction was greater than with either finasteride or doxazosin monotherapy (34% and 39% respectively).[12] Significant improvement in symptom scores was seen with all treatments with combination therapy being superior to either doxazosin ($p=0.006$) or finasteride ($p<0.001$) monotherapy. The risk of AUR and BPH related surgery was significantly reduced over the 4-year period with combination and finasteride monotherapy but not with doxazosin as expected.[12] On recent data analysis of MTOPS it has been concluded that men with PV ≥25 mL and PSA ≥1.5 ng/mL may benefit from combination therapy.[85] A large scale study to examine the effects of the dual 5ARI dutasteride, both as monotherapy and in combination with tamsulosin on the symptoms and progression of BPH is underway. The combination of Avodart and Tamsulosin (CombAT) study is a 4-year multicentre study with additional entry threshold of PV (>30 mL) and PSA(≥1.5 ng/mL) used to select patients at a higher risk of disease progression.[86] Assessment of symptom relief and risk of AUR and surgery in CombAT trial would allow examination of parameters contributing to the overall treatment effect. It would allow for assessment of those patients most likely to benefit from combination therapy rather than evaluating the role of combination therapy. At 2 years a sustained symptom improvement with combination therapy was demonstrated which was significantly greater than the improvement with either dutasteride or tamsulosin monotherapy.[87,88] At 24 months, the reductions in IPSS were -6.2 with combination therapy, -4.9 with dutasteride ($p<0.001$ vs. combination) and -4.3 with tamsulosin ($p<0.001$ vs. combination).[88] Improvement in BPH symptoms in first 12 months of treatment with combination therapy compared to monotherapy were shown for the first time in any study.[87] A significant improvement with combination therapy vs dutasteride was evident from month 3 and tamsulosin from month 6.[88] Improvement of quality of life was significantly greater for combination therapy than for either monotherapy at month 24.[88] In addition, improvements in real flow rate from baseline were significantly better than with either monotherapy from 6 month onwards upto 24 months. Mean change from baseline at 24 months were +2.4 mL/sec with combination therapy, +1.9 mL/sec with dutasteride and +0.9 mL/sec with tamsulosin.[88] Similar proportion of adverse effects were reported in each treatment group. In studies on combination therapy, symptom relief was maintained after withdrawal of alpha blockers in majority of patients with moderate symptoms, whereas there was worsening experienced by the patients with severe symptoms.[89,90]

Alpha-blocker with anticholinergics

Storage or filling symptoms in BPH are attributable to detrusor instability and interfere with daily life activities of the patient and have a negative impact on quality of life. Detrusor instability is thought to occur in up to 40-60% of patients with benign prostatic hyperplasia.[91] Keeping in mind the prevalence and severity of symptoms due to detrusor instability, addition of an anticholinergic agent to therapy has been tried to further improve quality of life. Athanosopoulon reported a series of 50 men with bladder outlet obstruction who had urodynamic proved detrusor instability.[92] Considerable improvement in quality of life was observed with combination therapy of tamsulosin and tolterodine without any detrimental effect on bladder emptying. Comparative studies have shown addition of anticholinergic agent to be safe in patients with bladder outlet obstruction.[93] Anticholinergic therapy is unlikely to interfere significantly in voiding phase of bladder function with a low likelihood of AUR.

Phytotherapy

Phytotherapy for treatment of LUTS is popular in some countries, notably France and Germany with upto one third of the market share of all preparation used for treatment of symptomatic BPH in western countries taken by these.[94] Numerous agents like palm plant, nettle, rye grass, pumpkin seed and cactus flower derivatives have been used for centuries. Each of these preparations contains single or a combination of active compounds. Though their mode of action remains unclear, these products are thought to produce their effects through hormonal effects and interference with normal cellular metabolism.[95-97] Large prospective randomized trials have shown efficacy of phytotherapy comparable to alpha receptor blockade and finasteride, above what could be expected of placebo.[98,99] Well-designed clinical trials are needed before these can be recommended.

Conclusion

Benign prostatic hyperplasia is a chronic, complex progressive disease that affects many men. Although symptom deterioration is the most frequent progression event, patients are often more concerned about events like AUR and BPH related surgery. The significant discomfort, pain, emotional, and economic burden associated with AUR and prostate surgery mandates an approach, which reduces the risk of progression as well as achieves symptom relief. Alpha-blockers promote rapid and long-term symptom relief whereas 5ARIs not only provide continued symptom improvement, but also reduce the risk of progression of disease. Men with an enlarged prostate (PV >30 mL) are at a particularly high risk for disease progression and an effective strategy should be particularly directed towards them. As it is difficult to accurately measure PV by means of DRE, an elevated serum PSA can accurately predict an enlarged prostate once prostate cancer has been ruled out. A PSA ≥1.5 ng/mL should be used to identify the patients at high risk of BPH progression, however a PSA level >4 ng/mL requires further evaluation and biopsy of prostate should be considered. Symptom scores and PVR volume are dynamic variables, which may be helpful in predicting men at risk for AUR. Alpha reductase inhibitors are the only agents that alter the underlying disease process and thereby prevent BPH progression. Although 5ARIs reduce the PSA levels by 50% after 6 months of therapy, they do not mask the PSA changes. Indeed, recent data suggests that 5ARI may enhance the sensitivity of serum PSA in detecting prostate cancer. Medical treatment is the initial choice in management of lower urinary tract symptoms suggestive of bladder outlet obstruction, but ultimate choice of first-line treatment rests at the discretion of the prescribing doctor.

Conflict of interest

None declared.

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Correspondence (Yazışma): Zahoor Ahmed Naikoo.
Sher E. Kashmir Institute of Medical Sciences, 190011 Srinagar, India.
Phone: 0194-2401353 e-mail: drahmedzahoor@gmail.com
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