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Review Article

THERAPEUTIC APPROACHES TO BPH

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ABSTRACT

Background: benign prostatic hypertrophy is a condition that affects an age group of 40-80 . this condition can have a negative impact on their quality of life. This review discusses posibble pharmacotherapy that can improve the quality of life and the options of minimally invasive surgeries in BPH

Areas of concern- Drugs such as selective alpha adrenergic blockers have been useful in improving the quality of life in BPH patients. Combination with 5 alpha reductase inhibitors , botulinum toxin A have also brought about significant improvement in the alleviation of outflow symptoms.

Author recommendation : Pharmacotherapy helps to prevent complications of BPH such as acute retention , prevents the progression of the disease and need for surgery.

Keywords: Alfuzosin ,Finasteride ,Botulinum toxin A,Minimally invasive surgeries,Transurethral resection of prostate.

INTRODUCTION

The geriatric population is ever increasing in this modern world with better medical facilities available to prevent early mortality. Ironically this population has been facing a large amount of morbidities. Benign prostatic hypertrophy is one among those conditions which has affected their quality of living. It is prevalent in the 40 to 80 years of age group with an incidence ranging from 14 to 56 % in different countries. Benign prostatic hypertrophy can lead to acute urinary retention and BPH related surgeries . This impact can be devastating for the geriatric age group. In this review applied anatomy and pathoohysiology of BPH have been revisited. The pharmacotherapy and minimally invasive surgical modalities have been discussed.

Applied Anatomy

In the male reproductive system the prostrate contributes itself by being the accessory gland which produces secretions which adds to the constituents of the seminal fluid1 . The prostate gland is a cone shaped gland situated in the lesser pelvis in front of the ampulla of the rectum and below the neck of the urinary bladder[1]. The prostate gland weighs around 8 g.Grossly it is represented by an apex , a base, anterior , posterior and inferolateral surfaces. The apex is directed and rests upon the urogenital diaphragm[1,2]. The junction where the base of the prostrate is continuous with the neck of the bladder has close proximity to the vesical and prostratic plexus. [3]The anterior surface of the gland is pierced by the urethra. The posterior surface of the gland receives the ejaculatory ducts. The postrate gland consists of 5 lobes. Anterior , posterior, median or middle and right and left lateral lobes. The anterior lobe has no glandular tissue , so adenoma from this part of the prostrate is very rare. The posterior lobe is associated with usually carcinoma of the prostrate[1,2,3]. The median lobe contains majority of the glandular tissue, so being a very common site for adenoma. Lateral lobes also contain glandular tissue from which adenomas may arise. The prostate gland has a true and a false capsule. The true capsule is a fibromuscular structure formed by the condensation of the gland itself peripherally[1]. This portion of the gland has no venous plexus. the pelvic fascia condenses to form the false capsule.Incorperated along the sides of this capsule is the prostratic venous plexus.The prostrate is divided into structural zones. They include a central zone, peripheral zone, transitional zone, and a periurethral zone. Nodular hyperplasia occur mostly in the central zone and carcinomas normally occur in the peripheral zone.

Circulation

subcapsular[1] and periurethral plexus contributed by the inferior vesical , middle rectal and internal pudendal arteries. Prostratic venous plexus communicates with the vesical plexus and also with the internal pudendal veins . They ultimately drain into the vesical and internal iliac vein

Nerve supply

supplied by both[1] sympathetic and parasympathetic nervous system.

Lymphatic drainage.

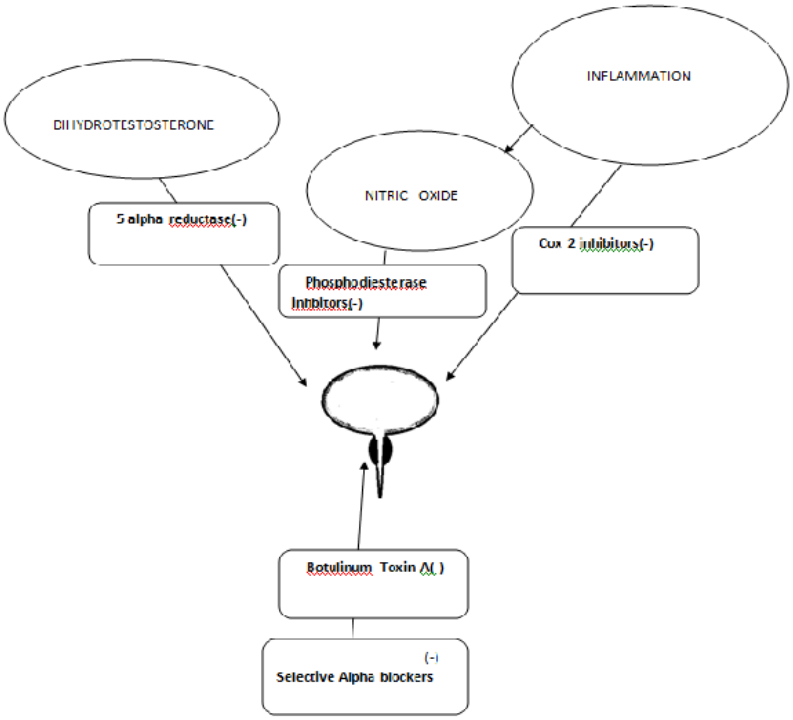
Prostrate drains into[1,2] the internal iliac nodes, sacral nodes, external iliac.

Pathophysiology (Vide.Fig.1)

Majority of the testosterone is produced by the testis[4]. The testosterone is converted by the enzyme 5 alpha reductase to dihydrotestosterone. The dihydrotestosterone binds to the prostatic glandular cells and leads to the entity, benign prostratic hypertrophy[4]. Dihydrotestosterone binds to the nuclear receptors in the cell which causes DNA , RNA and growth factor stimulation which ultimately to the hyperplasia of the gland . Paradoxical manifestation of this entity in old age when actually testosterone drops and non exacerbation of nodular hyperplasia on administration of testosterone proves that other factors may also contribute to benign prostratic hypertrophy[4]. Experimental studies shows that age related increase in estrogen contributes to the over expression of the DHT receptors on prostratic parenchymal cells .

Apart from this theory benign prostatic hypertrophy is hypothesized to be because of an infective or non infective inflammatory cause. Studies on benign prostratic hypertrophy specimens have demonsatrated heterogenous strains of bacteria and virus. The production of proinflammatory cytokines in response to the bacteria and virus may lead to prostatic growth .The hyperproliferative pathway caused by autoimmune response due to release of self antigens like prostate specific antigen following tissue injury like non infective prostatitis leads to benign prostatic hypertrophy. With age the cellular tolerance to prostate specific antigen could decrease leading to the autoimmune response.

Oxidative stress is also seen to contribute to benign prostatic hypertrophy. There is generation of free radicals with acute and chronic inflammation of the prostate. Free radicals suchs as nitric oxide and other species of oxygen will lead to oxidative stress of tissue and DNA leading to the hyperplastic transformation seen in benign prostatic hypertrophy. Nitric Oxide also leads to the the activation of the cycloxygenase enzymes which in turn leads to inflammation.



GrossPathology

[4]The inner periurethral glands are mostly involved in the nodular hyperplasia. The cut surface shows multiple , circumscribed nodules which bulges from the cut surfaces and they have solid appearance or may have cystic areas.

HISTOLOGY

[4]Microscopically hyperplastic glands are seen which are lined by tall, columnar epithelial cells which lie over flattened basal cells. The glandular lumen contain corpora amylaceae, a proteinaceous material. Areas of infarcts may also be seen in severe cases.

Clinical features

[5]Patients present with hesitancy, intermittent interruption of the urinary stream while voiding, symptoms of urinary obstruction, urinary urgency, frequency, nocturia.

Drugs used in bph

Alpha adrenergic antagonists

Alfuzosin

[6]This drug is a selective alpha 1 adrenergic antagonist. It is a competitive inhibitor of alpha 1 adrenergic receptors . This action brings about the decrease in tone of the smooth muscles of the proximal urethra, bladder base, prostatic capsule, prostate leading to the decrease in the bladder outlet obstruction associated with benign prostratic hypertrophy. Studies have shown a remarkable improvement in the urine flow , decrease in the post voidal residual urine, and the symptomatic score. This is a drug which can be used to treat those whose surgery is delayed or who prefer conservative treatment to surgery . [7]Alfuzosin is a drug that is very selective in its action that it has very less potential in causing orthostatic hypotension and blood pressure alterations in those already on antihypertensive drugs.[8]Headache, fatigue, respiratory tract infection are some of the side effects of this drug.

Tamsulosin

[9]This is the first alpha 1 adrenoreceptor antagonist .Tamsulosin acts at the alpha 1A and 1D receptor level. These receptors are present in the smooth muscles in association with the prostate and the prostatic capsule.[10] It increased the urine flow and reduced the lower urinary tract symptoms associated with benign prostatic hypertrophy. Studies show Tamsulosin 0.4mg to be as effective as 2.5 mg alfuzosin given 3 times daily. [11]Thus Tamsulosin is a drug with conveniant once a day regimen with very less chance for hypotensive effects .Its interaction with antihypertensive drugs to cause profound drop in blood pressure is very rare and there is no need to titrate the dose of tamsulosin. Abnormal ejaculation and dizziness are common adverse effects of tamsulosin. Postural hypotension ,palpitation, asthenia are very rare but possible adverse effects of the drug.

Silodosin

[12]Silodosin is also as effective as tamsulosin in the treatment of benign prostatic hyperplasia. Silodosin 4mg once daily is effective in alleviating the urinary symptoms associated with benign prostatic hypertrophy. [13]Studies have shown lesser cardiovascular effects when compared to tamsulosin . Silodosin usage is associated with abnormal ejaculation and mild hypotensive effects.

Doxazosin

[14]Doxazosin is yet another selective alpha 1 adrenergic antagonist which leads to the alleviation of the lower urinary tract symptoms associated with BPH. Studies comparing monotherapy of doxazosin and combined doxazosin and finasteride therapy have shown that combined therapy is more effective. [15]There were significant improvement in symptom score and peak urinary flow rate with combination therapy involving doxazosin. Combination therapy reduces the risk of long term retention of urine, the complications associated with benign prostatic hypertrophy, and delays the need for invasive treatment for benign prostratic hypertrophy. The common unwanted effects shown by monotherapy and combination therapy involving doxazosin were fatigue and dizziness.

Terazosin

[16]Terazosin is a drug with a chemical structure similar to prazosin . It is a long acting alpha adrenergic antagonist with an ability to reach peak plasma concentration in 1-2 hours and has a half life of about 12hours. Dose and plasma concentration of this drug shows a linear relationship. This drug can be administered as a single dose regimen . Terazosin action is not aaltrered in hypertensive patients due to its safety profile and its favourable lipid effects. Terazosin exhibits mild adverse effects but it exhibits with a frequency more than that of other alpha adrenergic antagonists which leads to treatment discontinuation.

5alpha Reductase Inhibitors

Dutasteride

[17]Dutasteride is a second generation selective irreversible inhibitor of type 1 and type 2- 5 alpha reductase enzymes which are overexpressed in case of benign prostatic hyperplasia . 5 alpha reductase enzyme is responsible for the conversion of testosterone to dihydrotestosterone. A daily single dose of 0.5 mg has been approved for its use in mild to moderate benign prostatic hypertrophy.It was seen to decrease the prostatic size ,decrease the risk of acute urinary retention and the chance for the patient to go for benign prostatic hypertrophy related surgeries. Dutasteride is also believed to reduce the risk of prostatic cancer.Dutasteride side effects may include dizziness, abnormal ejaculation, decreased libido.

Finasteride

[18]Finasteride is a competitive inhibitor of 5 alpha reductase with an affinity towards type 2 more than type one of the enzyme.[18,19] Finasteride can be administered as a daily single dose of 5mg to bring anout its effects.[18,19] Finasteride decreases the volume of the prostate ,prostate specific antigen levles and improves the obstructive symptoms expressed in benign prostatic hypertrophy. Long term usage of this drug produced side effects such as decreased libido, abnormal ejaculation.

Botulinum Toxin A

Botulinum toxin A is obtained from botulinum clostridium strains.[20,21] Botulinum toxin A acts by inhibiting the acetylchoine release at the nerve synapses in the prostatic smooth muscle alleviating the lower urinary tract symptoms associated with benign prostatic hypertrophy. [21,22]Depending on the size of the prostate 100 to 300U of the botulinum toxin A is administered transurethrally, transrectally or transperineally into the prostate. This can be useful in patients who are refractory to oral medication and are not ideal candidates for a surgery.

Gnrh Antagonists

GnRH Antagonists titrate the testosterone levels to a level which reduces the prostate volume without bringing about an adverse effect.[23]Cetrorelix is a GnRH antagonist extensively studied for its effectiveness in benign prostatic hypertrophy. The improvement in the peak flow rate of urine and international prostate scoring system was comparable to that of the effectiveness of alpha blockers used for benign prostatic hypertrophy. This drug did not seem to cause vasomotor or sexual adverse effects as it had only a transient effect on the drop of testosterone levels.

Phosphodiesterase 5 Inhibitors

[24]The rationale to see Phosphodiesterase 5 inhibitors as a possible treatment in benign prostatic hypertrophy was because of the involvement of nitric oxide in increasing the tension of prostatic smooth muscle. Thus phosphodiesterase 5 nhibitors were seen as a possible prostatic smooth muscle relaxant . phosphodiesterase inhibitors are normally used for erectile dysfunction.[25] Among the commonly used phosphodiesterase inhibitors tadalafil being the only drug approved for daily usage in erectile dysfunction, it is the ideal drug that can be administered for benign prostatic hypertrophy. Despite its effectiveness further studies are required for its approval for as a front line drug for benign prostatic hypertrophy.

Celecoxib

In view of the role of cycloxygenase 2 enzyme in benign prostatic hypertrophy ,COX-2 inhibition through drugs like celecoxib has been found to be promising[26]. Studies have shown that celecoxib decreases nocturnal frequency and improve the international prostate symptom score.

NX-1207

This is a new drug under investigation for the treatment of benign prostatic hypertrophy. [27]NX-1207 has been seen to produce a proapoptotic effect on the prostate. It is administered as a single dose as a intraprostatic injection. This drug has been shown to decrease the prostate size and improve the urinary flow. NX-127 has to undergo further studies for its efficacy and safety to be finally established.

Minimally Invasive Management Of Prostatic Hyperplasia[28]

Intraprostatic Stents

These are one of the initial least traumatic methods of managing symptomatic benign prostatic hypertrophy. Many types of stents are available differing in material ,length, diameter and design. Intraprostatic stents are used in mainly in patients who are not fit for surgery. There are temporary and permenant stents available according to the requirement. Temporary stents are tubular devices used for a short period of time to relieved bladder outlet obstruction. Temporary stents do not get incorporated into the urethral wall and they need to be removed every 6 to 36 months according to the material of the stent. The complications asscociated with these stents include stent migration,recurrent urinary tract infection, hematuria with clot retention,encrustation. Permenant stents are used to treat the patients with symptomatic benign prostatic hypertrophy permanently. Permenant stents initially was seen with enthusiasm and was seen to have a probable effect comparable to that of transurethral resection of prostate.Permenant stent usage unfortunately does not have enough place in literature in the present times in long term usage especially in benign prostatic hypertrophy. Some permenant stent usage have shown adverse effects such as irritative urinary symptoms, painful ejaculation, migration of the stent,epithelial hyperplasia . However stents made of nickel- titanium alloy such as the ultraflex stent has a capacity to expand when exposed to body heat and the chance for stent migration and epithelial hyperplasia is very low. Newer temproray biodegradable stents can be useful in treating temporary retention that can occur secondary to high energy microwave therapy for benign prostatic hypertrophy.

Transurethral Needle Ablation (Tuna)

Transurethral needle ablation of the prostate causes necrosis of the prostatic tissue thereby leading to the reduction of outflow resistance and volume of obstruction posed by the enlarged prostate. The ablation is brought about by increasing the prostatic temperature in excess of 60degree which is brought about by low level radiofrequency delivered by needles introdu ced into the prostate. Patients with lateral lobe enlargement and prostrate which is 60 g or less are seens to benefit from transurethral needle ablation. The adverse effects included urinary retention at a rate in between 13.3 to 41.6%, urinary tract infection in about 3.1% , haematuria.

Transurethral Microwave Therapy

Transurethral microwave therapy is a modality that uses sympathetic nerve degeneration and induction of apoptosis to decrease lower urinary tract symptoms associated with benign prostatic hypertrophy.In comparison with transurethral resection of prostate, transurethral microwave therapy required a higher rate of retreatment. There is a relatively high number of non responders so the success in this treatment modality cannot be guaranteed in every patient. It was found that this procedure carried less morbidity than that of transurethral resection of prostate but was not as effective as the later in relieving the bladder outlet obstruction associated with benign prostatic hypertrophy.

Laser Treatment

Usage of laser in treatment of benign prostatic hypertrophy is very promising in terms of its precision and success in other fields of surgery. Laser treatment is still under the development stage in being standardized upto the level of confidence gained by transurethral resection of prostate. The minimal invasiveness in laser technology is improving and the rate of complications such as prolonged cathetarisation, bacteriuria, urethral strictures have decreased. More studies and evidences are required to prove laser to be as good as transurethral resection of prostate in improving the quality of life.

Transurethral Vapourisation Of Prostate

Transurethral vapourisation of prostate uses concepts of vapourisation and dessication to be combined in the procedure. Further studies are required for transurethral vapourisation to be proved a modality to be completely dependant upon with respect to its efficacy and possible adverse effects.

Transurethral Resection Of Prostate

This is the gold standard of treatment in benign prostatic hypertrophy which has gained popularity throughout the world. This is indicated in patients whose quality of life is affected and has moderate to severe urinary symptoms. Recurrent infection, hematuria, azotemia, urinary retention are absolute indications for transurethral resection of prostate. Intra operative problems include transurethral resection syndrome,intraoperative priapism, bleeding. Post operative complications include bleeding, failure to void, clot retention

Transurethral Incision Of Prostate

This technique is simple and its indicated in younger patients with prostate smaller than 30 g .The procedure efficacy is comparable with that of transurethral resection of prostate in such a category.

CONCLUSION

Pharmacotherapy is the treatment for benign prostatic hypertrophy unless the disease has progressed to an extent where the symptom score prompts for surgery. Pharmacotherapy and minimally invasive surgeries are compliant to the patients especially old age groups for preventing complications of BPH and bringing about a halt in the progression of the condition.

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