MEDICAL MANAGEMENT OF LOWER URINARY TRACT SYMPTOMS (LUTS) DUE TO BPH , COMPARATIVE STUDY BETWEEN SELECTIVE α RECEPTOR BLOCKERS ALONE VERSUS COMBINATION OF SELECTIVE α RECEPTOR BLOCKERS & 5 α REDUCTASE ENZYME INHIBITORS

THESIS

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ABSTRACT

Benign prostatic hyperplasia (BPH) has been known for centuries to be a cause of urinary dysfunction in men .

This is a prospectively clinically designed study to compare the role of selective alpha adrenergic receptor blockers alone versus combination between selective α-adrenergic receptor blockers and 5α- reductase enzyme inhibitors in relieving moderate to severe LUTS due to BPH.

Duration of therapy was 6 months. Patients were men above 50 years suffering from symptoms that might be related to BPH, presenting with moderate to sever LUTS with I-PSS more than 7 , patients were excluded from the study if they were having a confirming malignancy of the prostate, bladder cancer, and previous rectal surgery or irradiation…etc.

Patients were subjected for a full urologic history and clinical examination, I-PSS is the standard questionnaire, quality of life questionnaire, sex score questionnaire (libido and potency)…etc.

Patients were given either, doxazosin 4mg, and finasteride 5mg + doxazosin 4mg.

Monthly follow up for all questionnaire, physical examination (including blood pressure measurement), urine analysis…etc .

It was found that the combination therapy has more effiicacy than monotherapy for patients presenting with moderate to severe LUTS due to BPH .

Key words:

1- BPH .
2- LUTS.
3- Selective alpha receptor blockers.
4- 5 alpha reductase enzyme inhibitors.

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Contents

Abbreviations

AUA : American Urological Association .
BPH : Benign Prostatic Hyperplasia .
BOO : Bladder Outlet Obstruction .
CELAP : Combined Endoscobic Laser Ablation Of The Prostate .
CHD : Congenital Heart Disease .
FGF : Fibroblast Growth Factor .
EGF : Epidemal Growth Factor .
D.M. : Diabetes Mellitus.
DRE : Digital Rectal Examination.
DHT : Dihydrotestosterone .
HOLEP : Holmium Laser .
H.S. : Highly Significant .
I-PSS : International Prostatic Symptom Score .
I V U : Intravenous Pyelography .
KTP : Potassium Titanyl Phosphate .
LDL : Low Density Lipoprotein .
LUTS : Lower Urinary Tract Symptoms .
LHRH : Leutenising Hormone Releasing Hormone .
MMAP : Marine Medical Assessment Program.
N.S. : Non Significant .
Nd.YAG : Neodymium – yttrium –aluminum-garnet
NIH : National Institute Of Health.
PAP : Prostatic Acid Phosphatase .
PDGF : Platelet Derived Growth Factor.
PSA : Prostatic Specific Antigen .
PUT : Plain Urinary Tract .
PVR : Postvoid Residual Urine.
Q max. : Maximum Flow Rate .
Q av. : Average Flow Rate .
S. : Significant .
TOMHS : Treatment Of Mild Hypertension Study.
TRUS : Trans Rectal Ultrasound.
TURP : Transurethral Resection Of The Prostate.
UTI : Urinary Tract Infection .

Introduction& Aim of work

Introduction :

Benign prostatic hyperplasia (BPH) has been known for centuries to be a cause of urinary dysfunction in men .

In a study of aging among normal volunteers a 51 % clinical incidence of BPH in men 60- 69 years of age was found. Almost all men, if they live long enough will experience minor voiding symptoms due to prostatic enlargement. Many men will experience more significant symptoms and seek medical advice and about one third of all men in United States Of America (USA) might undergo Prostatectomy by the time they reach 80 years of age ***(Barry , 1990) .***

The advent of medical therapy for men suffering from lower urinary tract symptoms (LUTS) due to BPH has had a greater impact on the professional practice patterns of American urologists than any other single event in the field of urology .

In 1986, transurethral resection of the prostate (TURP) constituted 38 % of all surgeries performed by the urologists in USA and activities centered around TURP comprised 25 % of the total professional work load.

In USA, the number of TURP procedures dropped from three hundred thousand. Procedures in 1987 to one hundred thousand procedures in 1996 . Among other factors , the availability of effective medical therapy was the main cause for such a decline ***(Holtgrewe ,1998***).

Aim of work :

Knowing that the prostate is androgen dependant organ under the effect of androgen stimulation, abolishing this androgen stimulatory action would influence the progression of LUTS due to BPH .

Furthermore, recognizing the large amount of smooth muscles in the bladder neck , prostate and prostatic urethra, one would appreciate the role

of α-adrenergic receptors antagonists in relieving the major obstructive symptoms due to BPH.

This is a prospectively designed study to compare the role of selective alpha adrenergic receptor blockers alone versus combination between selective α-adrenergic receptor blockers and 5α- reductase enzyme inhibitors in relieving moderate to severe LUTS due to BPH. Whether or not this combination therapy might improve the quality of life, relieve the symptoms of LUTS, reduce the number of surgeries regardless the size of the prostate .

Anatomy Of The Prostate

The prostate is shaped like an inverted pyramid with its base directed upwards being firmly adherent to the bladder and its apex directed downwards being firmly adherent to the urogenital diaphragm. It is a fibromuscular glandular organ that surrounds the prostatic urethra.

The prostate has a base and an apex, an anterior, posterior and inferolateral surfaces. The base is the upper surface adjacent to the bladder neck while the blunt apex is the lowest part. The anterior surface limits the retropubic space posteriorly and is connected inferiorly to the pubic bones by the puboprostatic ligaments. The inferolateral surfaces are clasped by the levator prostatae parts of the levator ani muscle. The posterior surface lies in front of the lower rectum and is separated from it by the rectovesical fascia. The ejaculatory duct pierces the posterior surface just below the bladder and pass obliquely through the gland for about 2 cm to open separately into the prostatic urethra about half way along its length on the verumontanum **(*Leshin et al , 2000)*.**

A thin layer of connective tissue at the periphery of the prostate forms a true capsule, outside which is a condensation of pelvic fascia forming the so called false capsule, a plexus of veins lies between these two capsules ***(Lepor et al ,1995)*** .

Zonal anatomy of the prostate :

In 1912 , Lowsley presented a detailed description of the anatomy of the human prostate, based on embryonic and foetal studies ,however, his scheme of median and lateral prostatic lobes was found to be inadequate as a model for the anatomy of the adult human prostate **.**

This early concept of the prostatic structure was modified by the work of Franks and by the more recent studies of McNeal and co workers who described four glandular regions of the prostate. The urethra is the key anatomic reference point. The tissue that lies ventral

to the urethra is fibromuscular, while the tissue that lies posterior and dorsal is glandular .

The glandular prostate can then be subdivided as follows:

A peripheral zone represents about seventy percent of the glandular part of the prostate. This zone forms the lateral and posterior or dorsal part of the organ. It may be regarded as a funnel that distally constitutes the apex of the prostate and cranially opens to receive the distal part of the wedge shaped central zone, the ducts of the peripheral zone open into the distal prostatic urethra. Seventy percent of prostate cancer cases arise from the peripheral zone ***(Walsh et al , 1990)***.

A central zone comprises about 25% of the glandular prostate , this zone is wedge shaped and surround the ejaculatory duct with its apex at the veromontanum and its base against the bladder neck, thus , the central zone is, at least in its distal part, surrounded by the peripheral zone and its ducts open into the prostatic urethra , in close proximity to the ejaculatory ducts .

The proximal urethral segment is related to the preprostatic sphincter and two tiny glandular portions of the prostate, the transition zone and the periurethral region. The preprostatic sphincter consists of rings of smooth muscles around the dorsal aspect of the urethra integrating with the ventral fibromuscular stroma and is thought to prevent the retrograde ejaculation.

A transitional zone represents 4 to 5 % of the glandular prostate. It is composed of two small areas of glandular tissue located lateral to the preprostatic sphincter and it is the site of origin of benign prostatic hyperplasia. The periurethral glandular region represent less than 1% of the glandular prostate ***(McNeal et al, 1990***).

The stroma of the transitional zone is composed of interlacing bundles of compact smooth muscle cells that blend with the adjacent stroma of the preprostatic sphincter and anterior fibromuscular stroma **(*Leshin et al ,2000).***

Incidence of BPH

In the Baltmore longitudinal study of aging, they analysed 1057 men with respect to the development of obstructive symptoms and the possibility of surgery for BPH. It was found that the prostatic size and the diagnosis of BPH both increase with age. By the seventh decade , nearly 60 % of all men had clinical evidence of BPH and by the eighth decade , this figure increased to greater than 80 % ***(Arrighi et al , 1991).***

It is clear that the incidence of BPH (both histological and clinical) increases with age ***(Miezkalski ,1994).***

Based upon a study of 707 adenomas enucleated at the John Hopkins Hospital, the weight of resected specimen increases with each decade over age of 50 years ***(Brandt et al,2000)***

Pathology of BPH

Benign enlargement of prostate , benign prostatic hyperplasia, nodular hyperplasia, hyperplasia consists of overgrowth of the epithelium and fibromuscular tissue of the transition zone and periurethral area. Lower urinary tract symptoms are caused by interference with muscular sphincteric function and obstruction of urine flow through the prostatic urethra. There is a positive but weak correlation between the amount of hyperplastic tissue and clinical symptoms ***(Senge et al , 1999).***

Grossly , BPH consists of variably sized nodules that are soft or firm, rubbery and yellow gray , and bulge from the cut surface upon transection. If there is prominent epithelial hyperplasia in addition to stromal hyperplasia , the abundant luminal spaces create soft and grossly spongy nodules which ooze a pale white watery fluid. If BPH is predominently fibromuscular, there may be diffuse enlargement or numerous trabeculations without prominent nodularity. Degenerative changes include calcification and infarction. BPH usually involve the transition zone, but occasionally nodules arise from the periurethral tissue at the bladder neck. Protrusion of bladder neck nodules into the bladder lumen is referred to as median lobe hyperplasia. Rarely, hyperplastic nodules are present in the peripheral zone (***Van Poppel et al , 2002*****).**

Microscopically, BPH is invariably nodular, composed of varying proportions of epithelium, fibrous connective tissue and smooth muscle. There are five types of nodules,including: adenomyofibromatous (most common), fibromuscular, muscular (uncommon), fiboadenomatous and stromal . In practice , pathologists do not classify BPH histologically because of the wide variation in composition. Common associated findings include chronic inflammation, acinar atrophy and luminal corpora amylacea and microcaliculi ***(Bostwick et al , 1999).***

Vascular insufficiency probably accounts for infarction of BPH nodule, seen in up to 20% of resected cases. The center of the nodule undergoes hemorrhagic necrosis, often with reactive changes in the residual epithelium at the periphery, including squamous metaplasia and transitional cell metaplasia (***Hartanto et al, 2000).***

Pathogenesis of BPH

Pathogenesis of BPH is uncertain, but multiple theories have been proposed. Aging and the presence of androgen stimulatory effect is the most accepted theory. Regression of BPH can be reversibly induced by luteinizing hormone releasing hormone (LHRH) agonists, confirming that androgens have an important supportive role in BPH (***Peter et al , 1997).***

*Aging theory :

There is an increase in cumulative lipid peroxidation with aging, resulting in an increase in tissue concentration of cofactors such as NAD and NADPH. This increases 5α-reductase concentration (being sensitive to changes in NADPH) and thus increasing the prostatic dihydrotestosterone (DHT) concentration, inducing epithelial and stromal growth of prostate resulting in BPH ***(Geller et al , 1991).***

*Oestrogenic theory :

The ratio of plasma oestrogen to testosterone increases with age , and this may result in stromal overgrowth because of the greater amount of hormone receptors in the stroma compared with epithelium (***Partin et al , 1998).***

*Embryonic reawakening theory :

The earliest lesion of BPH is a proliferation of epithelium probably under the influence of DHT, with branching and budding due to reawakening of the embryonic inductive adulthood (***McNeal et al , 1990)*** .

*Oxidoreductase theory :

Lower concentration of 17β-hydroxysteroid and 3α-hydroxysteroid enzymes is found in BPH patients compared to controls. These enzymes are responsible for DHT catabolism. It is postulated that the decrease in the concentration of these enzymes result in high level of DHT resulting in BPH ***(Cooner et al , 1998) .***

*Growth factor theory :

Inflammation and the release of growth factors such as platelet - derived growth factor (PDGF) may play a role in the development of BPH ***(Helpap et al , 1999).***

Pathophysiology of BPH

Benign Prostatic hyperplasia increases urethral resistance , resulting in compensatory changes in bladder function. However, the elevated detrusor pressure required to maintain urinary flow in the presence of increased outflow resistance occurs at the expence of normal bladder storage function. With Obstruction ,there is loss of the vesical compliance. The detrusor muscle, due to distal obstruction develops hyperplasia, hypertrophy and deposition of collagen fibers ***(McGuire et al ,1987).***

These changes,in addition to age related changes, lead to the development of detrusor instability or loss of normal control over the reflex detrusor response. These changes are responsible for the irritative symptoms that often trouble the patient most in the form of frequency, urgency, nocturia and urge incontinence ***(Christensen and Bruskewite ,1990).***

Importance of prostatic smooth muscle :

Regardless of the exact proportion of epithelial to stromal components in BPH, there is no question that prostatic smooth muscles represent a significant element of the obstruction associated with BPH ***(Shapiro et al , 1992)*** .

The prostatic smooth muscles as well as the prostatic capsule are rich in adrenergic nerve supply. Stimulation of the adrenergic nervous system clearly results in a dynamic increase in prostatic urethral resistance, however use of α- receptor blockers clearly diminish this response ***(Denis et al , 1998)*** .

The bladder response to obstruction :

Collagen deposition with the detrusal muscle fibers is associated with decreased detrusor contractility, with further deterioration of the force and caliber of the urinary stream, hesitancy, intermittency, increased residual

urine and finally might lead to retention of urine, and this phase is called decompensation phase (***Cheville et al , 2000)*** .

The major endoscopic detrusor change, due to obstruction, is appearance of trabeculations and cellules. If left untreated, mucosal herniation between detrusor muscle bundles occurs, causing diverticulae formation ***(Leong et al , 1998)*** .