Comparative Efficacy and Safety of a Fixed-Dose Combination Therapy of Tamsulosin and Tadalafil versus Tadalafil alone for BPH Patients with Lower Urinary Tract Symptoms and Erectile Dysfunction

Thesis

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Ahmed Ebeid

Dedication

To

My Dear Mother and
the soul of My Father

Who gave me too much
And received too little

To My Wife & My Brothers

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List of Abbreviations

Abb.	Full term

ACP ..... *American College of Physicians*
AR ..... *Adrenergic Receptor*
ATP ..... *Adenosine Triphosphate*
AUA ..... *American Urological Association*
AUR ..... *Acute Urinary Retention*
BOO ..... *Bladder Outlet Obstruction*
BPE ..... *Benign Prostatic Enlargement*
BPH ..... *Benign Prostatic Hyperplasia*
BUN ..... *Blood Urea Nitrogen*
cAMP ..... *Cyclic Adenosine Monophosphate*
CCs ..... *Corpora Cavernosa*
cGMP ..... *Cyclic Guanosine Monophosphate*
DHT ..... *Dihydrotestosterone*
DRE ..... *Digital Rectal Examination*
ED ..... *Erectile Dysfunction*
eGFR ..... *Estimated Glomerular Filtration Rate*
eNOS ..... *Endothelial Nitric Oxide Synthase*
FDA ..... *Food and Drug Administration*
GTP *Guanosine-50-Triphosphate*
H&E ..... *Hematoxylin and Eosin*
IIEF-5 ..... *International Index of Erectile Function*
IP3 ..... *Inositol Trisphosphate*
IPSS ..... *International Prostate Symptom Score*
IQR ..... *Inter-Quartile Range*
LH ..... *Luteinizing Hormone*
LUTS ..... *Lower Urinary Tract Symptoms*
MMAS ..... *Massachusetts Male Aging Study*
MUSE ..... *Medicated Urethral System for Erections*
NH2 ..... *Amino Terminus*

List of Abbreviations (Cont...)

Abb.	Full term

NIH .....National Institutes of Health
NO.....Nitric Oxide
NOS .....Nitric Oxide Synthase
P .....Phosphate
PAH .....Pulmonary Arterial Hypertension
PDE.....Phosphodiesterase
PDE5.....Phosphodiesterase Type 5
PGE1.....Prostaglandin E1.
PSA .....Prostate-Specific Antigen
PVR .....Postvoid Residual
PVRU.....Postvoid Residual Urine
PZ.....Peripheral Zone
QOL .....Quality of Life
S .....Serine
sGC .....Soluble Guanylate Cyclase
SHBG .....Sex Hormone-Binding Globulin
SPSS .....Statistical Package for Social Science
TGF .....Transforming Growth Factor
TSH .....Thyroid-Stimulating Hormone
TUIP .....Transurethral Incision of the Prostate
TUMT .....Transurethral Microwave Therapy
TUNA .....Transurethral Needle Ablation of the Prostate
TURP .....Transurethral Resection of the Prostate
TZ .....Transitional Zone
UGS .....Urogenital Sinus

ABSTRACT

Twenty Five patients received fixed-dose combinations of Tamsulosin 0.4mg/day and Tadalafil 5mg /day for 45 days (groupA) and Twenty Five patients received Tadalafil 5mg /day for 45 days (group B).

The study showed that the fixed-dose combinations of Tamsulosin and Tadalafil significantly improve IPSS score and Qmax more than with Tadalafil 5 mg/day alone. Furthermore, PVRU significantly decreased with the fixed-dose combinations of Tamsulosin and Tadalafil more than with Tadalafil alone. Fixed-dose combinations of Tamsulosin 0.4 mg plus Tadalafil 5 mg were determined to be safe, efficacious, and well tolerated in the subjects investigated, which suggests the new fixed-dose combinations therapy can offer clinically relevant benefits for patients with LUTS complaints and desiring amelioration for comorbid ED complaints.

Keywords: *Transforming Growth Factor - Transitional Zone*

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a disorder histologically characterized as the nonmalignant hyperplasia of prostatic cells. Most of patients with benign prostate hyperplasia present with lower urinary tract symptoms (LUTS) ***(Gravas et al., 2015).***

About half of men with BPH develop an enlarged prostate gland, called benign prostatic enlargement (BPE) among these, about half develop some degree of bladder outlet obstruction (BOO). BOO and/or changes in smooth muscle tone and resistance that can accompany BPH may result in lower urinary tract symptoms (LUTS) ***(Gravas et al., 2015).***

LUTS include storage disturbances (such as daytime urinary urgency and nocturia) and/or voiding disturbances (such as urinary hesitancy, weak urinary stream, straining to void, and prolonged voiding). LUTS affect an estimated 3 percent of men ages 45–49 years old increasing to around 30 percent of men over 85 years old. Urinary hesitancy, weak stream, and nocturia are the most commonly reported LUTS ***(Karami et al., 2016).***

Usually, BPH diagnosis is based on clinical presentation of LUTS or enlarged prostate on digital rectal examination. However, an enlarged prostate may not cause any urinary symptoms, so when LUTS are present, causes other than BPH still should be ruled out ***(Hutchison et al., 2006).***

BPH-LUTS are common in aging men worldwide. Given that BPH-LUTS often interferes with daily activities, many men with BPH-LUTS seek treatment to improve their quality of life ***(Yassin et al., 2006).***

Treatment decisions can typically be based on symptoms and degree of bother without need to perform specialized tests such as uroflowmetry and postvoid residual urine (PVR) measurement Lifestyle interventions such as modifying fluid intake or toileting behavior are typically the first-line treatments to reduce symptoms in patients with LUTS/BPH. When necessary, pharmacological treatment also may be initiated to reduce symptoms and prevent or delay disease progression ***(Strittmatter et al., 2013).***

Since the 1990s, there has been a substantial shift in BPH management from surgical to medical therapy. The current standard of care for LUTS/BPH includes α-adrenergic blockers and 5α-reductase inhibitors, used alone or in combination. These therapies are associated with bothering sexual side effects. The primary goals of LUTS attributed to BPH treatment are to reduce LUTS, improve prostate-related quality of life, and prevent or delay disease progression ***(Strittmatter et al., 2013).***

Erectile dysfunction (ED) is defined as the persistent or recurrent inability to achieve & maintain an erection sufficient for satisfactory sexual performance ***(Chitale et al., 2007).***

Lower urinary tract symptoms (LUTS), benign prostate hyperplasia (BPH), and erectile dysfunction (ED) are highly prevalent entities in aging men ***(Seftel et al., 2013).***

There is basic science evidence that LUTS/ BPH and ED share the same pathophysiologic common components that may be involved. Four theories supporting biological plausibility currently exist: (i) the reduced production of nitric oxide synthase/NO in the pelvis, which includes the penis and prostate; (ii) the autonomic hyperactivity and metabolic syndrome effects on LUTS, prostate growth, and ED; (iii) the presence of an increased rho-kinase activation/endothelin activity; and (iv) the diffuse atherosclerosis of prostate, penis, and bladder ***(Yassin et al., 2006).***

Considering the high incidence of ED and BPH in aging men and the same pathophysiology and the probability to treat both disorders with the same treatment (alpha blockers and/or phosphodiesterase type 5 [PDE5] inhibitors ***(Chitale et al., 2007).***

Alpha-blockers have been widely used for the treatment of LUTS/BPH for a long time Some alpha-blockers may cause ejaculatory dysfunction in some individuals.

Tadalafil, a phosphodiesterase type 5 inhibitor (PDE-5), was approved by the Food and Drug Administration (FDA) for the treatment of erectile dysfunction (ED) in 2003 and for the treatment of BPH in 2011 ***(Singh et al., 2014).***

The phosphodiesterase inhibitors are used in the treatment of ED and there are increasing data of effects of these drugs on bladder and urethral relaxation as well as of prostatic smooth muscles that may relief the symptoms of BPH ***(Wang et al., 2015).***

The inclusion of Tadalafil in complex of combined conservative therapy of patients with BPH not only improves sexual function but has a positive effect on symptoms of the disease and the psychological state of the patient ***(Regadas et al., 2012).***

Based on the wide variety of medications available to treat LUTS attributed to BPH, it is possible that tailoring treatment with single medications or medication combinations can maximize efficacy or effectiveness and minimize adverse effects.

The mechanism by which combination therapy produced greater improvement is that both alpha-1 blockers and PDE5 inhibitors, acting by two different mechanisms of action on common urogenital target organs, may have a synergistic effect on LUTS and ED ***(Fusco et al., 2013).***

Alpha-1 blockers, by blocking alpha-1-adrenergic receptors and reducing the sympathetic tone in penile smooth muscle and prostate/bladder neck, could enhance the NO-mediated relaxant influence of PDE5 inhibitors Similarily, there is evidence that PDE5 inhibitors enhance the inhibitory effects of alpha-1 blockers on neurogenic contractions of human prostate and bladder neck ***(Chang et al., 2005).***

The most widely used, validated instrument for assessment of LUTS is the International Prostate Symptom Score (IPSS) and for assessment of sexual function International Index of Erectile Function (IIEF-5) ***(Karami et al., 2016).***

AIM OF THE STUDY

To assess the efficacy and safety of fixed-dose combinations therapy of Tamsulosin & Tadalafil versus Tadalafil alone in treatment for BPH patient with lower urinary tract symptoms (LUTS) and erectile dysfunction (ED).