

A Retrospective Study to Evaluate the Efficacy of Combination of Daily Tadalafil and Solifenacin in Patients with Storage SymptomsRohit Singh¹, Arshad Hasan²¹Assistant Professor, Department of Urology, PMCH, Patna, Bihar, India²Senior Resident, Department of Urology, PMCH, Patna, Bihar, India

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Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to evaluate the efficacy of tadalafil 5mg+solifenacin 5mg combination in terms of lower urinary tract symptoms (LUTS) and erectile functions in benign prostate hyperplasia patients with predominant storage symptoms.

Methods: The present study was conducted in the Department of Urology. Male patients over the age of 40 who presented with LUTS with predominant storage symptoms were included in the study. A total of 100 patients were included in the study. Demographic data of the patients were recorded.

Results: The patients' mean age was 48.6±13.6 and the mean BMI was 25.5±8.2 kg/m². The mean IIEF-EF score of the patients was 13.6±6.4, the mean OABSS was 8.2±2.6, the IPSS-Voiding mean was 5.4±2.3. The mean IPSS-Storage was 13.3±1.8, the mean IPSS total score was 18.6±2.8. The mean PSA value of the patients was 1.3±0.7 ng/ml. When the symptom scores and bladder diaries of the patients before and after 12 weeks of treatment were compared, significant decrease in IPSS scores (both Voiding, Storage and total) (p<0.001 for each) significant increase in IIEF-EF scores (p<0.001) significant increase in Qmax value elevation was observed. When the bladder diaries were compared, the number of daytime micturitions, the number of nocturia and urgency decreased in the 12th month after tadalafil+solifenacin treatment (p<0.001). Among the patients participating in the study, dry mouth developed in 7 patients (7%), constipation in 6 patients (6%), dyspepsia in 4 patients (4%), and muscle pain in 3 patients (3%).

Conclusion: The combination of tadalafil 5mg and solifenacin 5mg daily is a safe and effective therapy for male patients with storage symptoms predominant LUTS/ED. Especially in patients suffering from storage functions, this combination therapy will be a good alternative if resistance is encountered in monotherapy. Prospective randomized controlled studies with large participation are needed to evaluate the efficacy of daily tadalafil+solifenacin treatment.

Keywords: benign prostate hyperplasia, storage, tadalafil, solifenacin, erectile function

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Introduction

The development of the benign prostatic hyperplasia (BPH) is usually associated with a metabolic disorder, hormonal dysfunction, and chronic inflammation. With the presence of at least two of these three processes, the probability of BPH developing is considered to be very high. [1,2] One of the important mechanisms of BPH is an increase of 5α-reductase activity and interstitial concentration of dihydrotestosterone, which stimulates the activity of interstitial cells of the gonads, smooth muscles, connective tissue, and prostatic epithelium in the presence of estrogens.

Metabolic syndrome can lead to atherosclerosis of the microcirculatory channel of the pelvic organs, including the prostate gland and detrusor. It can also be accompanied by an alteration of the nitric oxide-

cyclic guanosine monophosphate pathway, an enhancement of RhoA-Rho-kinase contractile signaling, and an increase of afferent adrenergic impulsion level. In addition, the violation of intercellular interaction and local mechanisms of normal growth of glandular tissue of the prostate gland regulation are very important in the pathogenesis of BPH. [3-5] Some of the described processes may be accompanied not only by obstruction, but also by lower urinary tract hyperactivity symptoms (LUTS), and also by sexual dysfunction. [6,7] Patients are concerned not only with weak stream, straining, and incomplete emptying, but also with nocturia, urgency, increased nighttime and daytime frequency of urination, decreased libido and sexual desire, and erectile dysfunction. [6,8,9]

Attempts have been made to determine the diagnostic value of assessing IPSS subscores. [10,11] Lee et al [10] investigated the importance of improvements in storage dysfunction in Korean men with moderate to severe LUTS/ BPH after combination therapy with an alpha-blocker and a 5-alpha reductase inhibitor, stratifying patients by severity of storage symptoms. However, the relative contribution of the sub score to total IPSS was not assessed. Liao et al [11] assessed the contribution of voiding and storage sub scores to total IPSS, using the voiding-to-storage subscore ratio to differentiate between voiding failure (ratio >1) and storage failure (ratio ≤1), but did not take into consideration the relative maximum contributions that voiding and storage sub scores make to total IPSS (approx. 40% and 60%, respectively). The limitation of using unvalidated individual subscores has previously been highlighted. [12]

Tadalafil, a PDE 5 inhibitor, specifically degrades cGMP and restores its smooth muscle relaxant effect. Tadalafil positively affects the lower urinary system (i) by decreasing the smooth muscle tone in the prostate, urethra, and bladder neck, (ii) by increasing the lower urinary tract blood flow by decreasing the vascular smooth muscle tone, (iii) by inhibiting the bladder afferent nerve activity (C- and Aδ-fibers). and (iv) reduction of inflammation and fibrosis through inhibition of interleukin-8 and Rho-kinase. [13-15] Solifenacin, an antimuscarinic agent, is a muscarinic receptor blocker that predominantly acts on the M3 subtype. It reduces bladder detrusor hyperactivity by suppressing acetylcholine activation. [16]

The aim of the present study was to evaluate the efficacy of tadalafil 5mg+solifenacin 5mg combination in terms of lower urinary tract symptoms (LUTS) and erectile functions in benign prostate hyperplasia patients with predominant storage symptoms.

Materials and Methods

The present study was conducted in the Department of Urology, PMCH, Patna, Bihar, India for 12 months. Male patients over the age of 40 who presented with LUTS with predominant storage symptoms were included in the study. A total of 100 patients were included in the study. Demographic data of the patients were recorded. International prostate symptom score (IPSS), overactive bladder symptom score (OABSS) for LUTS, and international erectile function index-erectile function (IIEF-EF) questionnaires were used for erectile function. Frequency of daily urinary frequency, frequency of nocturia, urgency and

urinary incontinence were analyzed with a three-day bladder diary. Post void residual urine volume and prostate volume (PV) (PVR) were measured by transabdominal ultra- sound. Prostate specific antigen (PSA) value (ng/mL) of the patients was recorded. Maximum urine flow rate (Qmax) was evaluated with uroflowmetry.

The patients were started on daily tadalafil 5mg and solifenacin 5mg treatment. Twelve weeks later, IPSS, OABSS and IIEF-EF scores of the patients were evaluated. Bladder diary, uroflowmeter and PVR measurements were recorded. Change and satisfaction rates were compared before and after 12 weeks of treatment. Side effects observed during the treatment were noted. Inclusion criteria: patients with mild to moderate erectile dysfunction (IIEF-EF between 12 and 21), patients with IPSS score >7, patients with Q max <15.

Exclusion criteria: PVR>50 ml, bladder neck sclerosis, neurogenic bladder, urethral stricture, active urinary tract infection, history of prostate cancer, use of 5ARI, nitrate use, history of unstable angina pectoris, history of renal hepatic failure, narrow-angle glaucoma patients, patients with myasthenia gravis. The IPSS questionnaire is an inquiry form consisting of 7 questions. [17] The score obtained from each question in the scale is between 0-5. The total score is between 0-35 and scores of 7 and above are interpreted in favor of LUTS.

The IIEF-EF inquiry form includes questions 1-5 and 15 of the IIEF, which consists of 15 questions. [18] A maximum of 30 points can be obtained in the survey, which is organized according to five-point Likert scoring. 1st,3,5th of IPSS. While the questions are about excretion 2,4. And 7. Questions are about the storage function. A total score of 21 and below was evaluated in favor of ED. [19] OABSS is a 4 -question survey used to evaluate the extremely active bladder symptoms. [20] A total of 0-15 points can be obtained from the questionnaire and 3 points and above are indicated as OAB.

Statistical Analysis

Data analysis was done with SPSS 25.0 (IBM, USA). The homogeneity of data were evaluated with the Kolmogorov-Smirnov test. The comparison the parameters before and after the treatment performed with Paired-samples t-test and Fisher's exact test. Significant p value was determined as p<0.05.

Results

Table 1: Demographic characteristics of the patients

Variables	Mean±SD	Min-Max
Age (years)	48.6±13.6	40-79
BMI (kg/m ²)	25.5±8.2	22.2-36.4
PSA (ng/dL)	1.3±0.7	0.3-3.1
IIEF-EF	13.6±6.4	0-25
OABSS	8.2±2.6	4-14
IPSS-Voiding	5.4±2.3	1-9
IPSS-Storage	13.3±1.8	10-17
IPSS-Total	18.6±2.8	11-22
Qmax	7.4±2.4	3-12
PVR (ml)	14.7±12.4	0-40

The patients’ mean age was 48.6±13.6 and the mean BMI was 25.5±8.2 kg/m². The mean IIEF-EF score of the patients was 13.6±6.4, the mean OABSS was 8.2±2.6, the IPSS-Voiding mean was 5.4±2.3. The mean IP-SS-Storage was 13.3±1.8, the mean IPSS total score was 18.6±2.8. The mean PSA value of the patients was 1.3±0.7 ng/ml.

Table 2: Comparison of data before and after tadalafil + solifenacin treatment

	Before treatment		After treatment		P Value
	Mean	SD	Mean	SD	
IIEF-EF	13.6	6.4	17.6	6.4	<0.001
OABSS	8.2	2.6	3.8	3.2	<0.001
PSA (ng/dL)	1.3	0.7	1.2	0.7	0.912
IPSS-Voiding	5.4	2.3	4.6	1.7	<0.001
IPSS-Storage	13.3	1.8	8.2	3.7	<0.001
IPSS	18.6	2.8	12.6	4.1	<0.001
Qmax	7.4	2.4	8.3	2.9	<0.001
PVR (ml), median (IQR)	10 (10-30)		20 (10-50)		<0.001

When the symptom scores and bladder diaries of the patients before and after 12 weeks of treatment were compared, significant decrease in IPSS scores (both Voiding, Storage and total) (p<0.001 for each) significant increase in IIEF-EF scores (p<0.001) significant increase in Qmax value elevation was observed. When the bladder diaries were compared,

the number of daytime micturitions, the number of nocturia and urgency decreased in the 12th month after tadalafil+solifenacin treatment (p<0.001). In the PMR measurement, at the end of the 12th week, significantly more residual urine remained in the patients (10.0 (10-30) vs. 20.0 (10-50); p<0.001).

Table 3: Side effects of the patients

Side Effects	n (%)
Dry Mouth	7 (7)
Constipation	6 (6)
Dyspepsia	4 (4)
Muscle Pain	3 (3)

Among the patients participating in the study, dry mouth developed in 7 patients (7%), constipation in 6 patients (6%), dyspepsia in 4 patients (4%), and muscle pain in 3 patients (3%).

Discussion

In aging men benign prostatic hyperplasia (BPH) is very common and it is a benign enlargement of prostate tissue and is caused by proliferation of

prostate epithelial and stromal cells. [21] The lower urinary tract symptoms (LUTS) associated with BPH, which greatly affect men’s quality of life (QoL), include storage, voiding, and post-voidal symptoms. [22] In many studies, it has been reported that nocturia, urgency, increased frequency of day and night urination, sexual dysfunction, and urge incontinence are common in men with BPH, as well as voiding symptoms. [23,24]

The mechanism of action of the long-acting PDE5 inhibitor tadalafil in the treatment of men with LUTS secondary to BPH is believed to be associated with stimulation of increased activity of the nitric oxide/cGMP/protein kinase G pathway via inhibition of PDE5 isoenzymes in different tissues of the lower urinary tract. It is postulated that this results in (1) smooth muscle relaxation in the bladder, urethra, prostate, and supporting vasculature, (2) increased blood perfusion to the pelvic area, and (3) modulation of sensory stimuli from this area. [25,26] The integrated analysis of almost 1500 men with LUTS presented here supports the suggested beneficial impact of tadalafil on the bladder, prostate, and urethra, with largely similar reductions in storage (the most bothersome issue) and voiding symptoms. The patients' mean age was 48.6 ± 13.6 and the mean BMI was 25.5 ± 8.2 kg/m². The mean IIEF-EF score of the patients was 13.6 ± 6.4 , the mean OABSS was 8.2 ± 2.6 , the IPSS-Voiding mean was 5.4 ± 2.3 . The mean IPSS-Storage was 13.3 ± 1.8 , the mean IPSS total score was 18.6 ± 2.8 . The mean PSA value of the patients was 1.3 ± 0.7 ng/ml. In our study, significant improvements were found in the IPSS-Excretion related scores according to the initial symptoms of the patients. In addition, the significant increase in Qmax also shows the effect of tadalafil on functional obstruction. Although the effect of alpha-blockers on LUTS-storage symptoms is not clear, it has been shown to affect storage symptoms by inhibiting urethral smooth muscle contraction. [27]

When the symptom scores and bladder diaries of the patients before and after 12 weeks of treatment were compared, significant decrease in IPSS scores (both Voiding, Storage and total) ($p < 0.001$ for each) significant increase in IIEF-EF scores ($p < 0.001$) significant increase in Qmax value elevation was observed. When the bladder diaries were compared, the number of daytime micturitions, the number of nocturia and urgency decreased in the 12th month after tadalafil+solifenacin treatment ($p < 0.001$). In the PMR measurement, at the end of the 12th week, significantly more residual urine remained in the patients (10.0 (10-30) vs. 20.0 (10-50); $p < 0.001$). Although the use of anticholinergics in combination with alpha-blockers has shown greater benefit for storage symptoms than alpha-blocker monotherapy, the incidence of voiding difficulty and increased residual urine is increased due to detrusor inhibition. [28] In the study of Urakami et al [29], they detected 16% urinary retention in the group receiving tamsulosin and solifenacin, and they found that PMR increased from 19 ml to 61 ml after 3 months of treatment. In our study, although the PMR volumes of the patients receiving tadalafil and solifenacin were statistically significant (16 vs 20, $p < 0.001$), no patient with clinical urinary retention was detected. This shows that the effect of tadalafil on LUTS storage functions is realized by a different

mechanism than alpha blockers and does not cause urinary retention. Changes in nitric oxide levels in the pelvis and prostate and the neurogenic effect of this change; smooth muscle contractility, increase adrenergic tone in autonomic hyperactivity/metabolic syndrome, upregulation of the rho kinase / endothelin pathway induced by obstruction resulting in increased smooth muscle tonicity, and coexistence of ED in LUTS patients due to pelvic atherosclerosis in metabolic syndrome. [30-32]

Among the patients participating in the study, dry mouth developed in 7 patients (7%), constipation in 6 patients (6%), dyspepsia in 4 patients (4%), and muscle pain in 3 patients (3%). Depending on the combined agents used, the incidence of side effects was found to be 19%. Concomitant use of tadalafil with alpha-blockers may decrease blood pressure and therefore caution should be exercised during its use. [33] However, dizziness or lightheadedness due to low blood pressure was not detected in the use of solifenacin together with tadalafil. dry mouth and constipation, which are the most common side effects, are thought to be due to solifenacin.

Conclusion

The combination of tadalafil 5mg and solifenacin 5mg daily is a safe and effective therapy for male patients with storage symptoms predominant LUTS/ED. Especially in patients suffering from storage functions, this combination therapy will be a good alternative if resistance is encountered in monotherapy. Prospective randomized controlled studies with large participation are needed to evaluate the efficacy of daily tadalafil+solifenacin treatment.

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