COMPARATIVE STUDY BETWEEN α-BLOCKERS AND COMBINATION OF α-BLOCKERS AND PHOSPHODIESTRASE 5-INHIBITORS IN TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Background: *Benign prostatic hyperplasia (BPH) is one of the most common conditions affecting middle-aged men. This condition can be symptomatic or asymptomatic. Up to 15-25% of men aged 50-65 years have lower urinary tract symptoms (LUTS).*

Aim of the Work*: To compare between the effect of alpha blocker (Tamsulosin 0.4 mg once at night) and a combination of alpha blockers (Tamsulosin 0.4 mg once at morning) and PDE5 inhibitors (Sildenafil 25 mg at night) in treatment of benign prostatic hyperplasia patients through evaluation of IPSS and post-voiding residual urine and uroflometry before and after treatment.*

Patients and Methods*: This was a prospective study done on 30 patients fulfilling inclusion criteria at Eldemerdash hospital between 1-9-2017 till 1-9-2018 and this study has two phases:*

Phase (1): included 30 patients complaining of LUTS 2ry to BPH assessed by uroflowmetry and IPSS and post voiding residual urine. Before taking any drugs and after treatment by alpha blocker (tamsulosin 0.4mg capsule once daily at night) for 3 months.

Phase (2): included the same 30 patients after treatment by phase (2) of alpha blocker (Tamsulosin 0.4 capsule once daily in the morning) and PDEI (sildenafil 25mg once daily in the night) for 3 months. These patient also assessed by IPSS, uroflowmetry and PVR urine.

Results: *The results of this study showed that there was a significant improvement after phase 1 treatment in IPSS, also there was a significant improvement after phase 2 more than phase 1. The PVRU and Q max was significantly improve after phase 1 but the change after phase 2 was insignificant.*

Conclusion: *Sildenafil citrate in combination with tamsulosin improved LUTS more than tamsulosin monotherapy with the merit of a comparable safety profile in patients with LUTS/BPH.*

Keywords: *Benign Prostatic Hyperplasia - α-Blockers - Phosphodiestrase 5-Inhibitors.*

INTRODUCTION:

BPH Development is under hormonal, genetic, and environmental control. There is evidence indicates that metabolic disorders and lifestyle factors are important in the etiology of BPH and LUTS, including obesity, diabetes, diet and exercise [(1)].

Androgens have a key role in the development and growth of the prostate as well as in the pathogenesis of BPH. Testosterone is converted to dihydro-testosterone (DHT) by 5-α-reductases (5-ARs) predominantly in the stromal tissue. The higher affinity for the androgen receptor (AR) to DHT allowing it to accumulate in the prostate even when circulating testosterone levels are low [(2)].

The evaluation and treatment of BPH depends on the symptoms that affect the patient's quality of life. The symptoms score most commonly used to evaluate prostatic patients is the International Prostate Symptom Score (IPSS) [(3)].

Treatment options can be based on degree of IPSS symptoms without need to specialized tests such as Qmax and postvoid residual urine (PVR) measurement, the first-line treatments to reduce symptoms in patients with LUTS/BPH is to modify lifestyle such as fluid intake or toileting behaviour. pharmacological treatments to reduce LUTS/BPH are α-adrenergic blockers and 5α-reductase inhibitors, used alone or in combination [(4)].

α-adrenergic blockers and 5-α reductase inhibitors are two classes of medications used as medical therapy for voiding symptoms due to BPH, anticholinergic agents or new β_3-agonist therapy may also be used in the patients with predominantly storage symptoms [(5)].

By relaxing the prostatic smooth muscles during the act of voiding the α-adrenergic blockers serve as an effective treatment of BPH. Doxazosin, terazosin, tamsulosin, alfuzosin and silodosin are all appropriate therapies for patients with BPH causing LUTS, Patients respond differently to each alpha blocker but they are generally considered to be equally effective in relieving LUTS [(6)].

One of common side effect in patients using tamsulosin or silodosin is the retrograde ejaculation (RE); some patients will find RE troublesome; however, and some patient not [(7)].

Recently, phosphodiestrase type 5 inhibitors (PDE5-Is) sildenafil, vardenafil and tadalafil which are widely used as first-line oral treatment for erectile dysfunction, are effective in the treatment of LUTS [(8)].

In human tissues, 11 phosphodiestrase (PDE) families have been distinguished, and there is significant variation in distribution and function in different tissues. It is known that isoenzymes 1, 2, 3, 4, 5, 7, 8, 9 and 10 are expressed in the human prostate, whereas isoenzymes 1, 3, 4 and 5 are present in the human destrusor. PDE-5 inhibitors inhibit degradation of cyclic guanosine monophosphate (cGMP) which is an intracellular second messenger that mediates several pharmacologic effects Therefore, PDE-5 inhibitors, by increasing cGMP in the lower urinary tract, can potentially modulate sensory signals, microvasculature dilation and smooth muscle cell relaxation in the prostate, urethra and bladder [(9)].

Several studies conclude that nitric oxide (NO)/cGMP system and related key proteins, including the cGMP-degrading PDE-5, are important factors in the control of the normal function of the prostate. This may affect the contractile activity of the smooth musculature, secretory granular function, as well as the regulation of proliferation of smooth muscle, granular epithelial cells and stromal connective tissue[(9)].

Several clinical trials on the effect of PDE-5 inhibitors on male LUTS have been published. In these studies, different PDE-5 inhibitors (sildenafil, vardenafil, tadalafil) and combinations of an α-blocker (alfuzosin or tamsulosin). According to a recent meta-analysis, the use of PDE-5 inhibitor alone was associated with a significant improvement of IPSS at the end of studies compared with placebo. The combination of an alpha

blocker and PDE-5 inhibitor significantly improved IPSS and Qmax at the end of the studies compared with alpha blockers alone[10].

AIM OF THE WORK:

The aim of this work is to compare between the effect of alpha blocker (Tamsulosin 0.4 mg once at night) and a combination of alpha blockers (Tamsulosin 0.4 mg once at morning) and PDE5 inhibitors (Sildenafil 25 mg at night) in treatment of benign prostatic hyperplasia patients through evaluation of IPSS and post-voiding residual urine and uroflometry before and after treatment.

PATIENTS AND METHODS:

Type of Study: A prospective randomized clinical study.

Study Setting: Urology department, faculty of medicine, Ain Shams University (El Demerdash Hospital).

Study Period: 1-9-2017 till 1-9-2018.

Study Population: 30 Men of 50-70 years old with a history of LUTS secondary to BPH. Patients agreed not to use BPH medications during the research other than the study medications.

- **Inclusion Criteria:**
  - BPH patients of age between 50-70 years complaining of mild to moderate IPSS scor.
  - Qmax between5 -15 mL/s with minimum voided volume of >150 mL at screening
  - Able to give written informed consent.
- **Exclusion Criteria:**
  - Malignancy.
  - Post-void residual volume (PVR) >150 mL.
  - Previous prostate surgery
  - Any causes other than BPH which may result in urinary symptoms or changes in flow rate (i.e., bladder malignancy, neurogenic bladder, bladder neck contracture, urethral stricture, acute or chronic prostatitis, or acute or chronic urinary tract infections).
  - Bladder stones
  - Use of any alpha adrenoreceptor blockers or Use of any PDE5i within 2 weeks of screening visit.
  - Unstable Angina.
  - History of Myocardial infarction.
  - Heart failure.
  - Significant Renal insufficiency
  - Significant Hepatic insufficiency

Sampling Method randomized clinical study.

- Sample Size 30 male patients.
- Ethical Considerations: Approval was obtained from the ethical committee at Ain Shams University before starting the research.
- Study Procedures: Checklist for assessment of all data relevant to the patients.

All patients were subjected to the following:

1- History taking:

- Personal history (IPSS)(table 1).
- Present history.
- Past history.
- Family history.

2- Clinical examination:

- Routine clinical examination.
- Digital rectal examination.

3- Investigation:

- **Uroflowmetry.**

- PSA.
- Urine analysis & culture sensitivity if needed.
- U/S abdomen & pelvis & post voiding residual Urine.

4- Written informed consent:

Table (1): The International Prostate Symptom Score[4] *(3)*

Urinary symptoms over the past month (symptom score criteria)	Not at all	Less than one time in five	Less than half the time	About half the time	More than half the time	Almost always
1. Incomplete emptying How often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Frequency How often have you had to urinate less than two hours after you finished urinating?	0	1	2	3	4	5
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Weak stream How often have you had a weak urinary stream?		0	1	2	3	4	5
6. Straining How often have you had to push or strain to begin urination?		0	1	2	3	4	5
		None	One time	Two times	Three times	Four times	Five or more times
7. Nocturia How many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?		0	1	2	3	4	5
Quality of life due to urinary problems							
	Delighted	Pleased	Mostly Satisfied	Mixed – about equally satisfied and unsatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Study design:

We have 30 patient will be enrolled in study which will pass in two phases each of them in three months:

First phase:

The included 30 patients complaining of LUTS 2ry to BPH assessed by Qmax and IPSS and PVR. Before taking any drugs and after treatment by alpha blocker (tamsulosin 0.4mg capsule once daily at night) for 3 months.

Second phase:

The included the same 30 patients after treatment by combination of alpha blocker (Tamsulosin 0.4 capsule once daily in the morning) and PDEI (sildenafil 25mg once daily in the night) for 3 months. These patient also assessed by IPSS, Qmax and PVR urine.

At the first visit:

1- A present, past, clinical and medical history was taken including history of present and past diseases, sexual life and concomitant drug treatments.

2- Patients using BPH drugs or medications that could interfere with bladder function (alpha blockers, anticholinergics and sympathomimetic drugs), or PDE5 inhibitors underwent two weeks medication free period before starting the study.

At the second visit:

Started after making sure that all patients included in the study under went two weeks medication free before starting the study:

1- Patients completed the IPSS were performed uroflowmetry and abdominal ultrasound pre-and post voiding to asses PVR befor taking any drugs and this is the base line of the study.

2- An IPSS of 12 points or more and a Qmax of 5-15 mL/s on a voided volume of 150 mL or more were required for study.

3- The included30 patients started phase one of the study by receiving fixed doses of Tamsulosin 0.4 mg/day for 3 months.

4- Patients were instructed to take the study medication at approximately the same time every day without restrictions of food intake or timing of sexual activity.

At the third visit:

Started after two weeks of taking the study medication to asses Safety by monitoring the incidence of patient-reported adverse events and changes in vital signs.

At the forth Visit:

Started at the end of the phase (1) first (3months) from taking the study medication to asses changes of study parameters (the International Prostate Symptom Score IPSS, uroflowmetery to asses Qmax, pelviabdominal U/S to asses PVR) from baseline after 3months of taking the study medication.

And in this visit the patients started Phase (2) for 3 months: include the same 30 patient starting treatment by combination of alpha blocker (Tamsulosin 0.4 capsule once daily in the morning) and PDEI (sildenafil 25mg once daily in the night) for 3 monthes.

At the fifth visit

Started after two weeks of taking the combination tamsulosin and sildenafil to asses Safety by monitoring the incidence of patient-reported adverse events and changes in vital signs.

At the sixth Visit:

Started at the end of the phase two from taking the study medication to reasses changes of study parameters(the IPSS, Qmax, PVR) under the effect of combination (tamsulosin and sildenafil) from baseline after 3 months of taking the study medication.

Statistical Analysis:

- Data was collected, tabulated and all results will be subjected to adequate statistical analysis.
- Using IBM *SPSS software package version 20.0.*
- Qualitative data were described using number and percent. Comparison between different groups regarding

categorical variables was tested using Chi-square test.

- Quantitative data were described using mean and standard deviation for normally distributed data while abnormally distributed data was expressed using median, minimum and maximum.
- For normally distributed data, comparison between two independent population were done using independent t-test while more than two population were analyzed F-test (ANOVA) to be used.
- Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.
- Mean value $(\bar{X}) = \frac{X}{n}$.
- *Where* X = the sum of all observations.
- n = the number of observations.
- The standard deviation S.D. = $\sqrt{\frac{\sum (X - \bar{X})^2}{n-1}}$ Where
- $\Sigma (Xi - X)^2$ = the sum of squares of differences of observations from the mean.

Student (Unpaired-sample) "t" test:

- It is used during comparison between the means of different sample groups. The "t" is calculated as follows:
- $t = \frac{X_1 - X_2}{\sqrt{\frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}}}$

Where

- X_1 = Mean of first group.
- X_2 = Mean of second group.
- S_1 = Standard deviation of the first group.
- S_2 = Standard deviation of the second group.
- n_1 = Sample size of the first group.
- n_2 = Sample size of the second group.

One way analysis of variance (ANOVA) was performed for comparison between more than two groups

- Variance ratio F was computed by the formula.

$$F_{(r-1),(n-1)} = \frac{\text{Mean square between classes}}{\text{Mean square within classes}}$$

Where

- r = number of groups
- n = total sample size

There was statistical significant relation between frequency at base line and after phase (1) and phase (2) ($P < 0.05$). There was statistical significant relation between baseline with phase (1), (2) ($P1, P2 < 0.05$) while there was no statistical significant relation between phase (1) with phase (2) regarding frequency ($P3 > 0.05$).

RESULTS:

Table (2) shows comparison between frequency at base line and after phase (1) and phase (2). Baseline ranged from 2-5 with mean value 3.43±0.858, phase (1) ranged from 1-3 with mean value 1.87±0.629 and phase (2) ranged from 1-3 with mean value 1.73±0.421.

Table (2): Comparison between frequency at base line and after phase (1) and phase (2)

Frequency	Baseline	Phase (1)	Phase (2)
Range	2.0-5	1.0-3	1.0-3.0
Mean	3.43	1.87	1.73
S.D.	0.858	0.629	0.421
F	22.3		
P	0.001*		
P1	0.003*		
P2	0.005*		
P3	0.168 N.S.		

P1 comparison between base line and phase (1) P2 comparison between baseline and phase (2)
P3 comparison between phase (1)and phase (2) F= ANOVA test P is significant if <0.05
* Significant at level 0.05 N.S. Not Significant **difference**

Table (3): shows comparison between urgency at baseline and after phase (1) and phase (2). Baseline ranged from 1-4 with mean value 2.63±0.718, phase (1) ranged from 0-2 with mean value 1.23±0.626 and phase (2) ranged from 0-2 with mean value 1.16±0.252. There was statistical significant relation between urgency at baseline and after phase (1) and phase (2) ($P < 0.05$). There was statistical significant relation between baseline with phase (1), (2) ($P1, P2 < 0.05$) while there was no statistical significant relation between phase (1) with phase (2) regarding urgency ($P3 > 0.05$).

Table (3): Comparison between urgency at baseline and after phase (1) and phase (2)

Urgency	Baseline	Phase (1)	Phase (2)
Range	1.0-4	0.0-2	0.0-2.0
Mean	2.63	1.23	1.16
S.D.	0.718	0.626	0.252
F	16.85		
P	0.008*		
P1	0.0021*		
P2	0.0013*		
P3	0.215 N.S.		

P1 comparison between base line and phase (1) P2 comparison between baseline and phase (2)
P3 comparison between phase (1) and phase (2) F= ANOVA test P is significant if <0.05
* Significant at level 0.05 N.S. Not Significant difference

Table (4) shows comparison between intermittent at base line and after phase (1) and phase (2). Baseline ranged from 0-3 with mean value 1.87±0.629, phase (1) ranged from 0-2 with mean value 0.87±0.571 and phase (2) ranged from 0-2 with mean value 0.74±0.201. There was no statistical significant relation between urgency at baseline and after phase (1) and phase (2) ($P < 0.05$). There was statistical significant relation between baseline with phase (1), (2) ($P1, P2 < 0.05$) while there was no statistical significant relation between phase (1) with phase (2) regarding intermittent ($P3 > 0.05$).

Table (4): Comparison between intermittent at base line and after phase (1) and phase (2)

Intermittent	Baseline	Phase (1)	Phase (2)
Range	0.0-3.0	0.0-2.0	0.0-2.0
Mean	1.87	0.87	0.74
S.D.	0.629	0.571	0.201
F	14.65		
P	0.0031*		
P1	0.0028*		
P2	0.0016*		
P3	0.252 N.S.		

P1 comparison between base line and phase (1) P2 comparison between baseline and phase (2)
P3 comparison between phase (1) and phase (2) F= ANOVA test P is significant if <0.05
* Significant at level 0.05 N.S. Not Significant difference.

Table (5) shows comparison between incomplete emptying at baseline and after phase (1) and phase (2). Baseline ranged from 1-3 with mean value 2.07±0.450, phase (1) ranged from 0-2 with mean value 0.93±0.640 and phase (2) ranged from 0-2 with mean value 0.81±0.528. There was statistical significant relation between incomplete emptying at baseline and after phase (1) and phase (2) ($P < 0.05$). There was statistical significant relation between baseline with phase (1), (2) ($P1, P2 < 0.05$) while there was no statistical significant relation between phase (1) with phase (2) regarding incomplete emptying ($P3 > 0.05$).

Table (5): Comparison between incomplete emptying at baseline and after phase (1) and phase (2)

Incomplete emptying	Baseline	Phase (1)	Phase (2)
Range	1.0-3	0.0-2	0.0-2
Mean	2.07	0.93	0.81
S.D.	0.450	0.640	0.528
F	9.25		
P	0.008*		
P1	0.012*		
P2	0.007*		
P3	0.113 N.S.		

P1 comparison between base line and phase (1) P2 comparison between baseline and phase (2)
P3 comparison between phase (1) and phase (2) F= ANOVA test
P is significant if <0.05
* Significant at level 0.05 N.S. Not Significant difference.

Table (6) shows comparison between straining at baseline and after phase (1) and phase (2). Baseline ranged from 1-3 with mean value 2.07±0.691, phase (1) ranged from 0-2 with mean value 1.00±0.587 and phase (2) ranged from 0-2 with mean value 0.81±0.621. There was statistical significant relation between straining at baseline and after phase (1) and phase (2) ($P < 0.05$). There was statistical significant relation between baseline with phase (1), (2) ($P1, P2 < 0.05$) while there was no statistical significant relation between phase (1) with phase (2) regarding straining ($P3 > 0.05$).

Table (6): Comparison between straining at baseline and after phase (1) and phase (2)

Straining	Baseline	Phase (1)	Phase (2)
Range	1.0-3	0.0-2.0	0.0-2.0
Mean	2.07	1.00	0.81
S.D.	0.691	0.587	0.621
F	8.79		
P	0.01*		
P1	0.03*		
P2	0.015*		
P3	0.165 N.S.		

P1 comparison between base line and phase (1) P2 comparison between baseline and phase (2)
P3 comparison between phase (1) and phase (2) F= ANOVA test P is significant if <0.05
* Significant at level 0.05 N.S. Not Significant difference

Table (7) shows comparison between weak stream at baseline and after phase (1) and phase (2). Baseline ranged from 1-3 with mean value 2.13±0.629, phase (1) ranged from 0-2 with mean value 1.03±0.556 and phase (2) ranged from 0-2 with mean value 0.90±0.411. There was statistical significant relation between weak stream at baseline and after phase (1) and phase (2) ($P < 0.05$). There was statistical significant relation between baseline with phase (1), (2) ($P1, P2 < 0.05$) while there was no statistical significant relation between phase (1) with phase (2) regarding weak stream ($P3 > 0.05$).

Table (7): Comparison between weak stream at baseline and after phase (1) and phase (2)

Weak stream	Baseline	Phase (1)	Phase (2)
Range	1.0-3.0	0.0-2	0.0-2
Mean	2.13	1.03	0.90
S.D.	0.629	0.556	0.411
F	17.65		
P	0.005*		
P1	0.002*		
P2	0.001*		
P3	0.107 N.S.		

P1 comparison between base line and phase (1) P2 comparison between baseline and phase (2)
P3 comparison between phase (1) and phase (2) F= ANOVA test P is significant if <0.05
* Significant difference N.S Not significant difference

Table (8) shows comparison between nocturia at baseline and after phase (1) and phase (2). Baseline ranged from 2-5 with mean value 2.90±0.712, phase (1) ranged from 0-2 with mean value 1.80±0.371 and phase (2) ranged from 0-2 with mean value 0.44±0.201. There was statistical significant relation between nocturia at baseline and after phase (1) and phase (2) ($P < 0.05$). There was statistical significant relation between baseline with phase (1), (2) ($P1, P2 < 0.05$) and between phase (1) with phase (2) regarding nocturia ($P3 < 0.05$).

Table (8): Comparison between nocturia at baseline and after phase (1) and phase (2)

Nocturia	Baseline	Phase (1)	Phase (2)
Range	2.0-5.0	0.0-2.0	0.0-1.0
Mean	2.90	1.8	0.44
S.D.	0.712	0.371	0.201
F	12.98		
P	0.011*		
P1	0.021*		
P2	0.011*		
P3	0.026*		

P1 comparison between base line and phase (1) P2 comparison between baseline and phase (2)
P3 comparison between phase (1) and phase (2) F= ANOVA test P is significant if <0.05
* Significant difference

Table (9) shows comparison between sum at baseline and after phase (1) and phase (2). Baseline ranged from 8-21 with mean value 17.1±3.234, phase (1) ranged from 5-14 with mean value 8.73±2.01 and phase (2) ranged from 2-10 with mean value 6.59±1.022. There was statistical significant relation between sum at baseline and after phase (1) and phase (2) ($P < 0.05$). There was statistical significant relation between baseline with phase (1), (2) ($P1, P2 < 0.05$) and between phase (1) with phase (2) regarding sum ($P3 < 0.05$).

Table (9): Comparison between sum at baseline and after phase (1) and phase (2)

Sum	Baseline	Phase (1)	Phase (2)
Range	8.0-21	5.0-14.0	2.0-10
Mean	17.1	8.73	6.59
S.D.	3.234	2.01	1.022
F	8.30		
P	0.018*		
P1	0.041*		
P2	0.028*		
P3	0.039*		

P1 comparison between base line and phase (1) P2 comparison between baseline and phase (2)
P3 comparison between phase (1) and phase (2) F= ANOVA test P is significant if <0.05
* Significant difference

Table (10) shows comparison between PVRU at baseline and after phase (1) and phase (2). Baseline ranged from 30-100 with mean value 60.80±21.928, phase (1) ranged from 10-60 with mean value 23.2±11.72 and phase (2) ranged from 0-50 with mean value 19.40 ± 11.705. There was statistical significant relation between PVRU at baseline and after phase (1) and phase (2) ($P < 0.05$). There was statistical significant relation between baseline with phase (1) and (2) ($P1, P2 < 0.05$) while there was no statistical significant relation between phase (1) and phase (2) ($P3 > 0.05$).

Table (10): Comparison between PVRU at baseline and after phase (1) and phase (2)

PVRU	Baseline	Phase (1)	Phase (2)
Range	30.0-100	10.0-60	0.0-50
Mean	60.80	23.2	19.40
S.D.	21.928	11.72	11.705
F	11.3		
P	0.005*		
P1	0.006*		
P2	0.001*		
P3	0.072 N.S.		

P1 comparison between base line and phase (1) P2 comparison between baseline and phase (2)
P3 comparison between phase (1) and phase (2) F= ANOVA test P is significant if <0.05
* Significant difference

Table (11) shows comparison between Q max at baseline and after phase (1) and phase (2). Baseline ranged from 7-18.3 with mean value 11.68±2.977, phase (1) ranged from 10-20.3 with mean value 16.89±2.62 and phase (2) ranged from 12-23 with mean value 17.33±2.82. There was statistical significant relation between Q max at baseline and after phase (1) and phase (2) ($P < 0.05$). There was statistical significant relation between baseline with phase (1) and (2) ($P1, P2 < 0.05$) while there was no statistical significant relation between phase (1) and phase (2) ($P3 > 0.05$).

Table (11): Comparison between Q max at baseline and after phase (1) and phase (2)

Q max	Baseline	Phase (1)	Phase (2)
Range	7.0-18.3	10.0-20.3	12.0-23
Mean	11.68	16.89	17.33
S.D.	2.977	2.62	2.82
F	10.6		
P	0.007*		
P1	0.006*		
P2	0.016*		
P3	0.081 N.S.		

P1 comparison between base line and phase (1) P2 comparison between baseline and phase (2)
P3 comparison between phase (1) and phase (2) F= ANOVA test P is significant if <0.05
* Significant difference

Table (12) shows distribution of adverse effect in the two phases. Retrograde ejaculation was higher in both phase 5(16.7%) and 6(20%) respectively followed by myalgia with 3(10%) in phase I and Postural hypotention, dyspepsia, headache and flushing with 4(13.3%).

Table (12): Distribution of adverse effect in the two phases

Adverse effect	Phase I		Phase II	
	No.	%	No.	%
Myalgia	3	10.0	2	6.7
Retrograde ejaculation	5	16.7	6	20.0
Postural hypotention	2	6.7	4	13.3
Dyspepsia	2	6.7	0	0.0
Flushing	2	6.7	4	13.3
Back pain	1	3.3	0	0.0
Dizziness	0	0.0	0	0.0
Headache	0	0.0	4	13.3
Flu-like symptoms	0	0.0	2	6.7

DISCUSSION:

Benign prostatic hyperplasia (BPH) is the most common cause of lower urinary tract symptoms (LUTS) in adult males. LUTS vary in severity, ranging from mild to severe, affecting patients' quality of life (QoL) accordingly. Approximately 40% of men by the age of 50 years and 80% of men by 80 years will have BPH, the symptoms of which include poor urinary stream, urinary hesitancy, feeling of incomplete bladder emptying, urgent and/or frequent urination, and urge incontinence [(11)].

Alpha-blockers (ABs) were the mostly prescribed drugs to manage patients with LUTS/BPH. ABs are usually the first line treatment for LUTS thanks to their rapid onset of action. By antagonizing alpha (1a)-adrenergic receptors in the prostate and urethra, they cause smooth muscle relaxation in lower urinary tract determining the decrease of the functional obstruction [(10)].

The aim of this work is to compare between the effect of alpha blocker (Tamsulosin 0.4 mg once at night) and a combination of alpha blockers (Tamsulosin 0.4 mg once at morning) and PDE5 inhibitors (Sildenafil 25 mg at night) in treatment of benign prostatic hyperplasia patients through evaluation of IPSS and post-voiding residual urine and uroflometry before and after treatment.

This study was prospective randomized clinical study, carried at urology department, faculty of medicine, Ain Shams University (El Demerdash Hospital), this study included 30 Men of 50-70 years old with a history of LUTS secondary to BPH. Patients agreed not to use BPH medications during the research other than the study medications.

This study has two phases: Phase (1): included 30 patients complaining of LUTS 2ry to BPH assessed by uroflowmetry and IPSS and post voiding residual urine. Before taking any drugs and after treatment by alpha blocker (tamsulosin 0.4mg capsule once daily at night) for 3 months. Phase (2): included the same 30 patients after treatment by alpha blocker (Tamsulosin 0.4 capsule once daily in the morning) and PDEI (sildenafil 25mg once daily in the night) for 3 months. These patient also assessed by IPSS, uroflowmetry and PVR urine.

Several studies have studied the efficacy of monotherapy with FDEI5 and tamsulosin. Also, there are studies on their combination with other drugs or comparing them with each other.

In our study, the different items of International prostate symptom score (IPSS) show a significant improvement after phase (1), and improve after phase (2) but without significant difference from phase (1), except the nocturia which was significantly decrease in phase (2) more than phase(1). Although there was no significant difference between phase (1) and (2) in other items of the IPSS score, but the significant improvement in nocturia causes decrease in total score in phase (2) more than phase (1) and so marked improvement in LUTS.

In our study there was a significant decrease in PVRU in both phases 1 & 2 but there was no significant decrease in comparing both phases.

Also the present results of this study showed that there was an increase in Q max significantly in both phases 1 and 2 but there was no significant difference between both phases of the study.

Fawzi et al. [12] is a prospective study, two-armed, randomised, double-blind comparative study between tamsulosin 0.4 mg once daily (OD) at day time plus sildenafil 25 mg OD at night and tamsulosin 0.4 mg OD at day time plus placebo at night in the treatment of patients with LUTS/BPH, they carried this study on 150 men with untreated LUTS/BPH with or without ED.

In *Fawzi et al.* [12] study, IPSSs were significantly improved in the two groups, but this improvement was more marked with combined therapy than for α1-adrenergic receptor blocker alone, and the 6-month scores were insignificantly improved compared to the 3-month scores in the two groups.

Regarding Qmax was significantly improved at the 3- and 6-month follow-ups in both groups, but this improvement was more marked with combined therapy (Group A) than for α1-adrenergic receptor blocker alone (Group B). Qmax was improved in both treatment groups and was not significantly different, and the 6-month scores were insignificantly improved compared to 3-month scores in both groups [12].

In agreement with *Fawzi et al.* [12] to our study there is significant improvement in IPSS with combination of tamsulin and sildenafil more than tamsulin alone.

In disagreement with *Fawzi et al.* [12] where there is improvement in Qmax with

combination of tamsulin and sildenafil more than tamsulin alone but in our study there is no significant improvement in Qmax.

Sebastianelli et al. [13], study the effect of Tadalafil 5 mg Alone or in Combination with Tamsulosin 0.4 mg for the Management of Men BPH, they carried out an observational trial aiming to assess the efficacy and safety of Tadalafil compared with Tadalafil plus Tamsulosin. Seventy-five patients complaining of ED and LUTS were treated for 12-weeks with Tadalafil plus placebo (TAD+PLA-group) or with combination therapy tadalafil plus tamsulosin (TAD+TAM-group), in this study they found that the total IPSS was significantly improved in both groups. Nevertheless, men treated with combination therapy showed a more remarkable improvement of IPSS compared with tadalafil alone.

In agreement *Sebastianelli et al.*[13] study results, the items of IPSS parameters were significantly improved at the end of the trial in the 2 treatment arms, supporting the evidence for the use of tadalafil 5 mg as monotherapy or in combination with tamsulosin 0.4 mg in men with BPH. In particular, they observed a clinically meaningful recovery of LUTS, since a decrease >25% or >3 points of total IPSS was achieved in both groups, In our study there is improvement in LUTS with combination more than monotherapy.

However, at the end of the trial, Qmax was significantly better in men treated with combination therapy compared to tadalafil only. Indeed, tadalafil 5 mg significantly improved Qmax after 12 weeks of monotherapy (mean improvement of Qmax: +2.24 mL/s). but in our study there is no significant deference in the improvement in Qmax between combination and monotheraby.

Tuncel et al. [14] study a total of 60 men with BPH-related LUTS were randomized to receive sildenafil citrate only (n = 20), tamsulosin only (n = 20), and the combination of both (n = 20) for 8 weeks. Changes from baseline in International Prostate Symptom Score (IPSS), maximum urinary fow rate (Qmax), post voiding residual urine volume (PRV), Sexual Health Inventory for Male (SHIM) score, 3rd and 4th questions of International Index of Erectile Function (IIEF) were assessed at the end of the treatment.

Also in this study they found that the improvement of IPSS was more remarkable in combination (40.1%) and tamsulosin only (36.2%) groups in comparison with sildenafil citrate only group (28.2%; $p < 0.001$). Improvement of Qmax and PVR were greater in tamsulosin only and combination than sildenafil citrate only group. SHIM scores signifcantly improved in sildenafil citrate only (65%) and combination (67.4%) than tamsulosin only (12.4%; $p < 0.001$).

Increases in the 3rd and 4th questions of IIEF were greater in sildenafil only and combination than tamsulosin only ($p < 0.001$) and as result; treatment with the combination of sildenafil citrate and tamsulosin was not superior to tamsulosin only to enhance voiding symptoms. Also, sexual function improvement was similar between the combination and sildenafil citrate only treatments[14].

In comparison to our study results *Tuncel et al.* [14] study says that Sildenafil citrate and tamsulosin combination is not superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction but in our study the combination improves IPSS and LUTS significantly than tamsulin alone.

McVary et al. [15] This was a 12-week, double-blind, placebo controlled study of sildenafil in men 45 years or older who scored 25 or less on the erectile function domain of the International Index of Erectile Function and 12 or greater on the International Prostate Symptom Score. End points were changes in International Index of Erectile Function domain scores, International Prostate Symptom Score

(irritative, obstructive and quality of life) The 189 men receiving sildenafil had significant improvements in erectile function domain score vs the 180 on placebo (9.17 vs 1.86, p <0.0001) and on all other International Index of Erectile Function domains.

In men on sildenafil vs placebo significant improvements were observed in International Prostate Symptom Score (–6.32 vs –1.93, p <0.0001), mean International Prostate Symptom Score quality of life score (–0.97 vs –0.29, p <0.0001). There was no difference in urinary flow between the groups (p = 0.08). Significantly more sildenafil vs placebo treated patients were satisfied with treatment (71.2 vs 41.7, p <0.0001). Sildenafil was well tolerated Improved erectile dysfunction and lower urinary tract symptoms with sildenafil in men with the 2 conditions were associated with improved quality of life and treatment satisfaction. Daily dosing with sildenafil may improve lower urinary tract symptoms [(15)].

In comparison to our study results; *McVary et al.*[(15)] concludes that Sildenafil was well tolerated Improved erectile dysfunction and lower urinary tract symptoms and daily dosing with sildenafil may improve lower urinary tract symptoms but in our study the combination of sildenafil and tamsulosin improve LUTS significantly more than tamsulosin alone and there is no study with sildenafil alone.

Disadvantages of this study

- The prostate size was not considered and we do not know if this may influence the efficacy of drugs in improving LUTS/BPH or if there is effect on the size of prostat or not.
- Sildenafil is a short acting drug and must be taken in consideration.

Conclusion:

Sildenafil citrate in combination with tamsulosin improved LUTS more than tamsulosin monotherapy with the merit of a comparable safety profile in patients with LUTS/BPH.

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دراسة مقارنة لتأثير مثبطات مستقبلات ألفا وتأثير الجمع بين مثبطات ألفا ومانع ثنائي الفوسفو إسترات فى علاج تضخم البروستاتا الحميد

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الخلفية: تضخم البروستاتا الحميد (BPH) هو اضطراب يتميز نسيجيا بأنه تضخم غير خبيث لخلايا البروستاتا معظم المرضى الذين يعانون من تضخم البروستاتا الحميد الموجود مع أعراض بالجزء السفلى من المسالك البولية مما يؤدى الى ضعف تدفق البول خارج المثانة.

إن تضخم البروستاتا الحميد من الممكن ان تظهر اعراضه فى سن مبكر بداية من سن الثلاثون حتى الخمسون عاما، وقد وجد ان نصف الرجال تقريبا يعانون من تضخم البروستاتا الحميد وتزيد هذه النسبة مع تقدم السن.

وتعتبر أعراض الجزء السفلى من المسالك البولية (LUTS) الناتج عن تضخم البروستاتا الحميد (BPH)، وعدم القدرة على الانتصاب (ED) هي الامراض السائدة للغاية في الرجال كبار السن.

الهدف: تقييم فعالية وسلامة الجرعة الثابتة من الجمع بين علاج تامسولوسين ٠,٤ مجم بالإضافة سيلدنافيل ٢٥ مجم مقابل علاج تامسولوسين ٠,٤ وحدها مرة واحدة يوميا في علاج مريض تضخم البروستاتا الحميد (BPH) مع أعراض بالجزء السفلى من المسالك البولية (LUTS) ودراسة ذلك على مختلف اعراض تضخم البروستاتا الحميد.

المرضى والطرق: عدد الحالات المشتمله عليها الدراسه هو ثلاثون مريضًا من سن ٥٠-٧٠ عامًا يعانون من اعراض بالجزء السفلى من المسالك البوليه (LUTS) بسبب تضخم البروستاتا الحميد (BPH) تم تقسيمهم إلى مرحلتين للعلاج فى المرحلة الاولى تلقى المرضى التامسولوسين ٠,٤ مجم فقط لاغير. وفى المرحلة الثانية تلقى المرضى التامسولوسين ٠,٤ مجم بالاضافة الى سيلدنافيل ٢٥ مجم يوميا لمدة ثلاثة اشهر.

النتائج: الجرعه الثابته من الجمع بين التامسولوسين سيلدنافيل ادى الى تحسن بشكل كبير فى درجه النتيجة الدولية لاعراض البروستاتا(IPSS) وكميه البول الخارجه من المثانه فى الثانيه الواحده اثناء التبول ((Qmax أكثر من سيلدنافيل ٢٥ ملجم وأيضا انخفاض كميه البول المتبقى بعد التبول (PVRU) بشكل كبير مع الجرعه الثابته من الجمع بين التامسولوسين و سيلدنافيل أكثر من السيلدنافيل وحدها.

الخلاصة: تم تحديد الجرعه الثابته من الجمع بين التامسولوسين و سيلدنافيل ٢٥مجم لتكون آمنة وفعالة وجيد التحمل في الموضوعات التي تم التحقيق فيها، مما يشير إلى أن العلاج الجديد (الجرعه الثابته من الجمع بين التامسولوسين و السيلدنافيل) يمكن أن تقدم فوائد للمرضى الذين يعانون من أعراض بالجزء السفلى من المسالك البولية LUTS.