



A COMPARATIVE STUDY OF TADALAFIL & TAMSULOSIN COMBINATION THERAPY VERSUS ALFUZOSIN MONOTHERAPY IN SEXUALLY ACTIVE PATIENTS OF BENIGN PROSTATIC HYPERPLASIA.

Urology

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ABSTRACT

BACKGROUND: The patients, suffering from LUTS due to BPH are generally treated with tamsulosin or silodosin. It was found that maximum patients are suffering from sexual dysfunctions while treating with those drugs. So in this study we want to observe and compare the tamsulosin and tadalafil combination with alfuzosin monotherapy. These two regimens were chosen because, as per finding of various previous studies, these two regimens can prevent and as well as treat the sexual adverse effects related to bph and tamsulosin/ silodosin monotherapy.

MATERIAL AND METHODS: In this study 38 patients were given Tamsulosin (0.4mg) & Tadalafil (5mg) fixed dose combination therapy and 38 patients were given Alfuzosin (10mg). Symptom scores were assessed with the help of International Prostate Symptom Score (IPS Score), Quality of Lifestyle Score (QoL Score) and International index of erectile dysfunction score (IIEF 5). Uroflowmetry was done to evaluate the change in Qmax. The evaluation of patients at each group was done at Day 1, 3 month, 6 months.

RESULTS: In this study, patients of both regimens experienced a similar kind of significant improvement of LUTS, maximum urinary flow (qmax) and better quality of life over time. In case of erectile dysfunction, patients of tamsulosin and tadalafil combination experienced a rapid improvement, but after 6 months of therapy both groups experienced similar improvement in sexual well being.

CONCLUSION: Alfuzosin is more cost effective and has similar efficacy in comparison to tamsulosin & tadalafil combination for treating LUTS due to BPH in sexually active male patients.

KEYWORDS

Alfuzosin, Tamsulosin, Tadalafil, LUTS, BPH, Erectile dysfunction.

INTRODUCTION:

Benign prostatic hyperplasia (BPH) is one of the most common genitourinary complication in men over 50 years of age and typically presents with lower urinary tract symptoms (LUTS). For past two decades drug treatment became more preferable than surgical intervention. Classes of medication used in BPH are alpha 1 adrenoreceptor blocker (tamsulosin/silodosin/alfuzosin), 5 alpha reductase inhibitor (finasteride/dutasteride), phosphodiesterase 5 inhibitors (tadalafil).

In recent literatures, it has been constantly indicating that these drug therapies are associated with several sexual side effects, i.e – erectile dysfunction (ED), decrease libido, orgasmic dysfunction and ejaculatory dysfunctions. However in clinical studies in 1990 reported that despite amelioration of LUTS, adverse effects of drug therapies begin to surface^[1].

The most common drug used worldwide in BPH is tamsulosin or silodosin but it has been reported that those drugs affect libido (2-7%), erectile function and ejaculatory disorder (18-64%)^[2,3,4,5,6]. Alfuzosin is another uroselective alpha one blocker. Various published literature showed that alfuzosin has very minimal sexual side effects or no sexual side effects at all^[2,3,4,7,8]. In fact Van morsel et al showed that Alfuzosin resulted improvement from baseline in ED and ejaculatory disorder^[9].

According to The 2015 European Association of Urology (EAU) guidelines, PDE5 inhibitors with alpha-blockers improve the International Prostate Symptom Score, the International Index of Erectile Function (IIEF) score, and maximum urinary flow rate compared with alpha blockers alone^[10,11,12]. Food and Drug Administration (FDA) also approved tamsulosin and tadalafil combination to be used in LUTS with ED^[13]. FDA, in its safety profile stated that tamsulosin and tadalafil do not exert clinically relevant blood pressure changes^[14]. Bechara et al concluded that Tamsulosin 0.4 mg/day plus tadalafil 20 mg/day was more effective than tamsulosin 0.4 mg/day alone to improve LUTS and erectile dysfunction and was also well tolerated^[15].

A major portion of the patients coming to our hospital are suffering from LUTS and a considerable portion of this patient group are sexually active. These patients are generally treated with tamsulosin or silodosin. While treating them with alpha blockers, it was found that maximum patients are suffering from sexual dysfunctions that

hampered their quality of life. So in this study we want to observe and compare the tamsulosin and tadalafil combination with alfuzosin monotherapy. The basic reason for choosing these two regimens, as supported by previous studies, is that these two regimens can prevent and as well as treat the sexual adverse effects related to bph and tamsulosin monotherapy and we did not find a single study where these two drugs were compared on head to head basis. As maximum patients of this hospital, come from low socioeconomic condition, cost effectiveness of these regimens can also be compared.

OBJECTIVE:

In this study we wanted to compare the efficacy and cost effectiveness between tamsulosin and tadalafil combination therapy and alfuzosin monotherapy in treating LUTS associated with BPH. We also wanted observe and compare sexual side effects and quality of life after treating with tamsulosin, tadalafil combination therapy and alfuzosin monotherapy.

MATERIALS AND METHODS

We had conducted the study on patients coming to the urology OPD of our hospital from September, 2019-August 2020 with the complaints of lower urinary tract symptoms due to BPH. Patients were chosen according to the inclusion and exclusion criteria.

STUDY TECHNIQUE:

It was a comparative, prospective, observational, non-invasive, parallel and randomised study which comprised of total 76 patients diagnosed with Benign Prostatic Hyperplasia along with Lower Urinary Tract Symptom, out of which, 38 patients were given Tamsulosin (0.4mg) & Tadalafil (5mg) fixed dose combination therapy and 38 patients were given Alfuzosin (10mg) as per computer randomization method. Inclusion criteria comprised of patients age less than 60, who are already diagnosed with Benign Prostate Hyperplasia (BPH) along with Lower Urinary Tract Symptom (LUTS) and not on any kind of treatment. They should not suffer from any other diseases like Diabetes mellitus/insipidus or hypertension or any other causes of sexual dysfunction. Those who were already on medication, excluded from the study.

STUDY DESIGN

For each patient, proper history regarding the disease and the

consumption of drug was taken. Symptom scores were assessed with the help of International Prostate Symptom Score (IPS Score-0-7 mildly symptomatic, 8-19- moderately symptomatic, 20-35- severely symptomatic.), Quality of Lifestyle Score (QoL Score-0-delighted, 1-pleased, 2-mostly satisfied, 3- mixed, 4-mostly dissatisfied, 5-unhappy, 6-terrible) and International index of erectile dysfunction score [IIEF 5- severe (5-7), moderate (8-11), mild to moderate (12-16), mild (17-21), and no ED (22-25)]. Uroflowmetry was done in all patients to evaluate the change in Qmax. The evaluation of patients of each group was done at Day 1, 3 month, 6 months.

ETHICAL CONSIDERATIONS:

This study was approved by Institutional ethics committee (Approval number – IPGME&R/RAC/084, dated- 16/09/2019). All subjects provided written informed consent for inclusion in the study and for undergoing the procedures described. All the procedures were adhered to the ethical guidelines of Declaration of Helsinki and its amendments.

RESULT:

STATISTICAL ANALYSIS

Statistical Analysis was performed with help of Epi Info (TM) 7.2.2.2 EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC).

Descriptive statistical analysis was performed to calculate the means with corresponding standard deviations (s.d.). Test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference proportions. t-test was used to compare two means. Also One Way Analysis of variance (ANOVA) followed by post hoc Tukey's Test was performed with the help of Critical Difference (CD) at 5% and 1% level of significance to compare the mean values. $p < 0.05$ was taken to be statistically significant.

Table-1: Comparison of mean age of the patients of the two groups

Mean Age (in years)	alfuzosin (n=38)	Tamsulosin combination with Tadalafil (n=38)	t-test	p-value
Mean±sd	52.63±4.29	53.16±3.74	0.57	0.57 NS
Median	52	53.5		
Range	43 - 60	45 - 60		

NS- Statistically not significant

t-test showed that there was no significant difference in mean age of the patients of the two groups ($p=0.57$). Thus the patients of the two groups were matched for their ages.

Table-2: Comparison of mean International Prostate Symptom Score (IPSS) of the patients of the two groups at different time intervals

Mean International Prostate Symptom Score (IPSS)	Alfuzosin (n=38)	Tamsulosin combination with Tadalafil (n=38)	t _{test}	p-value
At Day1				
Mean±sd	21.97±4.17	20.68±5.81	0.01	0.990 NS
Median	22	21		
Range	12 - 30	11 - 32		
At 3 month				
Mean±sd	18.50±3.63	16.58±4.71	1.991	0.05 NS
Median	18	17		
Range	10 - 26	7 - 28		
At 6 month				
Mean±sd	9.58±2.51	10.53±4.02	0.463	0.644 NS
Median	9	11		
Range	4 - 14	4 - 21		
F _{2,111} -value	126.44	41.29		
p-value	<0.001 S	<0.001 S		

S- Statistically significant

NS- Statistically not significant

t-test showed that there were no significant differences in mean IPSS of the patients of the two groups at different time intervals ($p > 0.05$).

However, One way ANOVA followed by Tukeys post hoc test showed

that in both the groups the mean IPSS of the patients decreased significantly over time interval as compared to the mean IPSS at Day1 ($p < 0.001$).

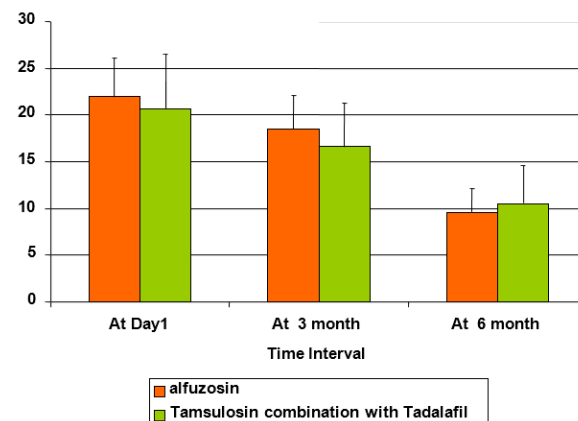


Fig1- Graphical representation of IPS Score of two groups in different time intervals.

Table-3: Comparison of mean erectile dysfunction (ED) score of the patients of the two groups at different time intervals

Mean erectile dysfunction (ED)	alfuzosin (n=38)	Tamsulosin combination with Tadalafil (n=38)	t _r -test	p-value
At Day1				
Mean±sd	19.82±4.20	14.87±4.74	1.112	0.270 NS
Median	20	14		
Range	11 - 28	7 - 24		
At 3 month				
Mean±sd	19.32±3.60	19.71±3.83	4.819	<0.001 S
Median	19	19		
Range	12 - 25	14 - 27		
At 6 month				
Mean±sd	20.92±3.03	24.37±2.71	1.506	0.136 NS
Median	21	25		
Range	16 - 27	18 - 28		
F _{2,111} -value	1.93	55.45		
p-value	0.14	<0.001 S		

S- Statistically significant, NS- Statistically not significant

t-test showed that there were no significant differences in mean erectile dysfunction (ED) of the patients of the two groups at Day1 and at 6 month ($p > 0.05$). However, at 3 month the mean erectile dysfunction (ED) score of the patients treated with Tamsulosin combination with Tadalafil was significantly higher than that of the patients treated with alfuzosin ($p < 0.001$).

However, One way ANOVA followed by Tukeys post hoc test showed that in both the groups the mean erectile dysfunction of the patients decreased significantly over time interval as compared to the mean erectile dysfunction at Day1 ($p < 0.001$).

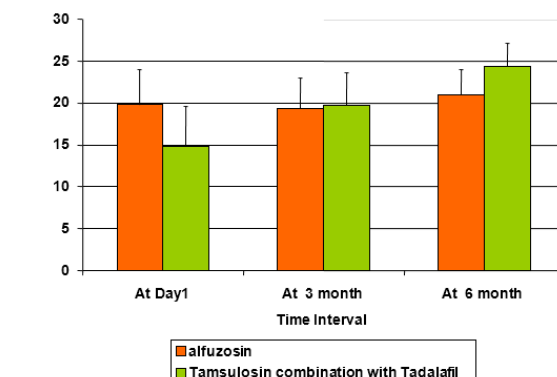


Fig2- Graphical representation of IIEF Score of two groups in different time intervals.

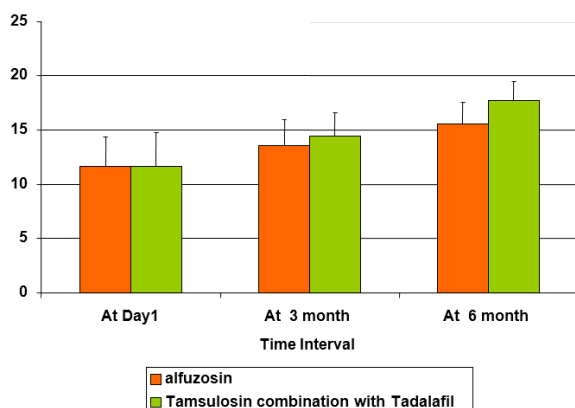
Table-4: Comparison of mean peak urinary flow (qmax) of the patients of the two groups at different time intervals

Mean peak urinary flow	alfuzosin (n=38)	Tamsulosin combination with Tadalafil (n=38)	t ₇₄ -test	p-value
At Day1				
Mean±sd	11.61±2.74	11.61±3.12	0.147	0.883 NS
Median	11.5	12		
Range	7 - 18	5 - 18		
At 3 month				
Mean±sd	13.55±2.41	14.45±2.13	1.715	0.091 NS
Median	13	14		
Range	10 - 19	10 - 18		
At 6 month				
Mean±sd	15.55±2.04	17.70±1.81	1.232	0.222 NS
Median	15	18		
Range	12 - 20	14 - 21		
F _{2,111} -value	25.44	60.91		
p-value	<0.001 S	<0.001 S		

S- Statistically significant, NS- Statistically not significant

t-test showed that there were no significant differences in mean peak urinary flow (qmax) of the patients of the two groups at different time intervals (p>0.05).

However, One way ANOVA followed by Tukeys post hoc test showed that in both the groups the mean peak urinary flow (qmax) of the patients increased significantly over time interval as compared to the mean peak urinary flow (qmax) at Day1 (p<0.001)

**Fig3- Graphical representation of maximum urinary flow rate (qmax) of two groups in different time intervals.****Table-5: Comparison of mean score of quality of life (QOL) of the patients of the two groups at different time intervals**

Mean score of quality of life (QOL)	Alfuzosin (n=38)	Tamsulosin combination with Tadalafil (n=38)	t ₁₄ -test	p-value
At Day1				
Mean±sd	3.50±1.06	3.84±0.92	5.227	<0.001 S
Median	4	4		
Range	1 - 6	2 - 6		
At 3 month				
Mean±sd	2.66±0.81	2.68±0.74	1.458	0.149 NS
Median	3	3		
Range	1 - 5	2 - 4		
At 6 month				
Mean±sd	1.50±0.65	1.69±0.61	1.3139	0.1929 NS
Median	1	2		
Range	1 - 3	1 - 3		
F _{2,111} -value	52.15	73.80		
p-value	<0.001 S	<0.001 S		

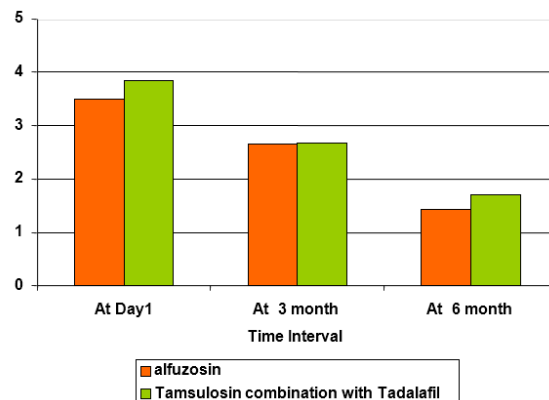
S- Statistically significant

NS- Statistically not significant

t-test showed that at Day1 the mean score of quality of life (QOL) of

the patients treated with Tamsulosin combination with Tadalafil were significantly higher than that of the patients treated with alfuzosin (p<0.001). But in t-test showed that there were no significant differences in QOL score of the patients of the two groups at different time intervals (p>0.05).

However, One way ANOVA followed by Tukeys post hoc test showed that in both the groups the mean score of quality of life (QOL) of the patients increased significantly over time interval as compared to the mean score of quality of life (QOL) at Day1 (p<0.001)

**Fig4- Graphical representation of QOL Score of two groups in different time intervals.**

DISCUSSION

Previously, sexual dysfunction in aged men was solely considered as an age related disorder. But as per recent epidemiological studies it is clearly evident that most men are sexually active even in their 70s^[16]. Sexual dysfunction in BPH patients seriously hampers their quality of life. So these patients not only want relief from the LUTS also demand their sexual well being^[17,18,19]. There is enough evidence to state that LUTS is a crucial and independent risk factor for sexual dysfunction in aged men^[20,21,22].

There are several valid explanations of erectile dysfunction in BPH patients which consists of decrease in nitric oxide synthase, increased autonomic nervous system activity, abnormal induction of rho kinase pathway and altered androgen environment^[23].

There are multiple studies which established the efficacy and safety of alpha blocker and tadalafil combination therapy in ED with LUTS. Glina et al also showed the safety of the combination^[24]. Kim et al concluded that the FDC (fixed dose combination) 0.4/5 mg therapy was safe, well tolerated, and efficacious, indicating that combination therapy could provide clinical benefits for patients with BPH-associated LUTS complaints and ameliorate the comorbidity of ED^[12]. Bechara et al concluded that Tamsulosin 0.4 mg/day plus tadalafil 20 mg/day was more effective than tamsulosin 0.4 mg/day alone to improve LUTS and erectile dysfunction and was also well tolerated^[14]. Das et al concluded that Alfuzosin 10mg given at daily dose was found to have higher efficacy than Tadalafil (5mg)^[25]. As per finding of Kim et al, we also used tamsulosin(0.4) and tadalafil (5) fixed dose combination in our study.

Jeoren et al showed that alfuzosin 10mg once daily for one year not only significantly improves LUTS and quality of life, it also improves sexual function in those patients suffering from LUTS with erectile and ejaculatory dysfunction^[8].

In this study we have found that patients of both regimens experienced a significant improvement of LUTS and maximum urinary flow (qmax). No significant difference was also found in between two groups.

In case of erectile dysfunction, patients of tamsulosin and tadalafil combination experienced a rapid improvement, but after 6 months of therapy both groups experienced similar improvement in sexual well being.

As we know quality of life in BPH patients is very much dependent on improvement of LUTS as well as sexual well being, patients of both

group experienced similar improvement after six months of therapy. In both the groups the mean score of quality of life (QOL) of the patients increased significantly over time interval.

LIMITATION OF THE STUDY:

The limitation of our study is the relatively small sample size and this study was done in a single centre.

CONCLUSION:

The average price of tamsulosin (0.4) and tadalafil(5) combination in Indian market is 25-35 rupees per dose, while tab alfuzosin (10) costs around 14-20 rupees. So, from the finding of this study we can conclude that alfuzosin is more cost effective and has similar efficacy in comparison to tamsulosin & tadalafil combination for treating LUTS due to BPH in sexually active male patients.

FINANCIAL SUPPORT AND SPONSORSHIP:

Nil

CONFLICT OF INTEREST:

Nil.

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