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Research Article

STUDY OF THERAPEUTIC EFFICACY & SAFETY OF TAMSULOSIN "ALONE AND COMBINATION WITH FINASTERIDE" IN BENIGN PROSTATIC HYPERPLASIA PATIENTS

***PRABHAKAR SINGH, **AMITA SINGH, ***G.P SHRIVASTAVA, ****BHUPENDRA RAJ**

*** Dept. of Pharmacology, S.S. Medical College, Rewa (MP) 486001, **Dept. of Physiology, S.S. Medical College, Rewa (MP) 486001, ***Dept. of Surgery, S.S. Medical College, Rewa (M.P) 486001, ****Deptt. of Pharmacology, S.S. Medical College, Rewa (MP)**
Email: prabhakarsingh999@gmail.com

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ABSTRACT

Benign prostatic hyperplasia is the most common cause of voiding dysfunction in men. The aim of study is comparison of the efficacy and safety of tamsulosin (0.4mg) alone v\s combination of tamsulosin (0.4mg) with fenasteride 5mg once daily in benign prostatic hyperplasia patients. In this randomized study 94 patients were enrolled, 46 patients were on tamsulosin and 48 on combination therapy, once daily for 12-weeks. Study was designed to compare the efficacy and safety of tamsulosin v/s combination. The primary measures were mean changes in total and/or individual I-PSS score, prostate volume and urinary flow rate from baseline to 12-weeks. Tamsulosin & combination both significantly improved lower urinary tract (BPH) symptoms with a mean change from baseline to endpoint in the I-PSS of -16.7 (from 20.20±8.9 to 3.5±1.08), P<0.0001 V/S -14.09 (from 17.47±7.14 to 3.38±1.93) P<0.0001, but efficacy between two group was not significant (P=0.85), life style questionnaire were significantly improved in both group. Adverse events were similar; most common observed adverse event was dizziness, (4.34%), in tamsulosin, it was slightly more than combination group (2.08%). While other disorders like headache (2.1 vs 2.08), abdominal distension (2.1 vs 2.08) & sexual disorder (2.08 vs 2.1) was same in both group. Both tamsulosin alone and combination regimen are highly effective for symptomatic treatment of BPH but there is no significant difference in their efficacy and safety (total\individual I-PSS improvement) between groups up to the endpoint of study. So we concluded that for short term treatment combination is not a cost-effective therapy.

Keywords: BPH (Benign prostatic hyperplasia); I-PSS (International-prostate symptom score); AUR (Acute urinary retention); BPO (Benign prostatic obstruction); LUTS (Lower urinary tract symptoms).

INTRODUCTION

Benign prostatic hyperplasia is the most common cause of voiding dysfunction in men. The prevalence of benign prostatic hyperplasia increases with age, as the average age of population advances an increasing prevalence of benign prostatic hyperplasia is expected[1]. Incidence of benign prostatic hyperplasia by the age 60 year 50% and by the 8th decade of life 85% of men are found to have histological evidence of benign prostatic hyperplasia[2]. Pathological evident of the disease appears in men between 40 and 50 years old[3]. Testosterone and other androgens are needed for the development of BPH. DHT is the major physiologically active androgen in the prostate and needed for the enlargement of the prostate. 5α-reductase is an enzyme requires for conversion of testosterone into DHT, suppression of DHT production through inhibition of 5α-reductase has been shown to improve clinical outcomes and prevent the advancement of diseases in benign prostatic hyperplasia patients[5]. Blocking 5α- reductase actively has been proven to reduce prostate size and prostatic symptoms[4]. In the prostatic capsule, adenoma and bladder neck there are 2 types of α-adrenergic receptors, designated as α-1 and α-2. The action of the α-2 receptors is same as α1 but the receptor which predominantly mediating the contractile properties of the human prostatic adenoma is the α-1 types. High density of α-receptors are present in the prostate and bladder neck than the bladder[6]. α-Receptor blockers have been proven to decrease the tone of prostatic capsule and adenoma, decreasing the pressure in the prostatic part of the urethra and bladder neck without affecting bladder pressure[7] and improve clinical effects in benign prostatic hyperplasia patients.

METHOD & STUDY DESIGN

This short-term (12 weeks) clinical study was conducted in Department of Pharmacology and Department of Surgery at S.S. Medical college and associated Sanjay Gandhi Memorial Hospital Rewa M.P. India with aim to compare the efficacy and safety of tamsulosin o.4 mg alone versus combination (with fenasteride 5mg) therapy once daily in patients with BPO. A total of 94 men were enrolled in the study, 46 patients take tamsulosin and 48 were on combination regimen. Patients were on I-PSS scoring system with the total score is more than 3 points; I-PSS scoring system is based on seven items: Sensation of not completely emptying of bladder; Increase frequency of micturition (within two hour); Stopped and started again several times when urinating; Difficulty to postpone urination; Weak urinary stream; Strain during urination ; Number of urinate during night.

Inclusion criteria

Male patients above 40 years with enlarge prostate size and LUTS including hesitancy, poor stream and terminal dribbling.

Exclusion Criteria

Patients are excluded in this study with a consistent residual urine volume >200 ml., history of previous bladder neck, prostate or pelvic region surgery, other condition which would affect micturition including neurological bladder disorder, bladder neck stenosis, urethral stricture, prostate cancer, bladder stone etc. History of hypersensitivity to α-adrenoceptor antagonists and take any other investigational drugs within the previous 3-months. All urological therapy had to be avoided until the end of the trial.

Study Design

Men treated with these drugs as modified–release capsule one daily after dinner; patients were assessed at enrolment, and after 1, 2, 4, 8 and 12-weeks. At visit-1 (enrolment visit); total\individual I-PSS score as well as vital signs, laboratory evaluation and H\O any recent or concomitant medication has been taken, the size of prostate was estimated by rectal palpation and abdominal ultrasound. At each visits; total\individual I-PSS and adverse events were assessed and vital signs were monitored.

Assessment of Efficacy

Parameters for efficacy were total and individual I-PSS score and urinary flow rate, significant response was defined as those with a ≥ 25% decrease in total I-PSS score. Efficacy assessments were made on patients who received treatment from baseline to complete 3-month and attend regular follow-up. Safety assessments includes; monitoring of the occurrence of adverse events, vital signs and laboratory determinations.

Statistical method

Within-group changes from baseline were assessed using the paired student t test. The significance level set at $P \leq 0.05$.

RESULTS

The men assigned to the tamsulosin and combination groups were similar in term of age, baseline demographic characteristics, symptoms and other variables. The maximum number of patients 44 (46.80%) were 60-69 age group, the majority of patients with benign prostatic hyperplasia 37 (39.36%) were Govt. servants which are showing in Table 1.

On the basis of I-PSS grading system, 45 (47.087%) were belong to grade-II (maximum) and 13 (13.82%) were belong to grade-I (minimum). AUR developed in 1 (2.4%) patient in tamsulosin group during treatment. 10 patients in tamsulosin (n= 46) and 16 in combination group (n=48) were enrolled in catheterized state (at 1st visit) and most of them remove their catheter within 15-25 days of treatment. 2 patient in tamsulosin(4.3%) and 3 in combination therapy underwent surgery.

Table 1: Basic Parameters, including Age, Occupation and I-PS Score grade of BPH patients

Age Group.		Tamsulosin		Combination Therapy (Tamsulosin 0.4mg with fenasteride 5mg)		Grand Total	
S. No	**In Years**	**No.**	**%**	**No.**	**%**	**No.**	**%**
1.	40-49	00	00	04	8.33	04	4.25
2.	50-59	05	10.86	08	16.66	13	13.82
3.	60-69	23	50.00	21	43.75	44	46.80
4.	70-79	14	30.43	12	25.0	26	27.65
5.	80-89	04	8.69	03	6.25	07	7.44
Total		46	100	48	100	94	100
Occupation							
1.	Govt. Servant	21	45.65	16	33.34	37	39.36
2.	Sedentary Worker	10	21.73	10	20.83	20	21.27
3.	Heavy Worker	11	23.91	15	31.25	26	27.65
4.	Businessmen	04	8.69	07	14.58	11	11.70
Total		46	100	48	100	94	100
I-PSS Score Grade							
1.	I (0-7)	05	10.86	08	16.00	13	13.82
2.	II (8-19)	21	45.65	24	50.00	45	47.87
3.	III (20-35)	20	43.47	16	33.00	36	38.29
Total		46	100	48	100	94	100

Mean of Demographic Parameters		Tamsulosin	Combination Therapy (Tamsulosin 0.4mg with fenasteride 5mg)
1	Age (Mean ± SD)	67.28 ± 7.99 (n=46)	63.33 ± 10.15 (n=48)
2	Prostate Volume (Mean ± SD)	36.28 ± 24.67 (n=15)	45.20 ± 22.16 (n=25)
3	PSA (Mean ± SD	3.41 ± 3.98 (n=2)	2.42 ± 0.45 (n=2)

Table 2: Mean Parameters (Mean ± SD) **of Age, Prostate Volume, PSA of BPH patients**

Changes in Prostate Volume			
1	Mean Prostate Volume at Baseline (in ml)	34.20 (n=9)	48.40 (n=16)
2	Mean Prostate Volume After 12 Weeks (in ml)	34.80 (n=9)	46.65 (n=16)

Prostate volume increased 0.6 ml in tamsulosin group (n=9), (mean ± SD; 34.2 to 34.8 ml.) and 1.39 ml decrease in (mean ± SD; 48.04 to 46.65 ml) in combination therapy (n=16) during 12-weeks follow-up, given in Table 2.

1 patient on tamsulosin (n=46) and 1 on combination (n= 48) increases their total symptom scores from baseline and 2 patients on combination therapy (n=48) have no change in total I-PSS score from baseline to 12-weeks after treatment.

Table 3: Efficacy of Drugs on Total I-PSS Symptom Scores in Between Baseline and after 1,2,4,8 and 12 Weeks of Interval

S. No.	Regimen	Change in total I-PSS from Ist Visit to last visit					
		Ist Visit (Mean ± SD)	Last Visit (Mean ± SD) Ist week	2nd Week	4th Week	8th Week	12thWeek
1.	Tamsulosin (0.4 mg)	20.20 ± 8.95	16.5 ± 3.41	13.87 ±10.42	6.9 ± 3.54	4.62 ± 2.87	3.5 ± 1.08
2.	Combination Therapy (Tamsulosin 0.4mg with fenasteride 5mg)	17.47 ± 7.14	11.58 ± 6.68	8.0 ± 5.42	6.63 ± 4.16	4.35 ± 2.23	3.38 ± 1.93

Statistical Calculation

Regimen	1 Week	2 Week	4 Week	8 Week	12 Week
Tamsulosin	P=0.44, T=0.786 df=12, Not Significant	P=0.185, T=1.38 df=16, Not Significant	P=0.0004, T=4.370 df=18, Significant	P=0.0002, T=4.704 df=16, Significant	P=<0.0001, T=5.858 df=18, Significant
Combination Therapy (Tamsulosin 0.4mg with fenasteride 5mg)	P=0.021, T=2.430 df=31, Significant	P=<0.0001, T=4.508 df=35, Significant	P=<0.0001, T=5.868 df=38, Significant	P=<.0001, T=7.906 df=39, Significant	P=<0.0001, T=8.765 df=40, Significant

Total I-PSS Symptom: The mean change from baseline in the total I-PSS score after 1-week of treatment with combination therapy was significantly (P 0.02) better than that of tamsulosin (P 0.44) After 4- weeks the mean changes in combination therapy, P 0.004 and in tamsulosin, P<0.0001 was significant. After 12-weeks mean change in total scores were similar in both tamsulosin and combination group (P<0.0001). The result is shown in Table 3.

In individual I-PSS Symptom: (1) Frequency score was extremely significant in combination (P<0.004) and tamsulosin group (P<0.0001), Shown in Figure 1.

(2) Intermittency Score: At end point of study intermittency symptom score disappear in tamsulosin (P=nil) and extremely significant in combination therapy (p<0.0001), Shown in Figure 2.

(3) Urgency Score: Total urgency score first significantly improved after 8-weeks of treatment with combination therapy (P<0.029) compare to tamsulosin (P 0.039).Shown in Figure 3.

(4) Nocturia Score: Nocturia symptom score was first appears statistically significant at end point of study (12-weeks) P 0.01 in combination and P 0.01 in tamsulosin and it were similar in both groups, shown in Figure 4.

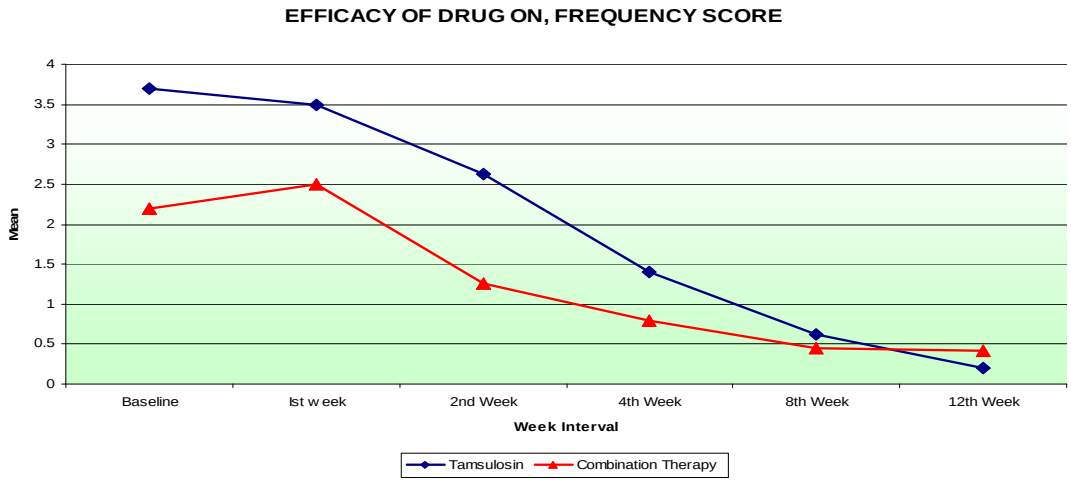

Fig. 1: Efficacy of Drugs on Frequency Score; and comparison of scores From Baseline to 1,2,4,8 and 12 weeks of Interval

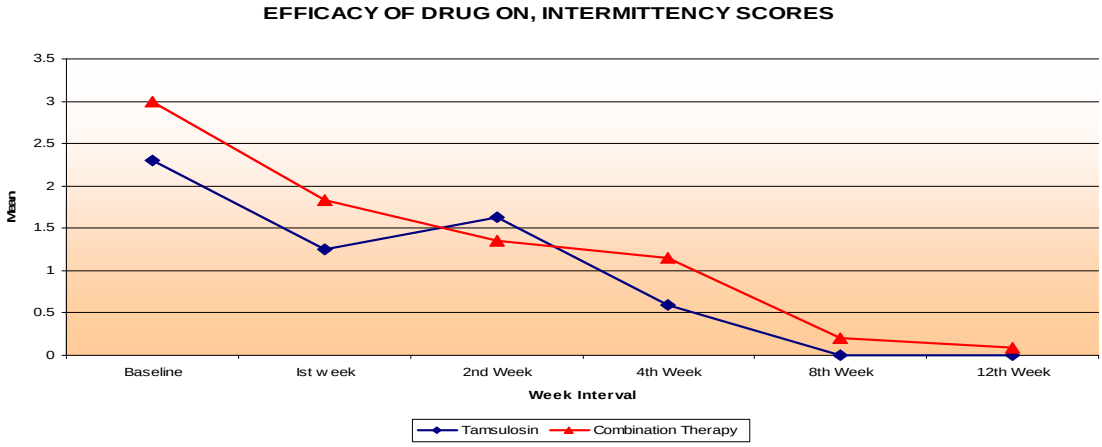

Fig. 2: Efficacy of Drugs on Intermittency Score; and comparison of scores From Baseline to 1,2,4,8 and 12 weeks of Interval

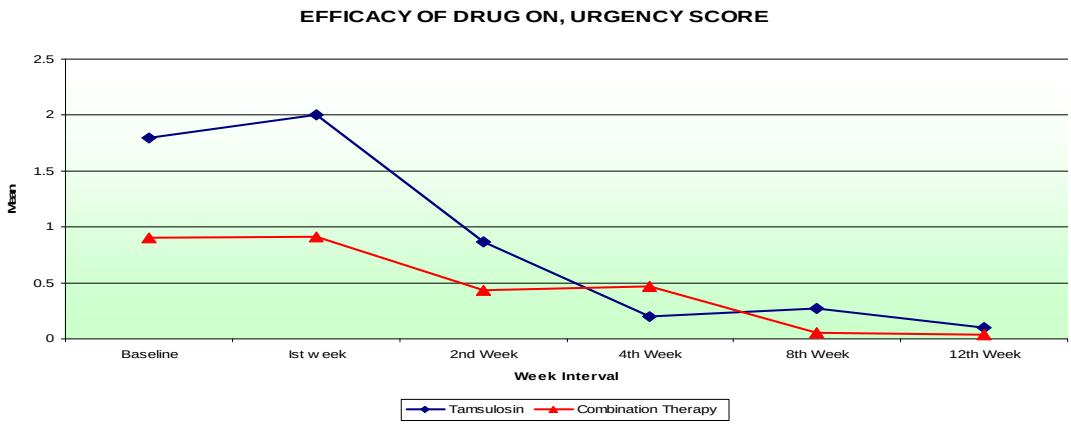

Fig. 3: Efficacy of Drugs on Urgency Score; and comparison of scores From Baseline to 1,2,4,8 and 12 weeks of Interval

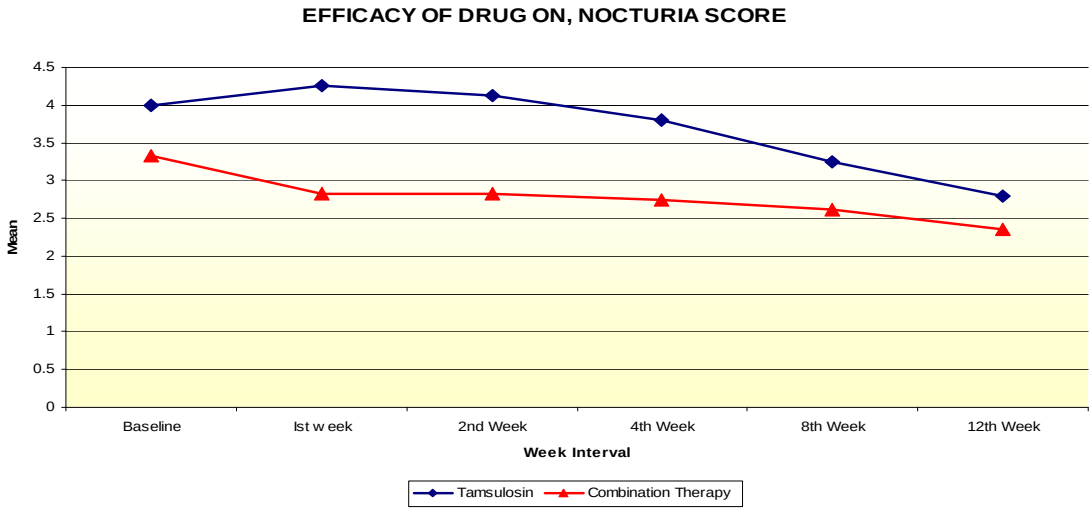

Fig. 4: Efficacy of Drugs on Nocturia Score; and comparison of scores From Baseline to 1,2,4,8 and 12 weeks of Interval

Table 4: Comparison of Total I-PSS between treatment Groups from Baseline to 1,2,4,8 and 12 Weeks of trail In between groups

Duration of Treatment	Values of Tamsulosin VS Combination therapy			
	Tamsulosin	Combination	T value	P value
Baseline	20.20 ±8.95	17.80 ± 7.29	0.79	0.43
1st Week	16.50 ± 3.41	11.58 ± 6.68	1.39	0.18
2nd Week	13.87 ± 10.42	8.0 ± 5.42	1.83	0.08
4th Week	6.69 ± 3.54	6.63 ± 4.16	0.17	0.86
8th Week	4.62 ± 2.87	4.35 ± 2.23	0.79	0.27
12th Week	3.50 ± 1.08	3.38 ± 1.93	0.18	0.85

Tamsulosin and combination therapy; both reduced the total & individual I-PSS scores significantly, but there is no significant difference in between groups up to the end point of study, data given in Table 4.

Table 5: Commonly observed adverse effect during study

S. No.	Adverse effects	Tamsulosin	Combination Therapy (Tamsulosin 0.4mg with fenasteride 5mg)
1	Dizziness	2 (4.34%)	1 (2.08%)
2	Headache	1 (2.1%)	1 (2.08%)
3	Tachycardia /Palpitation	0	0
4	Syncope	0	0
5	Asthenia	0	0
6	Somnolence	1 (2.1%)	0
7	Abdominal distension	1 (2.1%)	1 (2.08%)
8	Decreased libido	0	1 (2.08%)
9	Ejaculation disorder	1 (2.1%)	0
10	Others (Hypersomnia)	0	0

Total 4 (8.33%) patients were present with single complaint, in combination group, these were; 1(2.08%) headache, 1(2.08%) dizziness, 1(2.08%) abdominal distension, and 1(2.08%) decreased libido during follow-up and in tamsulosin group, the incidence of adverse effect is 6 (13.1%) patients (n=46) of which dizziness was maximum in 2 patients (4.34%), headache in 1 (2.1%), ejaculation disorder in 1 (2.1%) abdominal distension in 1 (2.1%), and somnolence in 1 (2.1%) patient. data is given in Table 5.

DISCUSSION

Benign prostatic hyperplasia and lower urinary tract symptoms can affect the quality of life in older men. However, in some men benign prostatic hyperplasia can cause acute urinary retention; a need for surgery, urinary incontinence, urinary tract infections and other complications. Treatment with alpha-blocker or a 5α-reductase inhibitor can ameliorate symptoms and improve urinary flow rate, finasteride substantially reduces the risk of acute urinary retention and the need for surgical treatment. Benign prostatic hyperplasia is the most common conditions associated with ageing in men, effecting 50% of those between the age of 50 and 60 years and as many as 90% of those older than 80 years of age[8]. Symptoms of benign prostatic hyperplasia such as urgency, dribbling and a weak urinary stream were present in the majority of men over 60 years of age[9]. In our study, maximum no. of cases belong to 60-69 year age groups and maximum sufferers were government servants this may be due to physical activity was inversely related with total benign prostatic hyperplasia[10] result to this, physically active men have a lower frequency of lower urinary tract (BPO) symptoms. Maximum patients were moderate grade (I-PSS>8-19) in this study, similar to *Ricouard et al (1997)*[11] In this study, mean age of these patients were 65.72 ± 8.69 year, this result is similar to various *EUROPEAN* study[11,12,13] and mean baseline prostate volume & serum PSA level was 45.22 ml & 2.75 ng/ml respectively, this was similar to others *like Fradet et al (1996).*[14,15] In present study tamsulosin 0.4 mg significantly improved total and individual symptoms score, the improvements in total I-PSS was 82.6%. This was similar to the previously reported study[16] in which the improvement in total I-PSS score was 34%. Previously, 2-open-labels, observational study[17] showed similar results, in study-1, the change in total score after 4-weeks was 8.5 point or 68% and in study-2, it was more than 10 point or 87% after 12-week. In present

study total symptom score first appear significant after 4-weeks, similar to *Wyndaele et al (2005)*.[18]In present study combination therapy had mean decrease in prostate volume was 1.39ml (2.89%) after 3-month of therapy this data was similar to *MTOPS* research study[19] group in that study, combination therapy had decrease in volume of 19% from baseline during 4.5 years of follow-up. Patients with combination therapy have no acute urinary retention after starting treatment and 3 men underwent surgery during treatment, this was similar to *MTOPS* research study group in which combination therapy reduces 81% risk and rate (0.1/100 person/year) of acute urinary retention. A prospective *European study*[8] showed that the incidence of acute urinary retention or transurethral prostatectomy was "0"%, with combination therapy. A significant change in total I-PSS first after 1-week of treatment (P=0.02) at end point of study it was extremely significant (P<0.0001). The improvement in total symptom scores were 81% and mean changes from baseline score were 14.4 points or 81% in combination group, this data was similar to previous *MTOPS* study group,[19] in that study mean reduction in symptom scores were 7.0 points (58 percent) from baseline (16.8) with combination therapy. There is significantly improvement in obstructive (p<0.00001incompleteemptying, p<0.0001 intermittency, P<0.0001 weak stream and p<0.0001 Straining) and Irritative (p<0.004 frequency, p 0.024 urgency and p 0.013 nocturia) symptoms with combination therapy at end points of study, this was similar to *Roehrborn et al, (2003),*[20] in which it significantly improved both obstructive and irritative symptom scores. Out of 48 patients in combination therapy, total 4 patients were associated with single complaint, these were followings; 1(2.08%) headache, 1(2.08%) dizziness, 1(2.08%) abdominal distension, and 1(2.08%) decreased libido during follow-up and this was similar to tamsulosin in which the incidence of adverse events in total population was 6 (13.1%) patients (n=46) dizziness was maximum in 2 patients (4.34%), headache in 1 (2.1%), ejaculation disorder in 1 (2.1%) abdominal distension in 1 (2.1%), and somnolence in 1 (2.1%) patient.

CONCLUSION

The aims of treatment is reliving the hindrance to the free flow of urine by obviating the enlarging prostate gland at bladder neck by one of the many surgical procedures or by medical (drug) treatment. In the past decade surgery (TURP) offers the best chance for improvement in symptoms but also has the highest rate of significant complications. Transurethral resection of the prostate is the most common surgical procedure. Therefore in these patients surgery and/or anesthesia proves to be a risky affair. Hence surgery in these patients should be contemplated with utmost care and precaution as they run a very high risk of morbidity and mortality. Another factor to be considered in these patients is a morbid fear for any operative procedure. The result of this study confirms the positive effect of the both regimens in total and individual I-PSS score. In comparative study once daily dosing of tamsulosin at bed time at a fix dose level (0.4mg) offers an efficient improvements in total and individual I-PSS score but have no effect on prostate volume, while combination therapy reduced prostate volume, risk of acute urinary retention and the need for invasive therapy. Adverse events were similar in both tamsulosin and combination group. This comparative study showed tamsulosin and combination therapy was safe and reduced the total & individual I-PSS score significantly, but there is no significant difference in between tamsulosin and combination groups up to the end point of study. So we concluded that, for short term treatment combination is not a cost-effective therapy.

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