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General Surgery

COMBINATION THERAPY OF DUTASTERIDE AND SILODOSIN – AN EFFECTIVE MODALITY TO TREAT LUTS IN BPH

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ABSTRACT Benign prostatic hyperplasia (BPH) is a chronic condition associated with lower urinary tract symptoms (LUTS). This study is focused to find out the efficacy of combination of dutasteride and silodosin in management of BPH. 120 cases were analyzed for a period of 1 year from July 2015 to June 2016 with BPH and were followed up at 3 months and 6 months after initiation of the therapy. Our study showed significant decrease in the total IPSS and the improvement in Qmax and PVRU. The most significant observation has been of 58 patients (52.73%) reporting ejaculation disorders.

KEYWORDS : Benign prostatic hyperplasia (BPH), lower urinary tract symptoms (LUTS), International prostate symptom score (IPSS), Maximum urinary flow rate (Qmax), Post void residual urine (PVRU).

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a chronic condition associated with lower urinary tract symptoms (LUTS). It affects more than half of men above 50 years and nearly 90% of men over 80 years. [1,2,3] The LUTS correlates poorly with the size and extent of bladder outlet obstruction.[4,5] Hence the goal of treatment in BPH patients is to get relief from symptoms, thus improving the quality of life and the disease progression to avoid further surgical intervention. As of today the Available treatment options are: medical therapy, minimally invasive therapy, and surgical intervention. Medical therapy currently includes two groups of medicines: alpha-blockers and 5-alpha reductase inhibhitors. Alpha-blockers which are currently used are Alfuzosin HCL, Doxazosin mesylate, Tamsulosin HCL, Terazosin HCL and Silodosin.

Silodosin is uroselective (selective α1A-blocker) and has fewer side effects compared to other non-selective drugs and provides rapid relief from symptoms but do not reduce prostate size.[3]

Dutasteride (5-alpha reductase inhibitors) inhibit conversion of testosterone to dihydrotestosterone which helps in reducing prostate size, resulting in improved urinary flow and prevents progression of prostate size in the long term.[6]

Much data is available regarding the efficacy of the individual drugs and the combination of tamsulosin and dutasteride however the efficacy of combination therapy of silodosin and dutasteride is still not established and few studies have reported very encouraging results[7]. Thus, this study is focused to find out the efficacy of combination medical therapy (combination of dutasteride and silodosin) in terms of improvement of LUTS and overall management of BPH.

MATERIAL AND METHODS

120 cases coming to the surgical department of Adesh institute of medical sciences and research Hospital during a period of 1 year from July 2015 to June 2016 with bladder outlet obstruction due to prostatomegaly were analyzed in this study. Out of which 10 patients were lost during follow up due to unknown reasons. Data was collected of remaining 110 patients for demographic patient characteristics, clinical history (including IPSS), physical examination (including digital rectal examination), laboratory and radiological investigations. Patients with IPSS scores of <8, 8-19, 19-35, were considered to have mild, moderate, and severe, symptoms respectively.

Uroflowmetry, urine routine and microscopic examination, serum prostate-specific antigen was done to exclude possibility of prostate carcinoma.

Ultrasonography was done for prostate volume, postvoid residual urine and to see any hypoechoic lesion in the prostate.

All eligible subjects received once daily dose of combination of silodosin 8 mg and dutasteride 0.5 mg for a period of six months.

Follow-up:

Patients were followed at 3 months and 6 months after initiation of the therapy. Primary efficacy criteria included improvement in the symptomatic scores (IPSS) and maximum flow rate (Qmax). Changes in prostate volume were noted. The patients who undergo BPH related surgery or who develop BPH related complications were noted. Safety was assessed by monitoring adverse events. Responders (clinically significant response) to drug are defined as a Qmax increase of >30 % or >3ml or IPSS > 25% decrease from baseline.

RESULTS

Baseline characteristics

The baseline characteristics of all the 110 patients in the study are shown in the table 1.

Table 1: Baseline characteristics

Variables	Baseline	Range
Age(in yrs)	66.42±9.84	51-87
Total IPSS	16.25±3.48	0- 35
Obstructive IPSS	6.29±2.11	0-20
Irritative IPSS	10.44±3.06	0-15
Q MAX (ml/s) ²	11.44±2.24	6-18
Post void residue (ml)	76.98±17.10	33-115
Prostate volume(cc)	56.05±20.48	30-66
PSA(ng/ml)	2.36±0.73	1.8- 2.8

The changes from baseline after treatment with combination of silodosin plus dutasteride for 3 months are shown in Table 2. In this study group, the total IPSS decreased from (16.25±3.48) to (11.74±2.42) (P<0.001), the obstructive IPSS decreased from (6.29±2.11) to (4.89±2.06) (P<0.001), the irritative IPSS decreased from (10.44±3.06) to (7.47±2.08) (P<0.001).

Table 2: International prostate symptom score (IPSS), Obstr uctive and Irritative IPSS

IPSS	Visit I	Visit II	Visit III	Significance		
				I-II	I-III	II-III
Total IPSS	16.25±3.48	13.31±2.68	11.74±2.42	<0.001 **	>0.001 **	<0.001 **

Obstructive IPSS	6.29±2.11	4.96±1.95	4.89±2.06	<0.001**	<0.001**	0.731
Irritative IPSS	10.44±3.06	8.25±2.09	7.47±2.08	<0.001**	>0.001**	<0.001**

Qmax

The changes in Qmax during active treatment are shown in the tables 3 and 4. There was a significant improvement in the Qmax compared to baseline. However percent improvement in Qmax is less than 30%.

Improvement percentage greater than 30% is seen in 78.2% of the studied population.

Table 3: Q MAX (ml/s)

QMAX (ml/s) ²	Visit I	Visit II	Visit III	Significance		
				I-II	I-III	II-III
Min-Max	6.00-18.00	7.00-15.00	8.00-16.00	0.021	<0.001**	<0.001**
Mean ± SD	11.44±2.24	12.24±1.89	13.25±1.69			

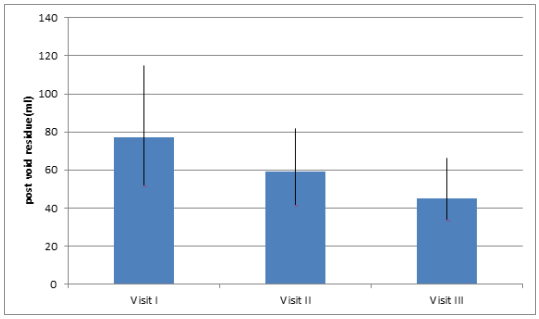

Fig 1: Qmax

Table 4: Qmax Increase more than 30 % for clinical significant response

QMax change	Number of patients	%
<30.0%	86	78.2
>30.0%	24	21.8
Total	110	100.0

Post void residue

The effects of combination therapy on post void residue are shown in the table 5 and figure 2. There was a significant decrease in the post void residue at the end of treatment compared to baseline. The improvement in post void residue started by the three month period of the treatment.

Table 5: post void residue (ml)

Postvoid residue (ml)	Visit I	Visit II	Visit III	Significance		
				I-II	I-III	II-III
Min-Max	51.00-115.00	41.00-82.00	33.00-66.00	<0.001**	<0.001**	<0.001**
Mean ± SD	76.98±17.10	58.98±10.73	45.12±8.71			

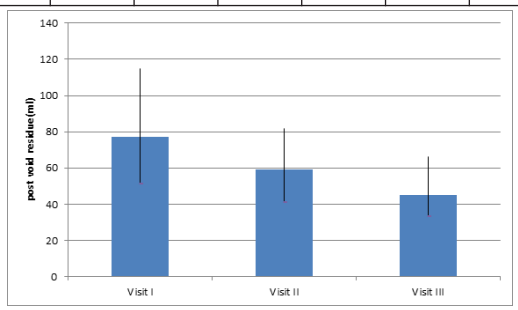

Fig 2: post void residue

In the total period of six months study, six patients had giddiness, four had features of decreased libido, two had acute retention, two experienced breast tenderness, fifty eight complained of ejaculation disorder, and two had impotence; the total incidence of individuals experiencing adverse effects in this group was 67.27% (74/110).

Table 6: Final outcome of patients studied

Side effects	Visit II		Visit III	
	No	%	No	%
1.Impotence	2	1.8	2	1.8
2.Altered libido	4	3.6	4	3.6
3.Ejaculation disorders	58	52.73	58	52.73
4.Breast disorders	0	0.0	2	1.8
5.Dizziness	0	0.0	6	5.2
6.Acute urinary retention	0	0.0	2	1.8
7.Prostate surgery	0	0.0	0	0.0

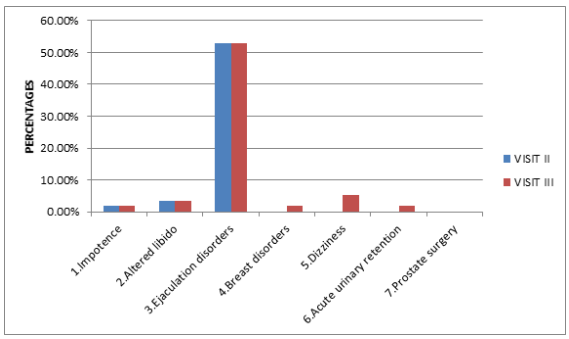

Fig 3: percentage of side effects

The changes from baseline after treatment with combination of silodosin plus dutasteride for 6 months are shown in Table. In this study group, the total IPSS decreased from (16.25±3.48) to (11.74±2.42) (P<0.001), the obstructive IPSS decreased from (6.29±2.11) to (4.89±2.06) (P<0.001), the irritative IPSS decreased from (10.44±3.06) to (7.47±2.08) (P<0.001), the Qmax increased from (11.44±2.24) ml/s to (13.25±1.69) ml/s (P<0.001), and the residual urine decreased from (76.98±17.10) ml to (45.12±8.71) ml (P<0.001). Improvement of IPSS is seen by 27.75%, obstructive IPSS by 22.25%, irritative IPSS by 28.35%, Qmax by15.91%, post void residue by 41.37% from the baseline values.

Table 7: Changes of Efficacy parameters from baseline to the end of treatment Period

Variables	Baseline	End of treatment	Improvement %	Significance
Total IPSS	16.25±3.48	11.74±2.42	27.75%	t=14.387;P<0.001**
Obstructive IPSS	6.29±2.11	4.89±2.06	22.25%	t=5.275;P<0.001**
Irritative IPSS	10.44±3.06	7.47±2.08	28.35%	t=9.723;P<0.001**
Q MAX (ml/s) ²	11.44±2.24	13.25±1.69	15.91%	t=5.404;P<0.001**
post void residue (ml)	76.98±17.10	45.12±8.71	41.37%	t=20.625;P<0.001**

DISCUSSION

IPSS and Qmax are important parameters to determine the severity of BPH symptoms, and are used to evaluate patient's response to treatment.[8] Our study shows significant decrease in the total IPSS and the improvement in the lower urinary tract symptoms from the beginning i.e. from the first week to the outpatient department of surgery. The total, obstructive and the irritative ipss decreased from (16.25±3.48) to (11.74±2.42) (P<0.001), (6.29±2.11) to (4.89±2.06) (P<0.001), (10.44±3.06) to (7.47±2.08) (P<0.001) respectively which shows the IPSS improvement was on an average of 27.25% compared to baseline. Roehrborn in their two different studies one of which was randomized trials have shown improvement of 38% and 39.2% respectively.[9, 10] This variation of results from our study could be probably because of having included patients of higher age group in our study and moreover IPSS is a subjective score. Our study also showed significant Improvements in the storage and voiding symptom sub scores irrespective of prostate volume.

Qmax

In our study, there is increase in the Qmax compared to baseline. Increase in the Qmax is observed from the first follow up period. Qmax

increased from (11.44±2.24) ml/s to (13.25±1.69) ml/s i.e. 1.81ml/s from the baseline (P<0.001). It is in comparison with two long duration, randomized controlled trials where Qmax is increased by 2.4 mL/s compared to baseline. [9, 10] Our study also shows a significant decrease in the residual volume of 31.86ml from the baseline i.e. from (76.98±17.10) ml to (45.12±8.71) ml (P<0.001). Although there has been similar results shown by the single therapy regimen in reducing the residual volume but the patients requiring the surgical intervention at later stage was higher in number compared to the combination therapy. In a study by yamanishi et al 78 patients out of 104 withdrew from the study because of following reasons i.e. 27 patients (26.0%) with unknown reason, adverse events in nine patients (8.7%) and unsatisfactory effects in 30 patients (28.8%). In those 30 patients who withdrew because of unsatisfactory effects, 21 patients underwent surgery.[11] These large no. of patients requiring surgery could be because of longer duration of study of 72 months where as our study was of 12 months only.

Side effects:

Adverse events reported in the study were consistent with the known safety profiles of dutasteride and silodosin and most commonly included ejaculation disorders, impotence, decreased libido, breast disorders (including enlargement and tenderness) and dizziness. No unexpected adverse events have occurred and none of these adverse events were serious enough to warrant withdrawl from the study.

The most significant observation in our study has been of 58 patients (52.73%) reporting ejaculation disorders as compared to other studies from Japan which reported retrograde ejaculation to the extent of 12 to 30%.12 Our observation of higher incidence of retrograde ejaculation could be explained by the fact that our study had 80% sexually active patients which were specifically questioned about this parameter on the day of beginning of therapy and on follow up also where as the other studies which have reported less incidence have no mention of patients who were sexually active in their study. Although there has been no data available in the literature on our observation of higher no. of patients getting retrograde ejaculations we did inquire about these figures from other practicing colleges of their day to day observations on this side effect, they too agreed to our observations. Interestingly, patients with ejaculatory dysfunction had the highest efficacy with silodosin, suggesting that the presence of ejaculatory dysfunction can be used as a surrogate for efficacy.[13]

Regarding tolerability in our study, none of our patients who had retrograde ejaculation discontinued the medicine as the improvement in lower urinary tract symptoms was significant and patients were satisfied. Moreover they were adequately councilled about the merits and demerits of this combination therapy.

The primary objectives of the medical treatment for LUTS/BPH are to produce rapid, sustained, and safe improvements in the lower urinary tract symptoms associated with benign prostatic hyperplasia that affect the quality of life in the majority of men over the age of 50. Although this study is short term and limited in the number of patients, it provides evidence that the combined therapy of an α1-adrenergic receptor antagonist (silodosin) plus an 5-alpha redutase inhibitor (dutasteride) is a good approach for meeting these objectives. And the profile of patients included in the study might be used as an indication of using combined therapy for patients with LUTS/BPH. Additional studies on a greater number of patients for longer period are needed to substantiate the preliminary evidence of this study.

CONCLUSION

To conclude, in patients with moderate-to-severe lower urinary tract symptoms and an enlarged prostate, combination therapy of dutasteride plus silodosin achieved significantly greater improvements from baseline BPH symptoms, flow rate, quality of life, and improved treatment satisfaction but with accompanied side effect of anejaculation in a significant number of patients.

REFERENCES:

1. Bob Jan, Seyed Saeid Dinnat, Amir Kazzai. Effect of combination treatment on patient-related outcome measures in benign prostatic hyperplasia: clinical utility of dutasteride and tamsuloin. Patient Related Outcome Measures. 2011; 2; 71-79.
2. Naslund MJ, Issa MM, Grogg AL, Eaddy MT, Black L. Clinical and economic outcomes in patients treated for enlarged prostate. Am J Manag Care. 2006; 12: 111–116.
3. Taneja SS. Treatment of Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia. The Urologic clinics of North America. 2016 Aug; 43(3): xiii.
4. Lepor H: Pathophysiology of lower urinary tract symptoms in the aging male population. Rev Urol 2005; 7: S3
5. Andersson KE and Gratzke C: Pharmacology of _1-adrenoceptor antagonists in the lower urinary tract and central nervous system. Nat Clin Pract Urol 2007; 4: 368.
6. Roehrborn CG. The effects of combination therapy with dutasteride plus tamsulosin on clinical outcomes in men with symptomatic BPH: 4-yearpost hoc analysis of European men in the CombAT study. Prostate Cancer Prostatic Dis. 2006; 9: 121–5.
7. Kapoor A. Benign prostatic hyperplasia (BPH) management in the primary care setting. Can J Urol. 2012 Oct 1;19(Suppl 1):10-7.
8. Wang JY, Liu M, Zhang YG, Zeng P, Ding Q, Huang J, et al. Relationship between lower urinary tract symptoms and objective measures of benign prostatic hyperplasia: a Chinese survey. Chin Med J 2008; 121: 2042-2045.
9. Roehrborn CG, Lukkarinen O, Mark S, et al. Long-term sustained improvement in symptoms of benign protatic hyperplasia with the dual 5a-reductase inhibitor dutasteride: results of 4-year studies. BJU Int. 2005; 96(4): 572-577.
10. Roehrborn CG, Siami P, Barkin J, Damião R, Major-Walker K, Morrill B, Montorsi F; CombAT Study Group. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the ComAT study. J Urol 2008; 179(2):616-21.
11. Yamanishi T, Kaga K, Fuse M, Shibata C, Kamai T, Uchiyama T. Six-year follow up of silodosin monotherapy for the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: What are the factors for continuation or withdrawal?. International Journal of Urology. 2015 Dec 1;22(12):1143-8.
12. Yoshida M, Kudoh J, Homma Y, Kawabe K. New clinical evidence of silodosin, an α1A selective adrenoceptor antagonist, in the treatment for lower urinary tract symptoms. International Journal of Urology. 2012 Apr 1;19(4):306-16.
13. Yukio H, Kazuki K, Masayuki T, Masaki Y. Ejaculation disorder is associated with increased efficacy of silodosin for benign prostatic hyperplasia. Urology2010;76(6):1446-1450.