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A CLINICAL STUDY OF BPH AND ITS MEDICAL MANAGEMENT WITH SPECIAL REFERENCE TO TAMSULOSIN

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ABSTRACT

Introduction : Currently α1-adrenoceptor blockers are widely used as first-line therapy to improve lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). The aim of this study was to evaluate the efficacy of Tamsulosin in BPH patients with mild to moderate symptoms.

Material and Methods: The present hospital based prospective interventional study was conducted in Department of Surgery and Urology Out-Patient Department, Assam Medical College and Hospital, Dibrugarh, during the time period of 1st June 2016 to 31st May 2017 and 49 cases of BPH with mild to moderate symptoms and prostate volume ≤30 cc were included in the study.

All patients were administered Tamsulosin (0.4 mg) once daily for 3 months after obtaining ethical clearance and administering informed consent. The patients were followed up for changes in PVR, IPSS, IPSS-QoL, PV and S.PSA which were recorded and analyzed using appropriate statistical tools.

Results: At the end of 1 month and 3 months, PVR (baseline 35.19±8.13 ml) was 19.1±4.47 ml and 16.67±3.51 ml, IPSS score (baseline 12.67±3.16) was 8.1±1.89 and 7.00±1.53, IPSS-QoL (baseline 4.45±0.84) was 2.69±0.54 and 2.08±0.44, change in PV was +0.34%, and 1.46% and S.PSA (baseline 1.9±1.1 ng/ml) was 1.8±1.0 ng/ml and 1.8±1.0 ng/ml respectively.

However at the end of 3 months, 19 patients (38.7%) were administered Tamsulosin 0.4mg for 3 more months due to persistence of symptoms. In these patients at the end of 6 months PVR was 18.31±2.34 ml, IPSS was 7.00±1.29, IPSS-QoL was 2.0±0.47, change in PV was +8.79% and S.PSA was 2.4±0.9ng/ml.

Conclusion: There is statistically significant improvement in PVR, IPSS and IPSS-QoL, although there is no effect on PV and S.PSA. Thus, Tamsulosin 0.4 mg can be used for effective relief of LUTS caused due to BPH in mild to moderate cases with PV ≤30 cc.

Abbreviations: BPH- Benign Prostatic Hyperplasia, PVR- Post Void Residual Urine, IPSS- International Prostate Symptom Score, IPSS-QoL- IPSS Quality of Life Index, PV- Prostate Volume, S.PSA- Serum Prostate Specific Antigen, LUTS- Lower Urinary Tract Symptoms.

KEYWORDS : Benign Prostatic Hyperplasia, α1-adrenoceptor blocker, Tamsulosin, PVR, IPSS and IPSS-QoL.

INTRODUCTION

BPH is a senile disorder of the geriatric men with histologically proven high incidence of 92.97% (n = 185) and 93.3% (n = 200) in India. It is the most common benign tumor in men with prevalence estimates ranging from 50% for men in their 50s to 90% for men in their 90s. Although not all men suffer from this condition, approximately 50% of those developing histological hyperplasia eventually will develop moderate-to-severe and bothersome, storage and voiding symptoms collectively called the lower urinary tract symptoms (LUTS).[1]

Benign prostatic hyperplasia (BPH) has been recognized as a major contributing factor for LUTS in aging men. It is also known that LUTS affect quality of life in the majority of those who reach average life expectancy. In addition, longitudinal population-based studies which best analyze the natural history of the disease have shown that BPH is a progressive disease. Progression includes increase of symptoms, acute urinary retention (AUR), and the need for BPH-related surgery. Therefore, it becomes evident that BPH-LUTS has significant economical implications, since an increasing number of elderly men will eventually seek help for this condition.[2]

In daily practice, therapeutic approach is usually initiated with medical treatment and, if drugs fail, minimally invasive interventions or other surgical procedures will follow.[2] Among the various surgical approaches, transurethral resection of prostate (TURP) has become the gold standard in the management of benign prostatic hyperplasia. Unfortunately transurethral resection of prostate has its own complications. Urinary infection, urinary retention, clot retention, hemorrhage requiring blood transfusion, TUR syndrome, impotence, urinary incontinence, rupture of prostatic urethra and retrograde ejaculation are the various complications associated with TURP. Some of these complications can severely affect the quality of life in the postoperative period following transurethral resection of prostate. This demands for the introduction of effective medical therapies, because they have lesser risk.

Three classes of medical therapies are currently utilized: Phytotherapy with uncertain mechanisms of action; 5α-reductase inhibitors, which reduce prostatic volume; and α-adrenergic-receptor antagonists, which decrease smooth muscle tone in the prostatic capsule and bladder neck. Many α-adrenergic-receptor antagonists have been evaluated in the treatment of LUTS; all of these agents were initially developed and approved for the treatment of hypertension, until the development of Tamsulosin.[3]

Tamsulosin is a subtype-selective α1A- and α1D-adrenoceptor antagonist. α1 adrenoceptor antagonists relax the smooth muscles of the bladder neck and prostate, decrease bladder outlet resistance and facilitate urinary flow without affecting detrusor smooth muscle contractility. α1 receptors predominate in the prostate gland, prostatic capsule, prostatic urethra and bladder. This relaxation of prostate and bladder smooth muscles is associated with improved maximal urine flow (Qmax) and alleviation of lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH).[3]

METHODS

After obtaining approval and clearance from the Intuitional Ethics Committee (Human) of Assam Medical College & Hospital, Dibrugarh, forty nine subjects with LUTS secondary to BPH were included for hospital based prospective study in Assam Medical College and Hospital, between June 2016 and May 2017. Written informed consent was obtained from all the subjects after fully explaining the study procedure to their satisfaction.

Patients with small Prostate (≤30gms) having mild to moderate symptoms (IPSS≤19) were included in the study. Patients with large Prostate (>30gms) having severe symptoms (IPSS>19), chronic retention of urine due to BPH with upper tract deterioration, prostatic enlargement due to carcinoma of prostate, prostatic enlargement due to acute and chronic prostatitis and prostatic abscess and patient presenting with fibrous prostate were excluded from the study.

Detailed history was taken and a thorough physical examination including digital rectal examination (DRE) was done in all patients. Depending on the symptoms and signs, the patients were categorized as mild and moderate as per the International prostate symptom Score (IPS Score). Transabdominal ultrasonography was done in all patients to assess the volume of prostate and post-voidal residual urine (PVR).

Serum prostate specific antigen (S.PSA) was done in all patients. A printed questionnaire was used to assess the severity of LUTS by the IPSS, based on the answers to seven questions regarding urinary symptoms (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia). The seven questions were as follows:

- Incomplete emptying: How often have you had the sensation of not emptying your bladder?
- Frequency: How often have you had to urinate less than every 2 h?
- Intermittency: How often have you found you stopped and started again several times when you urinated?
- Urgency: How often have you found it difficult to postpone urination?
- Weak stream: How often have you had a weak urinary stream?
- Straining: How often have you had to strain to start urination?
- (scores: 0 - not at all; 1 - <1 in 5 times; 2 - less than half the time; 3 - about half the time; 4 - more than half the time; 5 - almost always)
- Nocturia: How many times did you typically get up at night to urinate?
- (scores: 0 - none; 1 - 1 time; 2 - 2 times; 3 - 3 times; 4 - 4 times; 5 - 5 times)
- (total IPSS score: 1–7: Mild; 8–19: Moderate: 20–35: Severe)

A printed questionnaire was also used to assess IPSS-QoL: 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 it?

- (QLSs based on Likert scale: 0 - delighted; 1 - pleased; 2 - mostly satisfied; 3 - mixed; 4 - mostly dissatisfied; 5 - unhappy; 6 - terrible). The QLS is used to assess the impairment in QOL due to urinary symptom.

The selected patients were administered Tamsulosin 0.4 mg once daily in the morning for 3 months. The treatment response was monitored during subsequent follow-up visits after 1 month and 3 months with reassessment of IPSS and IPSS-QoL to identify response with regards to obstructive and irritative symptoms, USG was done to look for improvement in PVR volume and change in prostate volume. Serum PSA was also determined.

STATISTICALANALYSIS

Statistical analysis was carried out using the Statistical Softwares namely MedCalc 9.0.1. Microsoft word and Excel have been used to generate graphs, tables etc. Results on continuous measurements are presented on mean ± standard deviation (Min-Max) and results on categorical measurements are presented in number (%). Significance was tested using paired samples chi-square t- test. A p-value of less than 0.001 was considered to be statistically significant.

RESULT

In the present study, there were no drop-outs during the study and all the forty nine subjects were included in the analysis. However at the end of 3 months, 19 patients (38.7%) were administered Tamsulosin 0.4mg for 3 more months due to persistence of symptoms. In these patients at the end of 6 months PVR , IPSS , IPSS-QoL, change in PV and S.PSA was assessed.

The maximum numbers of cases were in the age group 50-59 years. The Mean age at presentation was calculated to be 56.5±12.6 years. The mean baseline PV was 27.3±2.4 cc, S.PSA 1.9 ± 1.1 ng/ml, PVR 35.2± 8.1ml, IPSS 12.67±3.16 and IPSS-QoL 4.45±0.84.

On follow-up at 30 days, 3 months and 6 months after treatment with Tamsulosin 0.4 mg, the mean IPSS improved from 12.67 ± 3.16 to 8.1 ± 1.89 at 30 days and 7.00±1.53 at 3 months. The mean IPSS of the 19 patients followed up till 6 months reduced to 7.00±1.29. This change was statistically significant ($P< 0.001$)**.

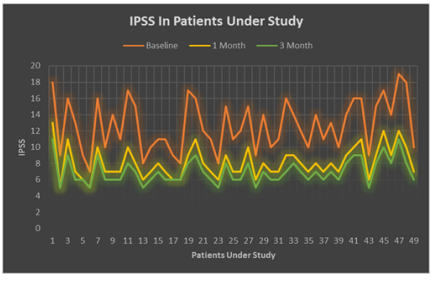

Fig1.1 Graph showing changes in IPSS after treatment with Tamsulosin 0.4 mg at 1 month and 3 months

The mean IPSS-QoL improved from 4.45 ± 0.84 to 2.69 ± 0.54 at 30 days and to 2.08±0.44 at 3 months after administering Tamsulosin 0.4mg. The mean IPSS-QoL of the 19 patients followed up till 6 months was 2.0±0.47. This change was statistically significant (P< 0.001)**.

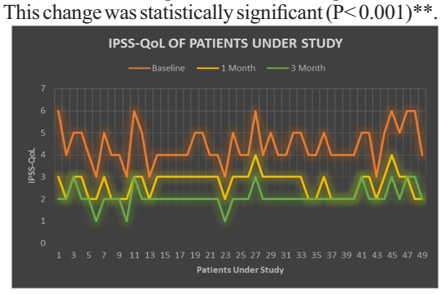

Fig1.2 Graph showing changes in IPSS-QoL after treatment with Tamsulosin 0.4mg at 1 month and 3 months

The mean PVR reduced from baseline 35.19±8.13 to 19.1±4.47 at 30 days and to 16.67±3.51 at 3 months after treatment with Tamsulosin 0.4mg. The mean PVR at 6 months of the 19 followed up patients was 18.31±2.34. This change was statistically significant (P< 0.001)**.

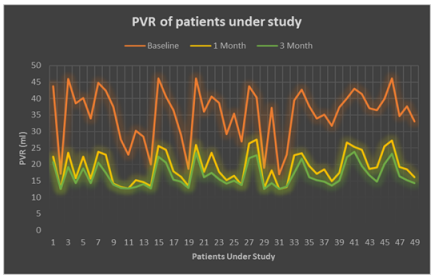

Fig 1.3 Graph showing changes in PVR after treatment with Tamsulosin 0.4 mg at 1 month and 3 months

There was 1.46% increase in PV after 3 months and 8.79 % increase in PV after 6 months showing that Tamsulosin does not reduce the prostate volume and there was no significant difference in S.PSA after treatment with Tamsulosin 0.4mg.

Table 1.1 Changes in PV after treatment with Tamsulosin 0.4 mg at 1 month and 3 months and 6 months

PROSTATE VOLUME (PV)	BASELINE	1 MONTH	3 MONTHS	6 MONTHS
MEAN±S.D.	27.3±2.4	27.4±2.5	27.7±2.6	29.7±1.2
95%CI	27.1-28.6	26.73-28.17	26.99-28.49	29.18-30.36
p VALUE		0.0003	0.0001	<0.0001
% CHANGE IN PV		+0.36	+1.46	+8.79

Table 1.2 Changes in S.PSA after treatment with Tamsulosin 0.4 mg at 1 month and 3 months and 6 months

S.PSA	BASELINE	1 MONTH	3 MONTHS	6 MONTHS
MEAN±S.D.	1.9±1.1	1.8±1.0	1.8±1.0	2.4±0.9
95%CI	1.68-2.15	1.66-2.14	1.66-2.14	1.85-2.88
p VALUE		0.0031	0.0102	0.0202

DISCUSSION

BPH is a progressive disease which is characterized by deterioration of symptoms over time and leads to serious outcomes such as acute retention of urine which in turn requires BPH related surgery in some patients. The sympathetic nervous system plays an important role in controlling the myogenic tone of the bladder outlet, hence its activity is partly responsible for urinary outflow resistance. The α1 adrenoreceptor antagonists i.e. doxazosin, terazosin, alfuzosin or tamsulosin, are able to decrease bladder outflow resistance resulting in significant relief of LUTS (20–65%) in men with symptomatic BPH.

Tamsulosin and its effect on LUTS (in terms of changes in IPSS, IPSS-QoL and PVR)

The mean PVR showed improvement from 35.19±8.13 ml (range 43.8-7.0) to 19.1±4.47 ml (range 27.6-12.5) at 30 days, 16.67±3.51 ml (range23.9-12.5) at 3 months and 18.31±2.34 ml (range 14.5-22.3) at 6 months. This change was statistically significant (P<0.001). The mean IPSS improved from baseline 12.67±3.16 (range 7-19) to 8.1±1.89 (range 5-13) at 30days, 7.00±1.53 (range 5-11) at 3 months and 7.00±1.29 (range 5-10) at 6 months. This change was also statistically

significant (P<0.001). Another parameter used was IPSS-QoL. The mean IPSS-QoL showed improvement from baseline 4.45±0.84 (range 3-6) to 2.69±0.54 (range 2-4) at 1 month while the mean IPSS-QoL at the end of 3 months was 2.08±0.44 (range 2-3) and 2.0±0.47 (range 2-3) at the end of 6 months. The change was statistically significant (P<0.001).

The results of the present study are comparable to the study conducted by Chenthil Perumal[4] et.al for comparison of the efficacy of naftopidil and tamsulosin hydrochloride in medical treatment of benign prostatic enlargement. A prospective randomized comparative study was carried on 60 patients of BPE by assigning half of them to treatment with tamsulosin and rest with naftopidil. Pre- and post-treatment uroflowmetry (UFM), post-void residue (PVR), International Prostate Symptoms Score (IPSS), were obtained at 15 and 30 days after starting treatment. In the study, the Tamsulosin group showed improvement in the baseline PVR from 102.90 ± 10.81 to 27.13 ± 5.47 at 30 days and IPSS score changed from 21.30 ± 2.84 to 6.47 ± 1.14 at 30 days. This change was significant (P< 0.001).

Kawabe[5] et al. from Tokyo, Japan undertook a study in 1990 to verify the efficacy and safety of the new α1A-adrenoceptor-selective antagonist silodosin compared with tamsulosin and placebo in patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). This randomized, double-blind, placebo-controlled study was conducted at 88 centres in Japan. Men aged ≥ 50 years with an International Prostate Symptom Score (IPSS) of ≥ 8, a quality-of-life (QoL) score of ≥ 3, a maximum urinary flow rate (Qmax) of <15 mL/ s, a prostate volume of ≥ 20 mL and a postvoid residual urine volume of <100 mL were eligible for enrolment. The result of the study showed that the change in the total IPSS (23.9) from baseline in the tamsulosin group was − 6.8. The change in QoL from baseline (4.7) was − 1.4 in tamsulosin group.

Abrams[6] et al. in 1995 conducted a study on 313 patients to evaluate the efficacy and safety of Tamsulosin 0.4 mg once daily (as a modified-release formulation) compared with placebo in patients with benign prostatic enlargement, lower urinary tract symptoms and prostatic 'obstruction' (symptomatic benign prostatic hyperplasia [BPH]). They reported that Tamsulosin produced greater improvements in Qmax (1.4 mL/s, 13.1%) than did placebo (0.4 mL/s, 3.8%) (P= 0.028) and a greater decrease in total symptom score (3.4 points, 35.8% reduction) than did placebo (2.2 points, 23.7% reduction) (P= 0.002). Significantly more tamsulosin-treated patients (67%) than placebo-treated patients (44%) had a ≥ 25% decrease in total symptom score after 12 weeks (P< 0.001). Treatment with tamsulosin for 12 weeks also produced significant improvements in average urinary flow rate (P= 0.040), irritative (P= 0.013) and obstructive (P= 0.014) symptom scores and symptoms of nocturia (P= 0.022) and hesitancy (P= 0.004). Tamsulosin was tolerated well by the patients.

Lepor[7] and coworkers (1998) conducted a multicenter, randomized, double-blind, placebo-controlled study of 756 American men with clinical BPH randomized to receive placebo or 0.4 or 0.8 mg of tamsulosin for 13 weeks. The symptom score improvements were significantly greater in the 0.8-mg tamsulosin group compared with the 0.4-mg group. Of the 618 subjects who completed the 13-week randomized study reported by Lepor and coworkers (1998), 418 (68%) continued into the 40-week extension study on the same double-blind medication and dose. The symptom and flow rate improvements observed at the end of the 13-week study were maintained throughout the 40-week extension study.

Age at presentation

BPH is age-related, and the prevalence increases with increasing age. Among many factors that contribute to prostate enlargement in BPH, the two most well-known etiologic factors were aging and androgen.
In the present study, the age at presentation ranges from 30 years to 90 years. The peak incidence was between 50-69 years (48.9%). The prevalence of BPH is 6.1% in the 30-39 years and increases to 26.5% in men aged 41 to 49 years.

Consistent with the theory that aging is an etiologic factor of BPH, similar results were reported by Cunningham GR *et al*, (2016) showing that the prevalence of histologically diagnosed prostatic hyperplasia increases from 8% in men aged 31–40 years, to 40–50% in men aged 51-60 years, to over 80% in men older than age 80years.[8]Lu S *et al*, (2014) reported that the prevalence of pathological BPH is 8% in the 4th decade of life; however, 50% of men develop pathological BPH at age 51-60 years.[9]

Tamsulosin and Prostate volume

In the present study, the percentage change in prostate volume after administration of Tamsulosin 0.4mg at 1 month and 3 months was +0.36% and +1.46% respectively and +8.79% at the end of 6 months. Thus, there was slight increase in the prostate volume.

Almost same result was reported by Claus G. Roehrborn et.al in the 2010 in their study: The Effects of Combination Therapy with Dutasteride and Tamsulosin on Clinical Outcomes in Men with Symptomatic Benign Prostatic Hyperplasia: 4-Year Results from the CombAT Study found that at month 48, the adjusted mean percentage change from baseline in total prostate volume was +4.6% ($p < 0.001$) for Tamsulosin and the adjusted mean percentage change from baseline in transition zone volume in a subset of 656 men was +18.2% ($p < 0.001$).[10]

M. Emberton[11] et al. in the year 2008 conducted a study on benign prostatic hyperplasia as a progressive disease: a guide to the risk factors and options for medical management. The preplanned 2-year analysis showed that α-blockers achieve rapid symptom relief but did not reduce the overall risk of AUR or BPH-related surgery, presumably because they had no effect on Prostate volume.

Tamsulosin and PSA (Prostate Specific Antigen)

In the present study, the mean PSA level was 1.9±1.1 ng/ml at baseline, 1.8±1.0 ng/ml and 2.4±0.9ng/ml after 3 months and 6 months of treatment respectively. There was no significant change in PSA after treatment with Tamsulosin.

The result is similar to the study conducted by Andrea Tubaro[12] et.al in the year 2010 to evaluate the effect of Tamsulosin on reducing the serum levels of prostate-specific antigen (PSA) in patients with lower urinary tract symptoms and an elevated PSA level. A total of 80 patients completed the study. The mean patient age was 66.3 years, and the mean PSA level was 7.8 ± 8.4 ng/mL at baseline and 7.1 ± 9.1 ng/mL after treatment (P< .001).

CONCLUSION

In the present study, it is observed that the α1-blocker treatment with Tamsulosin 0.4 mg for mild to moderately symptomatic BPH patients with prostate volume≤30 gms is associated with significant improvement in the PVR and the IPSS score in addition to disease specific QoL (IPSS-QoL) and urinary symptoms after the drug administration. Thus, based on the results of the study we can safely conclude that Tamsulosin 0.4 mg can be used for the effective relief of LUTS caused due to BPH in mild to moderate cases with prostate volume ≤30 gms. However, to clarify long-term improvement by the drug, further study needs to be performed.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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