Predictive Value of the Immediate Effect of First Dose of Tamsulosin on Lower Urinary Tract Symptoms Improvement in Benign Prostatic Hyperplasia Patients

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Abstract

Introduction and objectives: Tamsulosin is a highly selective 1A and 1D adrenergic receptors blocker. Beneficial effect on LUTS may occur fully in few weeks yet significant efficacy over placebo can occur within hours to days. Thus, we thought about studying this immediate beneficial effect of 1A blockers occurring within hours after the first dose. Moreover, studying if the magnitude of this effect, can predict the future improvement of LUTS.

Materials and methods: Our prospective study started from May 2016 until August 2017. All patients over 40 years old presented to urology outpatient clinic with BPH related symptoms were enrolled. Three hundred and ninety patients were enrolled into the study but only 340 patients were included and completed the four visits.

All patients instructed to take 0.4mg tamsulosin after breakfast for 3 months and were examined in four visits. The first visit was the baseline before beginning of tamsulosin UFM, PVR, IPSS, QoL, Labs, DRE and history taking. The second visit was after about 6 hours from administration of tamsulosin in which UFM and PVR were measured. The third visit was after 1 month and the fourth visit was after 3 months from administration of tamsulosin in these visits UFM, PVR and QoL were measured and compared to baseline.

Result: The mean Q max at 1st, 2nd, 3rd and 4th visits were 10.28±3.06 sec, 14.58±4.84sec, 14.46±4.94 sec and 14.28±5.07sec respectively p-value 0.04. Mean voiding time at 1st, 2nd, 3rd and 4th visits were 41.24±27.18 sec, 33.84±18.14sec and 31.96±22.02 sec and 30.14±17.52 sec respectively p-value 0.03). The mean (PVR) in 1st, 2nd, 3rd and 4th visits were 46.40±22.14ml, 27.76±26.10ml, 25.16±28.36ml and 25.58±28.10ml respectively p-value 0.001. The effect of 1st dose of tamsulosin after 6 hours significantly increase Q max and decrease voiding time and residual urine comparable to 1st and 3rd month. QOL was significantly improved after one month and three months P-value <0.001. IPSS was significantly improved after one month and three months with P-value (<0.001).

Conclusion: Our prospective study presents that the first dose of tamsulosin 0.4 mg is effective to improve UFM parameters immediately and can predict the mid-term change in UFM parameters as well as IPSS and QoL indices in the treatment of BPH-related LUTS so we can predict if this treatment will be enough from 1st dose or will need another line of treatment.

INTRODUCTION AND OBJECTIVES

Lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH) occurs in 23 % of men aged 50 years with moderate-to-severe LUTS may be occurred in up to 50% of men with BPH [1,2], El-Gilany and associate claimed that no community-based studies on the magnitude of the problem of BPH symptoms among elderly men in Egypt are available [3]. LUTS influence the quality of life (QoL) hence requires treatment; Pharmacological therapy with Alpha blockers is the first step.
of the treatment in patients with BPH [4] which gives a strong recommendation to have a method for response prediction. Tamsulosin HCl is the most widely used drug in the treatment of LUTS associated with BPH [5]. Tamsulosin is a highly selective Alpha-1A and Alpha-1D-adrenergic receptors blocker affecting prostate, bladder neck and urethra. Thus, tamsulosin provides comfortable micturition which improves Qol. [6]. The predictive value of the change in flowmetry parameters at the first dose of tamsulosin on the improvement of LUTS in BPH patients has been studied by Yigit and associate [7]. We aimed to reevaluate this predictive value of the change in flowmetry parameters at the first dose of tamsulosin on the improvement of LUTS in Egyptian BPH patients.

**MATERIALS AND METHODS**

A prospective study from May 2016 until August 2017 was done after approval by ethical committee of Beni-Suef University, written informed consent was obtained from all patients participated in the study. All patients over 40 years old presented to urology outpatient clinic at Beni-Suef University with BPH related symptoms were enrolled. Patients with previous medical or surgical treatment of the prostate, post-void residual urine volume (PVR) >150 ml and Symptoms suggesting neurogenic bladder, Urinary tract Stones, suspected prostate cancer (prostate-specific antigen (PSA)>4 ng/dl) and or abnormal digital rectal examination (DRE), were excluded. Physical examination including DRE, PSA, creatinine, urine analysis, urine culture and sensitivity were done to exclude patients with urinary tract infection, uroflowmetry (UFM) (Solar Uroflow, Medical Measurement Systems), and PVR, international prostate symptom score (IPSS), QoLindex, transrectal ultrasonography of prostate (TRUS) were performed.

Three hundred and ninety patients were enrolled into the study but only 340 patients were included and completed the four visits, all patients instructed to take 0.4mg tamsulosin after breakfast for 3 months, the first visit was the baseline before beginning of tamsulosin including UFM, PVR, IPSS, QoL, Labs, DRE and history taking. The second visit was after about 6 hours from administration of tamsulosin in which UFM and PVR were measured. The third visit was after 1 month and the fourth visit was after 3 months from administration of tamsulosin in these visits UFM, PVR, IPSS and QoL were measured and compared to baseline.

**Statistical analysis**

Data were checked for normality using the Shapiro-Wilk test. Data with a normal distribution were analyzed with parametric tests; data without a normal distribution were analyzed with nonparametric tests. To analyze the data from more than 2 independent groups, one-way analysis of variance (ANOVA) and Krukal-Wallis variance analysis were used. Data from 2 different periods in the same group were analyzed with the paired t-test and Wilcoxon signed rank test. Multiple comparisons after one-way ANOVA and Krukal-Wallis variance analysis were performed with Tukey HSD test within SPSS. Repeated-measures ANOVA with a Greenhouse-Geisser correction were used for repeated measures of different points of times of follow-up. Statistical significance level was .05

**RESULTS**

The study included 340 patients with mean age 63±6.18, mean PSA level 2.63± 0.89ng/dl and mean prostate volume 52.23 ± 24.59cc using TRUS, mean PSA density 0.06± 0.02 (ng/ml/cc) Table 1.

![Table 1. The mean Q max at 1st, 2nd, 3rd and 4th visits were 10.28±3.06 sec, 14.59±4.94 sec and 14.28±5.07 sec respectively (p-value 0.04). Mean voiding time at 1st, 2nd, 3rd and 4th visits were 41.24±27.18 sec, 33.84±18.14 sec, 31.96±22.02 sec and 30.14±17.52 sec respectively (p-value 0.03). The mean (PVR) in 1st, 2nd, 3rd and 4th visits were 46.40±22.14ml, 27.76±26.10ml, 25.16±28.36ml and 25.58±28.10ml respectively (p-value 0.001). The effect of 1st dose of tamsulosin after 6 hours significantly increase Q max and decrease voiding time and residual urine comparable to 1st and 3rd month, no statistical significant difference between 1st dose, one and three months in Q max, voiding time and residual urine.

QOL was significantly improved after one month and three months P-value <0.001. IPSS was significantly improved after one month and three months with P-value (<0.001). No statistical significant difference between one and three months in QOL and IPSS see table 2.

Multivariate analysis was done between improvement of IPSS and other parameters in the study group that showed there is no relation between prostate size, PSA, age, PVR, baseline IPSS,baseline QOL and response to tamsulosin with (p-value >0.05).

**DISCUSSION**

Medical therapy is the most commonly used option in treatment of BPH induced LUTS [8] so several investigators tried to predict who patients are most likely to respond to medical treatment and predict its failure in treatment of BPH induced LUTS, most of them indirectly tried to measure the severity of the disease to predict disease progression and failure of medical treatment. Most of these novel predictors are noninvasive depend on US measurement of intravesical prostatic protrusion [9], bladder/detrusor wall thickness [10], estimated bladder weight [11], prostatic urethral angle [12], other investigator user noninvasive and invasive pressure-flow testing [13], Measurement of most of these Parameters require specific training and there is a risk of observer error. We tried to follow those investigators in the same path and in the same context we explored the predictive value of the first dose of tamsulosin .4 mg using non invasive tests of PVR and uroflowmetry in a direct way to predict midterm results of medical treatment. These results could be used in patient counseling about the continuation of medical treatment or shift to another treatment option especially when side effects of medical treatment are clearly identified, looming, and the response to medical treatment is in doubt. Also could be used in early shift to combined therapy of alpha blocker and 5 alpha reeducates especially in patients with prostate size between 25cc and 45cc who can benefit from combined therapy to decrease the rate of failure of medical treatment [14].
In our study, we used standard dose of 0.4 mg tamsulosin, once daily orally administered after breakfast for 340 patients for three months, we aimed to investigate whether the first dose of oral tamsulosin 0.4 mg is effective in terms of UFM parameters and whether the first change of UFM parameters could predict the mid-term results in terms of UFM parameters and IPSS and QoL indices.

In our series, we used a selected population that suffers from “mild to severe LUTS” (mean IPSS of 20.62±4.02) and mean age of patients was 63±6.18 years. This was an ideal population for treatment with alpha-blockade [15].

We preferred to study the UFM at the 6th hour of the first dose since the peak serum level of tamsulosin occurs at 6 h. However, the tissue level occurs at the 7.6–10.9 days with continuous medication. In our study, we used 0.4 mg of tamsulosin because tamsulosin 0.4 mg was proved to be effective than tamsulosin 0.2 mg in a study by Chung and associate [16], which included 116 patients from 3 urology centers. The trial demonstrated that tamsulosin 0.4 mg has favorable efficacy and tolerability in patients with symptomatic BPH refractory to tamsulosin 0.2 mg.

Korstanje and his colleagues had done a study that contains Forty-one patients with benign prostatic hyperplasia (BPH) scheduled for open prostatectomy; they were given tamsulosin 0.4 mg for 6-21 days in order to reach steady-state plasma pharmacokinetic (PK). Patients were randomized over four groups to allow collection of plasma and tissue samples at different time points after last dose administration. Samples were collected during surgery and assayed for tamsulosin. The free fraction of tamsulosin was determined by ultracentrifugation of plasma and prostate tissue spiked with 14 C-tamsulosin.

He showed that maximum concentration of tamsulosin in plasma was at 4.4 h for total tamsulosin, while for prostate maximum concentration at 11.4 h post-dose. These data indicate that in patients with confirmed BPH the amount of tamsulosin freely available in the target tissue (prostate) is much higher than in plasma [16].

In our series, we used a selected population that suffers from “mild to moderate LUTS” and larger prostate volume. Yigit and associate in a similar work to ours selected 40 patients with moderate symptoms, the Mean IPSS was 16.46 ± 5.77 and Mean prostate volume was 35.77 ± 3.86 cc in TRUS, we selected more patients with larger prostate volume (52.23 ± 24.59) and higher mean IPSS (20.62±4.02) to confirm the result of Yigit in a large group of Middle eastern patients [7].

There was a statistically significant increase in Qmax and decrease in RU for about 326 patients (96%) from baseline at the first dose of tamsulosin as well as first and third months of the treatment. No significant difference in Qmax and RU between the first dose of tamsulosin as well as first and third months of the treatment. This means that first dose might predict the improvement of LUTS at the third month. Moreover, according to our results, prostate volume, age, PSA, baseline IPSS, baseline UFM parameters such as Qmax, voiding time and RU not a predictor of tamsulosin response. These findings are parallel with Kang and associates [17] and Yigit and associates [7].

There was statistically significant decrease in IPSS and QoL scores from baseline at first and third month of treatment. These results are similar to the report of Djavan et al. [18], and Yigit Akin [7] there was insignificant difference between results of IPSS, QOL in the first and third month.

In our community, patients with BPH tend to change the medication frequently since even family doctors can prescribe α blockers or other drugs such as phyto-therapy and 5 alpha-reductase inhibitors. Our imitations, not long-term due to patient compliance problems, validated Arabic version of IPSS and QOL and no placebo control.

**CONCLUSION**
Our prospective study presents that the first dose of tamsulosin 0.4 mg is effective to improve UFM parameters immediately and can predict the mid-term change in UFM parameters as well as IPSS and QoL indices in the treatment of BPH-related LUTS so we can predict if this treatment will be enough from 1st dose or will need another line of treatment.

REFERENCES