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The predictive ability of response to first dose of tamsulosin in symptomatic patient with benign prostatic obstruction

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Abstract

Background: To study the effects of the first single dose of tamsulosin 0.4 mg on lower urinary symptoms tract (LUTS) in patients with benign prostatic hyperplasia (BPH) and to evaluate the early response to treatment as an indication of the response at 3 months after treatment.

Patient and Methods: This was a prospective study that included patients> 45 years old with LUTS / BPH. In all patients, tamsulosin was administered orally 0.4 mg once a day for 3 months. The degree of international prostate symptoms (IPSS), quality of life (QoL), residual urine volume (PVR) and maximum urine flow rate (Q max) were measured before treatment, 6 hours, 10 days, 1 month and 3 months after treatment. Data before and after treatment were compared using appropriate statistical analysis tests.

Results: The group included 60 patients. They ranged in age from 45 to 70 years (56.38 ±7.25 years). No significant differences were observed between baseline data and the sixth hour after treatment. IPSS, QoL points, PVR and Qol data of 49 (81.7%) of the patients have improved significantly from the tenth day to the end of study after 3 months ($p < 0.05$). Eleven patients (%18.3) did not respond to the tamsulosin and another treatment options for their LUTS/BPH had been offered.

Conclusion: Tamsulosin hydrochloride has achieved a significant improvement of patients with LUTS/BPH in terms of IPSS, QoL points, PVR and Qol 10 days after treatment. There is no relationship between the tamsulosin effect achieved after the initial dose and its mid-term effectiveness.

Key words: First Dose, Tamsulosin, Predictive ability, Benign Prostatic Hyperplasia.

INTRODUCTION

Benign prostatic hyperplasia (BPH) causing lower urinary tract symptoms (LUTS) is a highly prevalent disease among elderly men. The incidence of symptomatic BPH in men aged 50 years is 23% and increases to 77% among men aged 60-70 years. LUTS related to BPH influence the quality of patient life (QoL) with time and therefore require treatment.[1,2,3]

Alpha blockers are used as first pharmacological step in treatment for male patients with benign prostatic hyperplasia. Tamsulosin hydrochloride is a long acting highly selective α 1a inhibitor leads to improvement of LUTS in patients with BPH due to relaxation of the smooth muscles in the prostate, bladder neck, and urethra. The improvement in LUTS can be assessed objectively by evaluating the uroflowmetry (UFM) parameters ; such as maximum urinary flow rate (Qmax), average urinary flow rate (Qave) and postvoiding residual urine volume (PVR), and subjectively by calculating the international prostate symptom score (IPSS) and quality of life (QoL) index.[4]

It is known that Tamsulosin has the serum peak levels 6 hours after oral administration, and its effect continues for 24 hours but its peak tissue levels can be achieved in 7-10 days. Therefore, there are several studies concerned about the time interval required to determine the successfulness or failure of the alpha blocker therapy with contradictory reports.[5]

The aim of the present study is to investigate the effect of the first dose of Tamsulosin hydrochloride 0,4 mg on LUTS due to BPH and the predictive value of early changes in UFM parameters on the LUTS improvement in terms of UFM parameters, IPSS, and QoL index in mid-term period.

PATIENTS AND METHODS

This study was a non-randomized prospective study comprised 60 patients >45 years old complained of LUTS related to BPH. The patients were recruited from urology outpatient clinics at AL-Hussein and Sayed Galal University hospitals from November 2018 to May 2019. The study had been approved from our local institute ethical committee and all patients had signed written informed consent.

The mean age of the studied patients was 56.38 ± 7.25, mean PSA level was 2.56 ± 0.66 ng/dl and mean prostate volume was55.07 ± 16.16 cc using pelvic abdominal US. The mean level of serum creatinine was 0.85 ± 0.18 mg/dl and mean levels of baseline of QoL was1.08 ± 0.65, IPSS was 17.53 ± 1.23 and PVRU was 82.92 ± 7.33, Qmax was 12.70 ± 1.71.

The studied patients had undergone general and abdominal examination with particular emphasis on digital rectal and focused neurological examination to asses prostatic size, consistency, median and lateral sulci and anal tone. All patients had blood analysis such as prostate-specific antigen (PSA), renal function tests (blood urea and serum creatinine), urinalysis and culture and sensitivity tests in addition to Uroflowmetry (UFM), pelvic ultrasonography to asses prostatic volume, and determination of post-voiding residual urine (PVR) urine. International prostate symptom score (IPSS) (>7), quality of life (QoL) index were calculated for the studied patients.

Patients who received alpha blockers and/or 5 alpha reductase antagonist and/or phytotherapy or having urinary tract infection , PVR (>100 ml) or those having any previous prostatic surgery or had suspicious prostatic cancer were excluded from the study.

After diagnosis of LUTS associated with BPH, tamsulosin 0.4 mg once daily was administrated orally after breakfast to all patients for 3 months.

The results of uroflowmetry, PVR, IPSS and QOL were evaluated before initiation of treatment as baseline then repeated after 6h,10 days, one month and three months after drug administration . Outcomes measured were compared with the baseline parameters that measured before treatment.

Patients were instructed during the study to avoid withholding micturition , exposure to cold ,prolonged setting and drugs that can affect bladder contraction or storage such as antihistamines and antimuscarinics

.Statistical analysis: The data was taken, revised, encoded and presented into the Social Science Statistical Group (IBM SPSS) type 20. The quantitative data were assessed as average, standard deviations , ranges when their distribution was found to be borderline, while qualitative data were provided as number and percentages. Descriptive results were reported for all studied parameters. Paired t tests and Chi-square test were used for statistical analysis. Univariate and multivariate logistic regression analysis was performed to identify factors predicting outcomes. Statistical significance was considered when p value = <0.05 and all p values were two-sided.

RESULTS

At the baseline the mean (QoL) was 1.08 ± 0.65 and there was no significant improvement after six hours (1.25±0.44)with P-value (<0.115) and there was significant improvement after ten days to be 1.37 ± 0.61with P-value (<0.021),with continuous improvement after one month and three months to reach 3.2±0.93 and 4.76 ± 0.43 respectively with p-value (0.001) which is highly significant (table1.(

The mean (IPSS) was 17.53 ± 1.23 at the baseline and there was no significant improvement after six hours with a mean (17.38 ± 1.32),with P-value (<0.219) and there was significant improvement after ten days to be 17.10 ± 1.45 with P-value (<0.010), continuous improvement was observed after one month and three months to reach 12.50 ± 2.95 and 9.45 ± 1.17 respectively with p-value (0.002) (table2).

At the baseline the mean (PVR) was 82.92 ± 7.33and there was no significant improvement after six hour 82.75 ± 7.17 with P-value (<0.089), there was improvement after ten days to be 81.32 ± 6.70 with P-value(<0.016), continuous improvement was observed after one month and three months to reach 66.67 ± 12.11and 46.82 ± 10.66 respectively with p-value (0.003) (table 3).

At the baseline the mean (Qmax) was 12.70 ± 1.71and there was no significant improvement after six hour 12.78 ± 1.76 with P-value (<0.218), there was improvement after ten days to be 12.91 ± 1.75 with P-value (<0.020), continuous improvement was observed after one month and three months to reach 16.72 ± 3.31 and 19.92 ± 1.79 respectively with p-value (0.002) (table 4).

Receiver operating characteristic curve (ROC) for IPSS, PVRU and Q max at 6 hours as predictors of non-responder cases showed that the best cut off point for IPSS at 6 hours to detect non responder cases was found > 17 with sensitivity of 81.82%, specificity of 57.14% and area under curve (AUC) of 71.5%, positive predictive value was 30.0 % and negative predictive value was 93.3 %. . Also, the best cut off point for PVRU at 6 hours to detect non responder cases was found > 80 with sensitivity of 90.91%, specificity of 51.02% and AUC of 74.3, positive predictive value was 29.4 % and negative predictive value was 96.2 %. while for Q max at 6 hours the best cut off point was found ≤ 13 with sensitivity of 90.91%, specificity of 44.90% and AUC of 68.4%., positive predictive value was 27.0 % and negative predictive value was 95.7 % (table 9 and figure 1) .

		All cases	Paired t-test		
		No. = 60	**t**	**P-value**	**Sig.**
QoL Pre-treatment	Mean ± SD Range	1.08 ± 0.65 1 – 6	–	–	–
QoL 6 hours post-treatment	Mean ± SD Range	1.25 ± 0.44 1 – 2	-1.602	0.115	NS
QoL 3r visit after 10 days	Mean ± SD Range	1.37 ± 0.61 1 – 3	-2.380	0.021	S
QoL One month post-treatment	Mean ± SD Range	3.18 ± 0.93 1 – 4	-14.202	0.002	HS
QoL 3 months post-treatment	Mean ± SD Range	4.76 ± 0.43 4 – 5	-31.767	0.001	HS

QoL, Quality of Life

Table 1: QoL score in the studied group before and after treatment

		All cases	Paired t-test		
		No. = 60	**T**	**P-value**	**Sig.**
IPSS Pre-treatment	Mean ± SD Range	17.53 ± 1.23 15 – 20	–	–	–
IPSS 6 hours post-treatment	Mean ± SD Range	17.38 ± 1.32 14 – 19	-1.242	0.219	NS
IPSS 3r visit after 10 days	Mean ± SD Range	17.10 ± 1.45 12 – 19	-2.677	0.010	S
IPSS One month post-treatment	Mean ± SD Range	12.50 ± 2.95 8 – 19	14.719	0.004	HS
IPSS 3 months post-treatment	Mean ± SD Range	9.45 ± 1.17 7 – 12	40.706	0.002	HS

IPSS, International Prostatic Symptom Score

Table 2: IPPS. in the studied group before and after treatment.

		All cases	Paired t-test		
		No. = 60	**t**	**P-value**	**Sig.**
PVR urine volume Pre-treatment	Mean ± SD Range	82.92 ± 7.33 69 – 95	–	–	–
PVR urine volume 6 hours post-treatment	Mean ± SD Range	82.75 ± 7.17 68 – 95	1.730	0.089	NS
PVR urine volume 3r visit after 10 days	Mean ± SD Range	81.32 ± 6.70 65 – 90	2.473	0.016	S
PVR urine volume One month post-treatment	Mean ± SD Range	66.67 ± 12.11 44 – 90	10.878	0.006	HS
PVR urine volume 3 months post-treatment	Mean ± SD Range	46.82 ± 10.66 20 – 66	19.423	0.003	HS

PVR, Post-voiding Residual

Table 3: PVR in the studied group before and after treatment

		All cases	Paired t-test		
		No. = 60	t	P-value	Sig.
Q_{max} Pre-treatment	Mean ± SD Range	12.70 ± 1.71 9.5 – 16.5	–	–	–
Q_{max} 6 hours post-treatment	Mean ± SD Range	12.78 ± 1.76 9.5 – 17	-1.246	0.218	NS
Q_{max} 3r visit after 10 days	Mean ± SD Range	12.91 ± 1.75 10 – 16.8	-2.383	0.020	S
Q_{max} One month post-treatment	Mean ± SD Range	16.72 ± 3.31 10 – 22.8	-10.808	0.009	HS
Q_{max} 3 months post-treatment	Mean ± SD Range	19.92 ± 1.79 15.7 – 23	-30.940	0.002	HS

Q_{max}, Maximum Flow Rate

Table 4: Q_{max} in the studied group before and after treatment

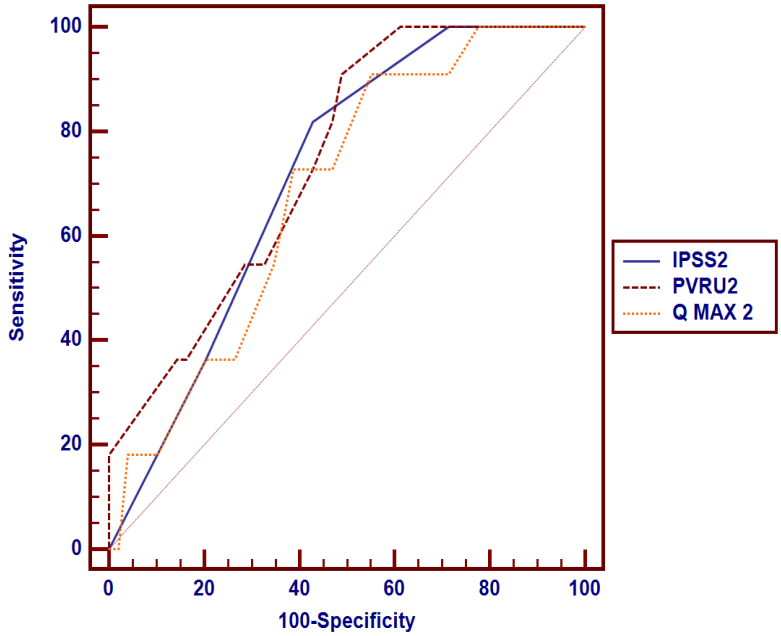

Figure 1: ROC curve for predictors of non-responding cases

DISCUSSION

Benign prostatic obstruction commonly affects men in their 50s, and 80 % of men in their 70s complain from LUTS, in the form of dynamic and static obstruction.[7]

Alpha blocker drugs, like tamsulosin, were introduced in symptomatic treatment of non-complicated BPH through blocking α1a-receptor-mediated sympathetic stimulation to relieve the obstruction by relaxing the smooth muscles in the prostate. The improvement on voiding can occur within hours of receiving the drugs, regardless of prostate volume, and without change in serum prostate-specific antigen or prostatic volume.[8]

Tamsulosin, a third-generation adrenaline receptor antibody, is a super-selective subtype a1-a and-d blocker for the treatment of LUTS associated with BPH. Therefore, tamsulosin may be considered as a best treatment alternative to prostatectomy or transurethral resection of prostate in the absence of indications of surgical lmanagment.[9]

The level of tamsulosin serum depends on the stomach condition ,with a high serum levels when it is taken on an empty stomach reaching 70% compared to administration after meal.[10]

After oral administration of tamsulosin, the drug is rapidly absorbed from the intestine and exhibits highly plasma protein binding, as well as the

bioavailability of approximately 100%. Tamsulosin is extensively metabolized by cytochrome p-450 in the liver.11 The dose of tamsulosin is 0.4 mg and it is taking daily in early morning.[12]

In this study, we used dose of 0.4 mg tamsulosin, once daily at breakfast for 60 patients with LUTS due to BPH for three months, we aimed to evaluate the response of the first dose of tamsulosin 0.4mg after 6hours, in terms of UFM parameters changes from baseline and whether these changes could predict the mid-term results.

Korstangi el al, conducted a study on 41 patients with benign prostatic obstruction (BPH) who were scheduled for open surgery and they had received tamsulosin 0.4 mg for 6-21 days to access the persistent pharmacological plasma drug (PK). Patients were randomly selected in four groups to allow for plasma and tissue samplings at many times after the last dose was administered. Samples were taken in the surgery and tamsulosin was calibrated. Tamsulosin free breakage were identify by the supercentrifuge of plasma and prostate tissue spiked with 14C-tamsulosin. The authors demonstrated that higher concentration of tamsulosin in plasma was achieved at 4.4 h after administration, while for prostate the higher concentration was achieved at 11.4 days after-dose.[13]

Our prospective study proved that the first dose of tamsulosin 0.4 mg is not effective at 6 hours after administration, but, at ten days there was statistically significant improvement in UFM parameters with a positive predictive value for the mid-term improvement in UFM parameters as well as IPSS and QoL indices in the treatment of LUTS associated with BPH.

We found that there was no statistically improvement difference of the studied parameters after 6 hours, while there was statistically significantly improvement after 10 days in (49) patients (81.7%) with increase in Qmax from the baseline mean of 12.70 ± 1.71 to 12.91 ± 1.75 with P-value (<0.020), and continuous improvement was observed after one month to reach 16.72 ± 3.31 with p-value (0.009) and after three months 19.92 ± 1.79 with p-value (0.002) and decrease in RU from the baseline mean of 82.92 ± 7.33 to 81.32 ± 6.70 with P-value(<0.016), continuous improvement was observed after one month to reach 66.67 ± 12.11 with p-value (0.006) and after three months 46.82 ± 10.66 with p-value (0.003). Also there was significant improvement in IPSS score from the baseline mean of 17.53 ± 1.23 to 17.10 ± 1.45 after ten days with P-value (<0.010), the improvement was observed after one month to reach 12.50 ± 2.95 with p-value (0.004) and after three months 9.45 ± 1.17 with p-value (0.002). Regarding the QoL index it showed significant improvement from a baseline mean of 1.08 ± 0.65 to 1.37 ± 0.61with P-value (<0.021) after ten days, then 3.18 ± 0.93 after one month with p-value (0.002) and finally 4.76 ± 0.43 with p-value (0.001) after three months which is highly significant.

On the other hand, the remaining 11(18.3%) patients had no significant improvement in their parameters such as UFM, PVR,IPSS at the first dose, ten days and first month, they did not continue follow up after one month due to failure of medical treatment, no significant improvement, and shifted to another treatment option.

Akin et al, studied (48) patients on tamsulosin 0.4 mg daily at breakfast for three months. UFM, PVR, IPSS, QoL were repeated at 6th hour of the first day, first month and third month of oral tamsulosin 0.4 mg treatment. All parameters were recorded as baseline, and changes in the UFM parameters, PVR, IPSS and QoL were evaluated in clinical visits. They reported statistically significant improvement in Qmax that improved in 33/48 patients (68.7%), from the baseline mean of 12.54 ± 4.59 to reach 15.58 ± 6.84 after six hour , and continuous improvement was observed after one month to reach 16.5 ± 7.81 with p- value (0.001) and 16.41 ± 7 with p- value ((<0.001) after three months. They also demonstrated decrease in RU from 56.31 ± 44.97at baseline to reach 48.15 ± 40.25 after six hours, with continuous improvement after one month to 38.9 ± 33.4 with p-value (0.001) and after three months to reach 37.71 ± 32.54 with p-value (<0.001). The IPSS score evaluation demonstrated a significant improvement from the baseline mean of 16.46 ± 5.77 to 12.79 ± 6.13 after one month with P-value (<0.001), and continuous improvement was observed after three months to reach 12.15 ± 5.75). There was statistically significant improvement in the QoL index where it decreased from 3.67 ± 1.08 at baseline to reach 2.71 ± 1.13 after one month with P-value (<0.001),with continuous improvement after three months to reach 2.4 ± 1.09 with P-value(0.001). However, 15 (31.3%) patient had no statistically improvement in UFM parameters at the first 6 hours, one month and after three months.[14]

Therefore, Korstanje et al, and Akin et al, reported that the improvement for tamsulosin treatment, was statistically significant after 6 hour as well as one month and three month of drug administration in contrast to our results which are not coinciding with these results since the improvement with tamsulosin treatment was statistically non significant after 6 hour but signification at ten days as well as one month and three month of the treatment.

Chung et al., had done study included 116 patients from three urology participated centers. He divided their study into two groups, first group included (90) patients who had received tamsulosin 0.2mg daily, the second group included (26) patients who had taken tamsulosin 0.4 mg once daily. All the studied patients had been followed up at 8,12,and 16 week, so we compared our results with the results of Chung in the group who received 0.4mg tamsulosin on the basis of (IPSS), (QoL), (Qmax),(RU).[15] They reported statistically significant improvement in all

(26) patients, increase in Qmax from a mean of 7.4±1.9 at baseline to 11.1±2.1 after 12 week, and decrease in RU from a mean of 19.6±21.3 to 15.4±22.1 after 12 week, in addition to significant improvement in IPSS score from a mean of 22.4±5.3 at baseline to 17.8±3.2 after 12 week, and QoL index from 5.3±0.6 to 4.2±0.4reach after12 week. These results were comparable to our study results after three months follow up for patients with LUTS associated with BPH receiving 0.4 mg tamsulosin once daily with a statistically significant improvement in all evaluated parameters from baseline to the third month.

CONCLUSION

In our study it is non-randomized, no controlled one ,we can conclude that response of the first dose of Tamsulosin hydrochloride after six hours cannot predictor the midterm effectiveness

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