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TERAZOSIN TREATMENT OF PATIENTS WITH LUTS/BPH. DOES IT IMPROVE THE FLOW?

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Objective To evaluate flowmetry changes associated with a significant symptomatic improvement in patients with benign prostatic hyperplasia (BPH) / lower urinary tract symptoms (LUTS) treated with terazosin.

Patients and Methods The study included 588 patients with BPH / LUTS treated with terazosin in a dose of 5 mg HS (Group I) and 121 patients with BPH / LUTS subjected to watchful waiting serving as a control group (Group II). All patients underwent digital rectal examination (DRE), International Prostate Symptoms Score (IPSS) and prostate specific antigen (PSA) evaluation to exclude cancer of the prostate. Further investigations included flowmetry and measurement of post-voiding residual urine. All patients were followed-up for at least 12 months.

Results The pre-treatment assessment showed an average IPSS of 15.7 (range 9 – 26), a quality of life assessment (QLA) average score of 4.3 (range 4 – 6), an average volume of the prostate of 39 ± 26.7 gm, an average PSA value of 1.9 n/ml and a normal serum creatinine in all patients. The pretreatment mean peak urinary flow rate (Qmax) was 9.7 ml/s, average flow rate (Qave) was 5.1 ml/s and post-void residual (PVR) was 74.9 ml. At 3 months follow-up, 499 (85%) patients of Group I reported satisfaction and continued treatment. At one year, 436 (74%) out of these patients showed an improvement >30% in IPSS and QLA and had a mean Qmax of 12.0 ml/s (+ 2.3 ml/s), a mean Qave of 6.1 ml/s (+ 1.0 ml/s) and a mean PVR of 46.7 ml (- 28.2 ml). However, the change in Qmax ranged from – 35.5% to + 100% with a positive change in 76% and a negative change in 24%. Of the patients with symptomatic improvement, only 40% showed an increase in Qmax >30%, while 4.8% showed a decrease in Qmax of more than 30%. In the control group only 37 patients showed a symptomatic improvement >30% with only one patient showing an improvement of Qmax >30%, which is statistically significantly less than in the active treatment group.

Conclusion In spite of a significant symptomatic improvement in 74% of the patients treated with terazosin at one year follow-up, only 40% showed an improvement of Qmax >30%. An actual deterioration >30% of the Qmax was seen in 4.8% of the symptomatically improved patients which denotes that the symptomatic improvement does not parallel flowmetry improvement.

Keywords Benign prostatic hyperplasia, Terazosin, alpha-blockers, flowmetry

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a condition that affects many men after the middle age. Approximately 50% of men aged 60 years or older have evidence of BPH[1]. In a community-based study, an age specific prevalence rate of symptomatic BPH (lower urinary tract symptoms, LUTS) showed that it was present in 1 in every 7 men aged 40-49, rising to nearly 1 in every 2 men aged 60-69 years[2]. The symptoms of bladder outflow obstruction from BPH are thought to consist of two components: a static part due to prostate enlargement and a dynamic part due to the prostate smooth muscle tone[3]. Terazosin has been given to relieve the dynamic component by relaxing the smooth muscles and improving the flow. The effects of Terazosin on symptom scores and urinary flow rates have been previously documented[4-6]. This study was done to assess a possible improvement in flowmetry parallel to the symptomatic improvement.

Table 1: Comparison of Pre- and Post-Treatment Values in 436 Patients after 12 Months of Treatment

	Pre-Treatment	Post-Treatment	Change
IPSS	15.7	6.3	- 59.9%
QLA	4.3	2.1	- 51.2%
Qmax	9.7 ml/s	12.0 ml/s	+ 23.7%
Qave	5.1 ml/s	6.1 ml/s	+ 19.6%
PVR	74.9 ml/s	46.7 ml/s	- 37.6%

PATIENTS AND METHODS

Five hundred and eighty-eight men aged 50 years and more (mean age 67.3 ± 12.8) with LUTS/ BPH were enrolled in this study. The inclusion criteria consisted of: an international prostate symptoms score (IPSS) ≥8, a quality of life score (QLA) ≥3, a maximum flow rate (Qmax) < 15 ml/s and a voided volume ≥ 150 ml. The post-voiding residual urine was measured by ultrasound (bladder scan). Patients taking drugs and patients with complications such as urinary tract infection or with associated diseases affecting the lower urinary tract were excluded.

All patients underwent a thorough clinical evaluation including IPSS and DRE. Serum creatinine and PSA measurement as well as complete urinalysis were carried out to exclude prostate cancer. Other investigations (e.g. ultrasound, biopsy, diagnostic cystoscopy etc.) were done on an individual basis as indicated. The patients' mean prostate volume was 39 ± 26.7 grams, while the mean PSA was 1.9 ± 1.38 u/ul. Terazosin was given in a gradually increasing dose up to 5 mg once per day before bedtime.

A control group of 121 patients with LUTS/ BPH who preferred watchful waiting rather than Terazosin treatment were used for comparison. The patients of the control group underwent the same investigations and were followed up at the same intervals as those of the Terazosin group.

Flowmetry was done using a computerized urodynamic machine (Dantec). Two to three flowmetric measurements were done for each patient, and the best one representing the patient's voiding as judged by the patient and without artifacts (e.g. wag artifact by eye balling) was included in this study. The statistical analysis was done using SPSS 7.5 software.

RESULTS

At three months follow up, 499 out of the 588 (85%) patients included in the study reported a satisfactory symptomatic improvement with a decrease ≥30% in their IPSS and QLA scores. At 12 months, a re-evaluation of IPSS, QLA, flowmetry and PVR was done (Table 1). Out of 499 patients, 436 (74%) continued treatment for one year and were satisfied with the treatment (IPPS improvement > 30%). These were the patients evaluated in our study. About 13% (63 patients) dropped out at one year for different reasons: in 16 patients complications occurred, three patients did not like taking pills every day, while 44 patients were not satisfied with the treatment.

The pre-treatment IPSS score ranging from 9 to 26 (mean 15.7) dropped to post-treatment values ranging from 4 to 13 (mean 6.3). The QLA score dropped from a pre-treatment value of 4 – 6 (mean 4.3) to 1 - 4 (mean 2.1) post treatment. The data of the pre-treatment and 12 months post- treatment flowmetry and PVR are presented in Table 2. The direction of change in flowmetry is presented in Table 3. The changes in Qmax, Qave and PVR were statistically highly significant as proved by the 2-tailed Student t test for paired samples (p= 0.000, 0.001, and 0.002 respectively). No significant change in the voided volume was seen (p= 0.528).

The pre-treatment mean Qmax for patients with an increase > 30% in their Qmax at 12 months had been 8.9 ml/s, while the pre-treatment mean Qmax for patients with an increase < 30% in their Q max at 12 months had been 9.6 ml/s. The pre-treatment mean Qmax for those patients who had a decrease in their Qmax had been 10.3 ml/s. Using the linear regression analysis the change in Qmax was found to be statistically independent of the voided volume and the post-voiding residual urine. It was found to be negatively dependent on the pre-treatment Qmax (Table 4).

The flowmetry changes in the control group are demonstrated in Table 3. At 12 months follow up a symptomatic improvement > 30% occurred in only 37 (30.6%) patients which is

Table 2: Detailed Flowmetry Findings Before and 12 Months After Treatment in Patients with Symptomatic Improvement

Variables	Min	Max	Mean	SD	Confidence-Interval
Qmax 1*	4.1	15.2	9.5	2.8	8.6 : 10.4
Qmax 2**	5.5	24.9	11.4	4.3	12.8 : 10.2
^Qmax***	-5.0	10.0	1.9	3.2	0.99 : 2.99
Qmax%	-35.5%	100%	22.9%	32.7%	12.7% " 33.2%
Qave 1*	2.0	8.9	5.1	1.7	4.5 : 5.6
Qave 2**	2.0	13.7	6.1	2.4	5.2 : 6.8
^Qave***	-2.0	6.2	0.9	1.7	1.5 : 0.42
Qave%	-31.8%	182%	22.37%	41.2%	9.5% : 35.2%
V ura 1*	151	644	213	110	178 : 249
V ura 2**	192	499	222	95	192 : 251
^V ura***	-240	189	8.6	88.5	-18.9 : 36.3
PVR 1*	00	480	74.8	102.4	42.9 : 106.8
PVR 2**	00	280	46.8	61.8	27.5 : 66.1
^PVR***	-75	219	27.4	57.4	9.5 : 45.3

* = variable before starting treatment; **= variable after starting treatment; ^***= change after 12 months treatment

statistically significantly less than the improvement recorded in the patients treated with terazosin. Only in one patient (0.8%) flowmetry had increased by >30% which is statistically significantly less than the results obtained in patients treated with terazosin.

DISCUSSION

During the last two decades, the therapeutic efficacy of alpha 1 adrenoceptors has been clearly demonstrated in several clinical trials[7] and today these drugs are the first-line medical treatment for lower urinary tract symptoms suggestive of bladder outlet obstruction. The advantage of terazosin in patients with LUTS/BPH is its reversibility. It can be withdrawn in cases where patients do not respond or where side effects occur. In our clinical practice, a trial of terazosin treatment has been started and only patients who benefit continue the treatment.

In this study, a group of patients with LUTS/BPH and a poor urinary flow rate were treated with terazosin 5 mg H.S. At 12 months, 436 out of 588 (74%) showed a satisfactory symptomatic response (IPSS >30%). This compares favourably to the results of the International Terazosin Trial (ITT)[5] where only 58% of the patients had experienced an IPSS improvement ≥ 30%. On the other hand, Lepor et al.[8] found that about 77.1% of his patients showed a 30% improvement in the total symptom score compared to the base line which is similar to the results of this study.

In our study, 63 (13%) patients discontinued terazosin treatment at one year, in spite of an initial symptomatic improvement, while in the ITT study the percentage of patients discontinuing terazosin treatment was 20.4%[5]. According to other double blind studies on BPH, 15% of patients treated by terazosin discontinued therapy[9].

As mentioned before it was postulated that terazosin improves the symptoms of BPH by improving the flow due to relaxation (decreased tone) of the prostatic interstitial and capsular muscles. The total improvement in Qmax in this study was + 2.3 ml/s (+ 23.7%). This parallels the findings of many studies. In

Table 3: Direction of Change in Qmax in 436 Patients after Completion of 12 Months of Treatment

Direction of Change	No of Pts.	% of Total	Controls	%
Increased Qmax	332	76.1%	25	20.6%
Decreased Qmax	104	23.8%	88	72.7%
Increased Qmax ≥ 30%	176	40.4%	1	0.8%
Decreased Qmax ≤ 30%	21	4.8%	7	5.8%

Table 4: Linear Regression of the Change in Qmax on Other Variables

Variable	Regression Coefficient (b)	S.E.	T Statistics	Significance
Qmax 1	-1.009	0.028	-36.103	0.000
Qave 1	2.073	0.046	0.455	0.652
V ura 1	3.318	0.000	0.674	0.502
PVR 1	9.668	0.000	0.259	0.259

the V.A. study carried out by Lepor et al.[4] the patients treated by terazosin showed a mean increase of Qmax of 2.7 ml/s (+25.7%) which is similar to this study. The ITT study[5] reported on an increase of the Qmax from 9.8 ml/s to 12.9 ml/s (+31.8%), while in another study[8] Qmax increased by 23% above base line, which is again similar to this study.

In this study only about 40% of the patients who showed a significant symptomatic improvement also showed a parallel significant (≥30%) increase in Qmax. This is similar to the findings reported by Lepor et al.[8] who found at the follow-up visits of their patients that the Qmax was significantly higher than the baseline (≥30%) in only 40-59% of the patients.

In the regression model used, the regression coefficient (b) was negative and statistically significant when comparing the change in Qmax to the pretreatment Qmax (Table 4). This indicates that patients with a lower Qmax at the start of the treatment had a more considerable increase of Qmax after treatment. This was also verified when the mean pretreatment Qmax was calculated separately for patients with improvement or deterioration of their post-treatment Qmax. The pretreatment mean Qmax of patients with an increase >30% in their Qmax at 12 months was 8.9 ml/s while that for patients who had a decrease in their Qmax after treatment was 10.3 ml/s.

In this study a decrease of Qmax was noted in 23.8% of the patients and 4.8% out of the total group had a decrease ≥30% in their Qmax in spite of a significant symptomatic improvement. These findings raise the question as to how to explain the significant subjective improvement in 74% of patients at 12 months with only 40% objective significant (>30%) improvement in flowmetry and 4.8% objective significant (>30%) deterioration in flow. Also, does terazosin work only by improving the flow?

This points to the possibility that in aging males a LUTS symptom improvement might also be achieved via non-prostate smooth muscle events mediated by alpha-adrenoceptors. It is postulated that the extraprostatic action of alpha-antagonists may considerably contribute to the overall symptomatic improvement that is observed after initiation of

therapy[10]. It was shown that the extraprostatic effects of terazosin on the bladder, spinal cord and efferent pathway[10,11] might be just as important as the effects on the peri-urethral or smooth muscle tone. These findings cannot be attributed to placebo effects of a close follow up, as the changes are statistically different between the active treatment group and the control cases (watchful waiting).

In conclusion, the clinical improvement in BPH/LUTS observed with terazosin in this study showed no direct correlation with an improvement in flow rates. This raises the possibility of multiple actions of terazosin to improve the symptoms associated with BPH.

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Editorial Comment:

This is a very well designed study. However, my concern is that including patients having a Qmax of 15 ml/s may not be fair, because 15 ml/s does not represent an obstruction severe enough to require treatment, except if this is associated with other severe symptoms. In such cases it has to be pointed out clearly that, for example, patients with a Qmax of 10 ml/s or more have an unsatisfactory IPSS which qualifies them for being enrolled in the study.

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Reply of the author:

An important aspect of management of patients with LUTS/BPH (with moderate to severe symptoms according to IPSS) is the quality of life (QLA), i.e. an improvement of their symptoms. As seen in this study, about 5% of our patients preferred to continue treatment as it improved the QLA in spite of a decrease in Qmax. For this reason, patients with a Qmax of 10 – 15 ml/s were included, provided they had moderate to severe symptoms and were severely bothered by their symptoms. Also, a good proportion of patients with a Qmax of 15 ml/s suffer from obstruction as recently shown in the ICS-BPH study[1]. In this study, the Qmax of 15 ml/s had a specificity of 38%,

a positive predictive value of 67% and a sensitivity of 82% for detecting outflow obstruction in patients with LUTS/BPH.

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RESUME

Le Traitement par la Terazosine chez les Patients Présentant des Signes D'obstruction du Bas Appareil Urinaire/HBP. Améliore-t-il le Débit Urinaire ?

Objectif Evaluer les variations de la débimétrie associées à une amélioration significative des symptômes chez des patients présentant une hypertrophie bénigne de la prostate ou des signes d'obstruction du bas appareil urinaire traités par la térazosine. **Patients et Méthodes** L'étude a porté sur une série de 588 patients présentant une HBP/LUTS traitée par Térazosine à la dose de 5 mg HS (Groupe I) et 121 patients présentant les mêmes symptômes et soumis à une surveillance comme groupe témoin (Group II). Tous les patients ont bénéficié d'un toucher rectal, remplissage d'un questionnaire IPSS et dosage du taux sanguin de PSA afin d'exclure un cancer de la prostate. Des investigations plus approfondies incluant une débimétrie et une mesure du résidu post-mictionnel ont été réalisées. Tous les patients ont été suivis pendant au moins 12 mois. **Résultats** L'évaluation pré-thérapeutique a montré un score IPSS moyen de 15,7 (extrêmes de 9 et 26), un score moyen de Qualité de vie de 4,3 (extrêmes de 4 et 6), un poids moyen de la prostate de 39 ± 26.7 gm, un taux moyen de PSA de 1,9 ng/ml et une créatininémie normale chez tous les patients. Le débit maximal (Qmax) avant traitement était en moyenne de 9.7 ml/s, le débit moyen (Qave) était de 5,1 ml/s. Le résidu post-mictionnel était en moyenne de 74,9 ml. Après un suivi de 3 mois, 499 (85%) patients du Groupe I ont montré leur satisfaction et ont continué le traitement. A un an, 436 (74%) de ces patients ont montré une amélioration >30% de leur score IPSS et score Qualité de vie (QoL) et ont eu un Qmax moyen de 12 ml/s (+ 2,3 ml/s), Un débit moyen de 6,1 ml/s (+ 1.0 ml/s) et résidu post-mictionnel moyen de 46,7 ml (- 28,2 ml). Cependant, les modifications du Qmax variaient de – 35,5% à + 100% avec un changement positif dans 76% et un changement négatif dans 24%. Parmi les patients qui ont eu une amélioration des symptômes, seuls 40% ont montré une augmentation du Qmax >30%, tandis que 4,8% ont montré une diminution de Qmax de plus de 30%. Dans le groupe contrôle, seuls 37 patients ont montré une amélioration des symptômes de plus de 30% avec un seul patient montrant une amélioration de plus de 30%, ce qui est statistiquement moins significatif que dans le groupe sous traitement. **Conclusion** En dépit d'une amélioration symptomatique chez 74% des patients traits par la Térazosine, seuls 40% ont montré une augmentation de Qmax de plus de 30 % après un an de suivi. Une détérioration de Qmax >30% a été trouvée chez 4,8% des patients dont les symptômes ont été améliorés, ce qui dénote qu'il n'y a pas de parallélisme entre l'amélioration des symptômes et celle de la débimétrie.

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