RESEARCH ARTICLES

IS QUALITATIVE HISTOLOGICAL INTERPRETATION OF THE PROSTATIC BIOPSY SPECIMEN HELPFUL IN PREDICTING CLINICAL OUTCOME OF TERAZOSIN THERAPY?

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ABSTRACT

Purpose: *The aim of this study was to determine the role of qualitative histological interpretation of the prostate gland in predicting the clinical outcome of terazosin therapy.* ***Patients and Methods:*** *Thirty-six male patients with symptomatic benign prostatic hyperplasia (BPH) and with a serum PSA 4-10 ng/ml underwent transrectal prostate ultrasonography and biopsy prior to terazosin therapy. Histological sections were stained with hematoxylin-eosin. A qualitative conventional light microscopic analysis (CLMA) and then color-assisted quantitative morphometric image analysis (MA) of the specimens were done. Results of these two techniques (CLMA and MA) were interpreted according to terazosin therapy results.* ***Results:*** *When CLMA was used, 50% or more stromal content was significantly related to the percent change of urinary flow rate (Qmax) but not with International Prostate Symptom Score (IPSS) after the terazosin therapy. Similarly, MA results showed a significant relationship between the percent of stroma and the percent change of Qmax, but not with the percent change of IPSS after terazosin therapy.* ***Conclusion:*** *Qualitative CLMA or quantitative MA of BPH tissue composition can be used in predicting clinical outcome of terazosin therapy, but it is suitable only in patients for whom prostatic biopsy is inevitable in order to rule out prostate cancer.*

Key Words: *Benign Prostatic Hyperplasia, Terazosin, Biopsy, Histological Analysis.*

INTRODUCTION

The prostate is frequently afflicted by disease in males beyond the age of 60, and the single most common pathological process implicated is benign prostatic hyperplasia (BPH). The condition of BPH, when it interferes with bladder neck urine flow, frequently requires treatment. Traditionally the remedy for BPH is surgical but only 20-30 % of symptomatic men actually undergo prostatectomy. The development of non-surgical therapy for BPH has been empirical, since the specific pathophysiological properties of the prostate gland predisposing to the development of symptomatic BPH have not been found (1).

Pharmacotherapy with the use of an alpha adrenergic receptor blocker or 5-alpha reductase inhibitor has been considered as an alternative treatment method but it is effective only in a selected number of patients (2-5). BPH is a proliferative process that involves both the stromal and epithelial elements of the prostate (6-

13). The success of pharmacologic agents may depend on the percent area of stroma or epithelium determined by histological studies (7,9). Morphometric histological interpretation of the prostate could be made with computerized color image analysis (8-13). Tissue samples for histological determination could be obtained by the use of transrectal prostate biopsy, an invasive method, with a considerable morbidity rate (14).

The present study was designed in BPH patients with a serum PSA 4-10 ng/ml, who underwent transrectal prostate biopsy prior to terazosin therapy. The aim of the study was to evaluate the role of qualitative conventional light microscopic histological analysis (CLMA) or color-assisted quantitative morphometric image analysis (MA) of the prostate gland in predicting the clinical outcome of terazosin.

PATIENTS AND METHODS

Patients with symptomatic BPH were evaluated with a complete history and physical examination, complete blood count, routine biochemical analysis, serum PSA, urinalysis and uroflowmetry. The severity of symptomatic BPH was determined using the International Prostate Symptom Score (IPSS) questionnaire. Serum PSA was measured in patients before any prostatic manipulation, using the Tandem-R assay method. Forty-three male patients, who had an IPSS greater than 7, a peak urinary flow rate (Qmax) of less than 15ml/sec and a serum PSA between 4-10 ng/ml, underwent transrectal prostate ultrasonography, and transrectal prostate biopsy prior to iniatiation of terazosin therapy. Of the 43 patients thirty-six 51-81 (mean 62.8) year-old patients whose transrectal prostate biopsy revealed benign prostatic hyperplasia were included in this study. The mean pre-treatment IPSS, serum PSA level, Qmax and prostate volume values of the 36 patients were 17.7$\pm$3 (13-27), 5.7$\pm$1.5 (4.1-9.8) ng/ml, 10.5$\pm$2.1 (6-13) ml/sn and 35.5$\pm$5 (16-65) ml, respectively.

The patients with a history of urethral stricture, neurogenic disease, diabetes mellitus, bladder neck or urethral operation, or previous treatment for BPH were excluded from the study. Also, patients with any abnormality at digital rectal examination, blood or urine analysis or transrectal ultrasonography were excluded.

Wiest Urocompact 6000 Uroflowmeter was used for uroflowmetry throughout the study. If the patient voided less than 150 cc, another attempt was encouraged after additional fluid intake. Prostate ultrasonography was performed using the 7 mHz Bruel and Kjaer transrectal transducer (B&K 3535 scanner, 8551 rectal probe, B&K Medical Asc., Glostrup, Denmark) by the same urologist. The prostate volume was estimated by a computer software program based upon the assumption that the prostate is an elliptical structure. Following rectal enema and prophylactic antibiotic (500 mg ciprofloxacin orally one hour before and six hours after the procedure), eight random biopsies of the prostate, the including six from the peripheral zone and two from transitional zone, were done.

Histological Method:

The histological samples were transrectal prostate biopsy specimens fixed in buffered formalin, embedded in paraffin and sectioned at 5mm. Tissue sections were stained with hematoxylin-eosin.

For the CLMA, two pathologists reviewed all the histological sections prospectively using a magnification of x100. All available sections were systematically reviewed by each pathologist separately, and the percent of stroma was determined subjectively. Each patient was classified into one of the predetermined stromal percentage groups (group I=0-50%, group II=51-100%). In the case of incompatibility the two pathologists reviewed the specimen again and an agreement between the two observers was reached after careful interpretation. When the two observers could not agree, the senior pathologist decided.

MA of stroma, glandular epithelium and glandular lumina was performed using Samba 2000 software image analyzer system combined with a light Leitz microscope equipped with a SONY color video camera and MPR II 14-inch color monitor. Samba 2000 is a color system image analysis which discriminates color differences of stained tissue sections. The area densities corresponding to each of these tissue components were calculated for each full screen of MPR II color monitor, digitized by a personal computer. At least 20 (x400) different fields were examined in each tissue section. All glandular

epithelium and glandular lumina were substracted from the total specimen area and percent of stroma (SP) was calculated for each patient.

Terazosin Dose Response:

Terazosin was titrated to a daily dosage of 5mg over a ten-day interval, providing adverse events were not observed. The titration schedule proceeded as follows: 1mg, days 1-3; 2mg, days 4-10, and 5mg days 11-90. Terazosin was always administered at bedtime. All thirty-six patients tolerated 5mg dosage for three months. All patients were evaluated for IPSS, serum PSA level, urinalysis and Qmax in the third month. Clinical response to terazosin therapy was defined by changes in IPSS and Qmax.

The relationships between clinical response and histological interpretation were evaluated.

Statistical method:

Paired Samples, Fisher's Exact and Linear Regression tests were employed in statistical analyses.

RESULTS

After the terazosin therapy the mean improvement in IPSS and Qmax were 23.5+15.9 % and 66.1+54.9 %, respectively. Improvements in these parameters were statistically important ($p<0.001$, Paired Samples Test). Mild dizziness associated with terazosin was observed in three (8.3%) patients.

According to the SP obtained from CLMA, there were 13 (36.1%), 23 (63.9%) in group I and II, respectively (Figure 1A-B). A statistically significant relationship was found between the pre-treatment and post-treatment IPSS values in group I and II. Although there was a statistically significant difference between the pre-treatment and post-treatment Qmax values in group II (>50% stroma), no difference was noted in group I (<50% stroma) (Table 1).

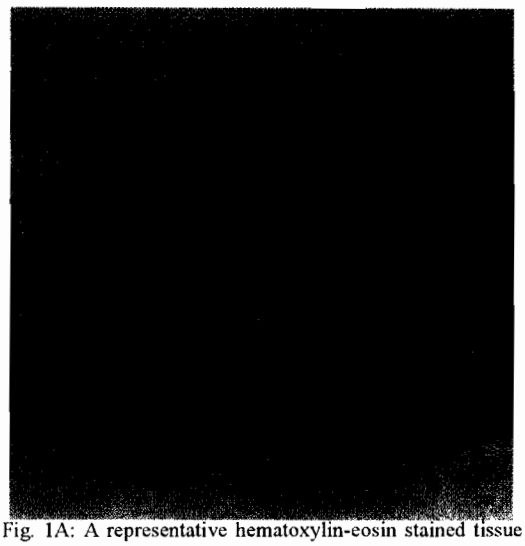

Fig. 1A: A representative hematoxylin-eosin stained tissue section of a patient with A SP of 0-50 % (Group I).

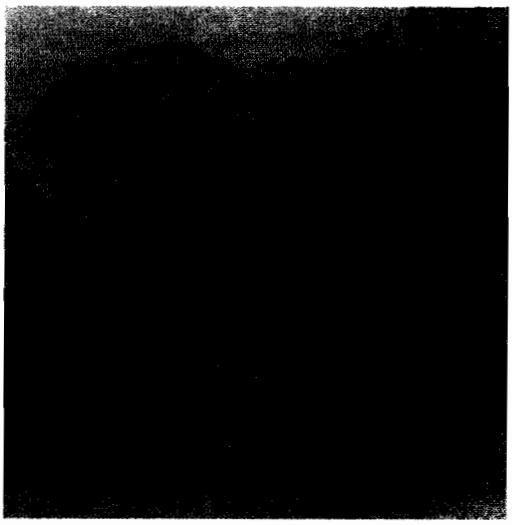

Fig. 1B: A representative hematoxylin-eosin stained tissue section of a patient with A SP of 51-100 % (Group II).

Table 1 : Pre-treatment and Post-treatment IPSS and Qmax (ml/sec) Values for the qualitative CLMA histological groups.

Histologic Evaluation	Pre-treatment IPSS	Post-treatment IPSS	Statistics*	Pre-treatment Qmax	Post-treatment Qmax	Statistics*
Group I	17.1+2.7	13.9+3.6	P<0.05	11.2+1.7	15.0+6.8	P>0.05
Group II	18.1+3.1	13.0+2.9	P<0.001	10.2+2.0	18.6+5.9	P<0.001

* Paired Samples Test

Table 2 : The relation of CLMA and MA determined stromal groups.

	Quantitative MA <50 %	Quantitative MA >50%	Total
Qualitative CLMA < 50%	4	9	13 (36.1%)
Qualitative CLMA > 50%	7	16	23(63.9%)
Total	11(30.6%)	25(69.4%)	36

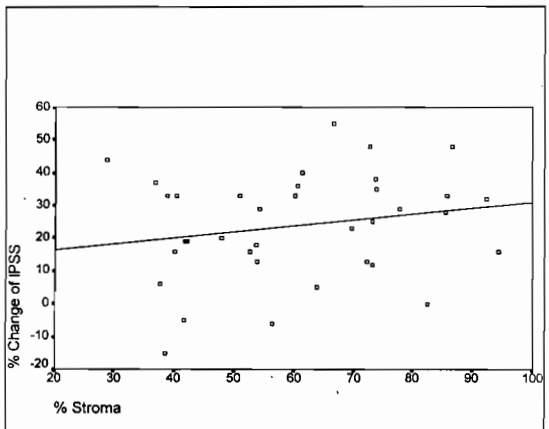

Fig. 2A: The relationship between SP according to samba 2000 and the percent change of IPSS (r=0.20, p>0.22).

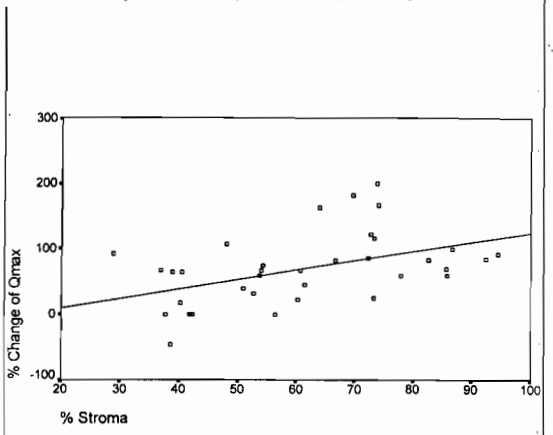

Fig. 2B: The relationship between SP according to samba 2000 and the percent change of Qmax (r=0.48, p=0.002).

By using MA, 25 (69.4%) of 36 patients had a SP bigger than 50 %. According to MA, the relationship between SP and the percent change of IPSS and Qmax are shown in Figures 2A and 2B. Although a statistically significant relationship was not found between the SP and the percent change of IPSS ($p>0.05$) after terazosin therapy, there was a statistically important relationship between SP and the percent change of Qmax ($p<0.05$).

The relationship of MA and CLMA determined stromal groups are shown in table 2. When the number of CLMA-detected stromal prostates was compared with MA-detected stromal prostates (>50%), the difference was not statistically significant (Fisher's Exact Test, $p>0.05$).

DISCUSSION

Alpha-1 blockers are capable of reducing outflow obstruction caused by prostate smooth muscle, the locus of the alpha adrenergic receptors (7,15). The long acting alpha-1-specific adrenoreceptor blocker terazosin was initially developed as an anti-hypertensive agent, and then approved for symptomatic BPH. It has an excellent safety profile and efficacy in the treatment of BPH. The overall mean change in Qmax (66%) was not very different from the result (58%) obtained in Shapiro and associates' study (7). However, it was reported that terazosin was not uniformly effective in relieving BPH-related symptoms and flow restriction (3,15).

An explanation for the varying response pattern to terazosin may be the variation in prostate tissue composition noted in different individuals. Theoretically, terazosin would be more efficient in stromal-rich prostates than the epithelial-rich prostates. Because baseline evaluation parameters are not directly related to the clinical response to alpha blockade therapy, it is important to evaluate the histologic type of BPH before instituting pharmacologic treatment (3,7,9). Currently, this can be done either by quantitative histopathological analysis (7) or by MRI (16). Due to its complications, including hematuria, hemospermia, pain, urinary retention, urinary infection and septicemia, transrectal prostate biopsy can not be used in routine clinical practice in order to determine histologic composition of BPH (14). However, in the "PSA era" a subset of patients with BPH are inevitably biopsied because of suspicious PSA levels, and their pathological specimens can easily be examined for tissue composition. From this point

of view, we used histological analysis as a method to select the most appropriate patients for terazosin therapy.

Bartsch et al. (6) and Siegel et al. (8) reported the quantitative morphometrical analysis of the prostate by using the point stereology method. Later, Shapiro et al. (11-13) described the first application of computer-assisted color image analysis and/or double immunoenzymatic staining with specific antibodies for smooth muscle and epithelium in the prostate in order to determine the percentage area density of smooth muscle, connective tissue, glandular epithelium and glandular lumen in the prostate gland. It was reported that BPH was primarily a stromal process (6,8,9,11,13). We found that 63.9% and 69.4% of patients had a SP value above 50% by using CLMA and MA, respectively. Our results confirm the previous reports, indicating that hyperplasic prostates result mainly from a stromal tissue hyperplasia.

In our study, we found a direct relationship between SP obtained from CLMA and clinical outcome of terazosin. Our hypothesis was that men with stromal rich prostates would respond better to the terazosin, while the optimal pharmacologic treatment of men with epithelial rich prostates is 5-α reductase inhibitors. Terazosin was found to be more effective, supporting our hypothesis, in patients with a SP above 50 % (Group II) than in patients with a SP below 50 % (Group I). Similarly, SP obtained from MA was significantly correlated with the percent change of Qmax but not with IPSS, following terazosin therapy. These results parallel closely the results obtained from Shapiro and associates' study (7), who observed a direct relationship between the percent area density of prostate smooth muscle and the percentage increase in peak urinary flow rate (but not with the percent decrease in total symptom score), which suggests that the therapeutic response to terazosin therapy is related to relaxation of prostate smooth muscle (7). Furthermore, these results may also indicate the role of detrusor overactivity or hypocontractility in BPH, which was found in up to 50% of patients, and that prostatism symptoms are not BPH-specific (17).

With the use of special staining methods, the stroma can be further differentiated into separate smooth muscle and fibrous compartments, the relative amounts of which may also vary considerably between different prostates (12,13). Although Shapiro et al. (7) have demonstrated the utility of this subdivision, using immunoenzymatic staining techniques to correlate prostatic smooth muscle density and BPH responsiveness to alpha-blocking agents, subdivision of the stroma may not be practical using a conventional hematoxylin-eosin stain, as in the present work (13). Our study indicates that prostatic tissue composition, as determined by conventional hematoxylin-eosin stained histological tissue sections obtained from transrectal prostate biopsy, may be crucial in predicting an individual's treatment response to alpha-blocking agents.

To what extent does a limited tissue sample accurately reflect whole-gland prostatic histologic type? Although major differences in primary BPH tissue composition may exist between prostate glands, it has been shown that within individual prostates the process is rather symmetric, and in fact, as little tissue as in a single biopsy core may allow accurate characterization of a hyperplastic prostate gland (10,18).

Another controversy about our study may be the potential for subjectivity of our histological CLMA method. In order to overcome or minimize this pitfall, two different pathologists were incorporated to the study. Furthermore, we used computer-assisted quantitative MA for detecting tissue composition of the BPH in order to correlate these two methods. The compatibility of our CLMA results with MA shows that our suggestions were acceptable and the CLMA method seems to be an efficient and reliable method. The main purpose of applying qualitative CLMA was due to its simplicity. The other quantitative point count stereology or computer-assisted color image analysis with immunoenzymatic staining methods are sophisticated, time-consuming and expensive methods. Our cost-effective CLMA method is reproducible and can easily be performed by every pathologist. Results obtained from a larger trial would also be of interest and further clinical studies confirming the validity of our method are indicated.

In conclusion, our study suggests that histological analysis of the prostate tissue is

appropriate for determining the clinical outcome of terazosin. Because it is an invasive diagnostic procedure, pathological assessment of BPH composition with transrectal prostate biopsy is not suitable. However, patients in whom prostatic biopsy is inevitable to rule out prostate cancer, histological interpretation of BPH either with qualitative or quantitative methods can be helpful in predicting clinical outcome of terazosin therapy.

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