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COMBINATION MEDICAL THERAPY (α -BLOCKADE AND ANDROGEN SUPPRESSION) IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

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Summary

This is a prospective study designed to compare the outcome of two different lines of medical therapy for Benign Prostatic Hyperplasia (BPH), namely: α blockers alone versus α blockers and androgen suppressors in combination. One hundred patients were included in the study, which was conducted during the period from September 1998 to March 2001. Detailed history was taken with thorough physical examination and investigations. Patients also underwent ultrasonography and intravenous urography to assess the upper tract function and postvoiding residual volume. The American Uorological Association (AUA) Symptom Score, urinary flow rate and the volume of residual urine were assessed in all patients and were used for comparison. The patients were randomized into two equal groups, each consisting of 50 patients. Those in group I were given Doxazosin (4 mg/day) alone while those in group II were given a combination of Doxazosin (4 mg/day) and Finasteride (5 mg/day). It is concluded that the results obtained with combination therapy are more promising and significantly better than those obtained with a single agent. All the parameters of comparison, i.e. the AUA score, urinary flow rate and volume of residual urine, improve with both methods but to a much greater extent in group II, the combination therapy group.

Introduction

Benign prostatic hyperplasia (BPH) has been known for several centuries to be a cause of urinary dysfunction. It was mentioned in the Egyptian papyri as early as 1500 BC and was discussed by Hippocrates 1000 years later[1]. The clinical manifestations of BPH include lower urinary tract symptoms, poor bladder emptying, urinary retention, detrusor instability, urinary tract infection (UTI), hematuria and renal insufficiency[2]. Many investigators found no, or weak, relationship between prostate size, severity of bladder outlet obstruction and

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severity of symptoms[3]. A poll among German urologists showed that clinical BPH accounted for only 40% of all urological diagnoses[4]. The management of BPH is under constant review and discussion and new therapies are becoming increasingly available. A notable new approach is the move from surgical to medical treatment that includes alpha-blockers, androgen suppressors, aromatase inhibitors and plant extracts[5]. Medical therapy, however, should not be offered to individuals presenting with absolute indications for surgical intervention like those with recurrent urinary retention, recurrent UTI, renal insufficiency, bladder calculi and recurrent gross hematuria. Such patients need prostatectomy, the most effective BPH treatment option[6]. The rationale for alpha-blockers in the treatment of BPH is, in part, due to prostate smooth muscle-mediated bladder outlet obstruction[7]. The role of adrenoceptors in regulating the tone of prostate smooth muscle has been known since the 1970s. The human body contains α1 (subtypes α1A, α1B and α1D) and α 2 receptors. Lepor and Sharpino demonstrated the 98% of all α1 receptors are localized in the prostate stroma with subtype α1A predominating[7]. Alpha-receptor antagonists may be classified according to α1 adrenoceptor selectivity and serum elimination half life into: Non selective (*phenoxybenzamine*), α1 selective (*Prazosin*, *Alfuzosin* and *Indoramin*), long acting α1 (*Terazosin* and *Doxazosin*) and subtype α1A selective (*Tamsulosin*).

Androgen deprivation, on the other hand, appears to decrease prostate volume by causing involution of the glandular component of the gland with no stromal regression[8]. Finasteride represents the paradigm for androgen suppression. It is a competitive inhibitor of 5-α reductase that is a selective inhibitor of the type II isozymes, which explains why it does not reduce dihydrotestosterone level to that of castration. Finasteride reduces prostate volume by approximately 20% [9].

It seems, therefore, logical to use combination medical therapy in order to produce favorable effects on both the glandular (*androgen suppression*) and stromal (α *blockers*) components of the hyperplastic gland. The aim of the study is to compare the outcome of two different lines of medical therapy for BPH, namely: α blockers alone versus α blockers and androgen suppressors in combination using the American Urological Association (AUA) Symptom Score, urinary flow rate and residual urine as the parameters for comparison.

Patients and Methods

One hundred patients were included in this study, which was conducted during the period from September 1998 to March 2001. All patients had no absolute indication for surgery. Detailed history was taken with thorough physical examination, including digital rectal examination (DRE). Laboratory investigations ordered were urinalysis, urine culture and sensitivity, renal function tests and prostate specific antigen (PSA). Patients also underwent ultrasonography and intravenous urography to assess the upper tract function and postvoiding residual volume. The AUA Symptom Score (Table I), urinary flow rate and the volume of residual urine were assessed in all patients, too.

The patients were randomly allocated to two equal groups, each consisting of 50 patients. Those in group I were given Doxazosin (4 mg/day) at bed time while those in group II were given a combination of Doxazosin (4 mg/day) at bed time and Finasteride (5 mg/day) at the morning and they were reassessed again after month of therapy.

Urinary symptoms (symptom score) criteria	not at all	less than 1 in 5	less than half the times	about half the times	more than half the times	almost always
1.Incomplete emptying	0	1	2	3	4	5
2.Frequency	0	1	2	3	4	5
3.Intermittency	0	1	2	3	4	5
4.Urgency	0	1	2	3	4	5
5.Weak stream	0	1	2	3	4	5
6.Straining	0	1	2	3	4	5
7.Nocturia	**Non 0**	**Once 1**	**Twice 2**	**3 times 3**	**4 times 4**	**5 times 5**

AUA Symptom Score= The total points of the seven questions.
[0-7 = mild symptoms, 8-20 = moderate, >20 = severe]
Table I. Questionnaire for American Urological Association Score.

	Aua		Flow rate		Residual urine	
	Group I	**Group II**	**Group I**	**Group II**	**Group I**	**Group II**
Before Rx	10.26	10.38	9.42	9.36	92.6	97.2
After Rx	8.42	8.48	11.16	11.86	68.6	54.6
$\geq$ 30% improvement	20 %	28 %	20 %	40 %	32 %	52 %

Table II. Important data for both groups.

Results

The average age of patients in group I was 50 years and in group II was 51 years.

In group I (Doxazosin only), 20% of the patients showed more than 30% increase in their urinary flow rate with the average increase of 1.74ml/sec. While 20% and 32% showed more than 30% reduction in the AUA Symptom Score (with the average decrease of 1.84) and in the volume of residual urine (with the average decrease of 24ml) respectively. In contrast, 40% of patients in group II (Doxazosin + Finasteride) showed more than 30% increase in their urinary flow rate with the average increase of 2.5ml/sec., while 28% and 52% showed more than 30% reduction in the AUA Symptom Score (with the average decrease of 1.9) and residual urine volume (with the average decrease of 42.6ml) respectively.

Discussion

One of the most striking new trends in the management of BPH is the move from surgical treatment to medical treatment, which is considered as an alternative for individuals who are

deemed appropriate candidates for prostatectomy but who lack absolute indications for surgery[10]. Doxazosin was chosen because it has a long half life (22 hours), gradual onset of action and a peak plasma concentration that is achieved 2-6 hours post-dose. In addition, Doxazosin was demonstrated to selectively induce apoptosis in the glandular epithelial and stromal smooth muscle cells of the hyperplastic human prostate without affecting the rate of proliferation of these cell populations[11].

In group I, there was a reduction of 1.84 in the mean AUA symptom Score with 20% of the patients showing more than 30% reduction in the score compared to 1.9 reduction in the mean AUA Score with 28% of the patients showing more than 30% reduction in the score for group II. However, this reduction in the mean AUA Score was statistically not significant.

On the other hand, the mean flow rate showed an increase of 1.74 ml/second and 20% of the patients had more than 30% increase in their urinary flow rate for group I compared to an increase of 2.5 ml/second and 40% of patients with more than 30% increase in their urinary flow rate for group II. And when it came to the volume of residual urine, there was a reduction of 24 ml in the mean value with 32% of the patients showing more than 30% reduction in residual volume for group I compared to 42.6 ml reduction in the mean value with 52% of the patients showing more than 30% reduction in residual volume for group II. One can clearly see from the above figures that the outcome of medical therapy was clearly superior in group II with respect to improvement in flow rate and reduction of the volume of residual urine.

We conclude that the results obtained with combination therapy are more promising and significantly better than those obtained with a single agent. A larger study with a bigger sample and a longer follow up is recommended, though.

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