Effect of Short-term Dutasteride Therapy on Prostate Vascularity in Patients With Benign Prostatic Hyperplasia: A Pilot Study

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OBJECTIVES
In this study we assessed the possible influence of dutasteride (types 1 and 2 isoenzymes of 5-alpha-reductase inhibitors) on prostate tissue vascularity. We also attempted to evaluate whether preoperative treatment with dutasteride could help to avoid excessive bleeding in patients undergoing transurethral resection of prostate (TUR-P).

METHODS
This pilot study has 3 phases. All patients enrolled in the study had a prostate-specific antigen < 4 ng/mL and normal digital rectal examination. In the first phase we included 10 patients with benign prostatic hyperplasia treated with alpha-blockers. The end point of this phase was to choose the preset that could exclude noise signals and be reproducible. In the second phase, we included 32 patients in whom color Doppler sonography (CDS) was performed before and 6 weeks after treatment with 0.5 mg dutasteride per day. We counted every discrete color Doppler signal (CD-spot). To compare the CDS data, we used the Student t test, and P < .05 was considered significant. Afterward, 46 patients joined the third phase. Patients were assigned to the control and study groups according to sequentially numbered sealed envelopes. Patients in the study group received 0.5 mg dutasteride 6 weeks before TUR-P.

RESULTS
In the first phase: color Doppler preset with pulse repetition frequency of 0.3 kHz was chosen as the most sensible. In the second phase, a significant decline in CD-spots count was detected in 23 (72%) patients (P < .05) and was more distinctive in the periurethral zone. In the third phase, only 43 of the patients continued with TUR-P (in 3 patients, voiding symptoms improved). Operating time and volume of irrigation fluid were significantly different (50.55 minutes/42.65 minutes, P = .014; 8.03/13.10 L, P = .047).

CONCLUSIONS
Six weeks of dutasteride treatment may reduce prostate tissue vascularity in the periurethral area proximal to the verumontanum. The third phase of our study confirmed that preoperative treatment with dutasteride could improve operative performance and avoid TUR syndrome.

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In our study, we used this technique to demonstrate a possible reduction in prostate tissue vascular density after a 6-week treatment with dutasteride. We also tried to evaluate the effects of preoperative treatment with dutasteride on bleeding during TUR-P.

**MATERIALS AND METHODS**

**Patients**

This pilot study has 3 phases. All patients enrolled in the study had a prostate-specific antigen (PSA) of < 4 ng/mL and a normal digital rectal examination. The exclusion criteria were infections, acute urinary retention, indwelling catheter, and contraindications to TUR-P. After the nature of the procedure had been fully explained, informed consent was obtained from each patient. The same urologist (K.S.) performed all examinations. The patients were examined in the left lateral decubitus position, using the Diagnostic Ultrasound System (ProFocus 2202, B&K Medical, Denmark). The entire prostate gland was examined using a steplike technique with 0.5 cm for each step. The transition zone volume was measured based on the maximal width of the zone in the axial projection, anterior-posterior diameter, and length from the verumontanum to the bladder neck in the sagittal projection. Color preset was optimized to detect the lowest and slowest blood flow within the prostate. We counted every discrete color Doppler signal (CD-spot). To identify the specific influence of dutasteride on prostatic vascularity in the periurethral area, we performed spectroscopic analysis of color signals on the step-slice images proximal to verumontanum before and after dutasteride.

In the first phase, we included 10 patients with BPH treated with alpha-blockers. The end point of this phase was to choose the preset that will detect the lowest and slowest blood flow within the prostate, exclude noise signals and be reproducible. Seven CD presets were compared: pulse repetition frequency (PRF) ranged from 0.8-0.2 kHz. For all presets, we used the same color gain, noise reject, and persist levels, whereas a high-pass filter was adjusted in every preset to exclude the noise and improve flow signals. A point of maximal displayed vascularity was recorded in a steplike technique with 0.5 cm for each step.

In the second phase of the study, 32 patients with BPH were included. TRUS-CD was performed before and 6 weeks after treatment with 0.5 mg dutasteride per day. The same settings were used during follow-up examination. Doppler flow was evaluated and subjectively scored.

The goal of the third phase of our study was to assess the effect of preoperative treatment with dutasteride on intraoperative bleeding. This phase included only the patients who were previously treated with alpha-blockers and scheduled for TUR-P. All of these patients received explanations about the possible positive (improvements in voiding symptoms and storage symptoms) and negative (impotence, decreased libido, and ejaculation consequences of dutasteride) consequences of dutasteride. All the patients made independent decisions on preoperative treatment with dutasteride. To avoid the influence of the cost of dutasteride on their decision, patients were provided with free samples of dutasteride that had been given to the physicians. As a result, patients were divided into 2 groups: one taking dutasteride and alpha-blockers (potential study group) and the other continuing only with alpha-blockers (potential control group). Afterward, patients in both groups received sequentially numbered sealed envelopes and patients with the number 2 on their envelope were included in the study. Accordingly, 46 patients were enrolled in the third phase: 24 in the study and 22 in the control groups.

In the operating room, the following data were recorded: operating time (from start to urethral catheter insertion), volume of irrigation fluid, weight of the resected prostate chips (before formalin), and signs of TUR syndrome, if present. TUR syndrome was defined as nausea, vomiting, confusion, visual disturbance, bradycardia, and hypotension with hypotension occurring during or immediately after TUR-P. Postoperative hemoglobin (Hb) was obtained, and blood transfusion was given, if necessary, based on the result (< 10 g/dL). During the follow-up visits patients assessed the results of TUR-P as satisfactory or not.

**Statistical analysis**

The results are expressed as the arithmetic mean ± standard deviation (SD). To compare patient parameters, prostate and transition zone volumes, and weight of resected tissue between the 2 groups we used the Student t test. To compare CD-spot data, we also used the Student t test. To assess the difference in categorical variables (blood transfusion rate, TUR syndrome, and satisfaction from operation) between patients subsets, the χ² test was used. For this purpose, we used SPSS 10.0 statistical software (SPSS, Inc, Chicago, IL) and P < .05 was considered significant.

**RESULTS**

In the first phase, we found CD preset with PRF of 0.3 kHz as the most practical, because it maximizes the visualization of color flow within the prostate without producing noise in tissue. This preset was consecutively used in the second phase which included 32 patients with prostate volumes ranged from 35.7-53.9 mL. Mean CD-spots before and after the treatment were 11.6 ± 6.38 and 8.22 ± 5.24, respectively. Significant decline in CD-spots count was detected in 23 (72%) patients (P < .05) (Figure 1) and was more distinctive in the step-images proximal to verumontanum in the transitional zone adjacent to periurethral area (Figure 2). Regardless of any significant decrease in CD-spots count in the periurethral area, we failed to find any significant difference between venous and arterial blood flow in this area, based on the spectral analysis. Voiding symptoms significantly improved in 3 (2 in the study and 1 in the control group) of 46 patients enrolled in the third phase. Consequently, they refused surgery. The mean ages of the patients enrolled in the study and control groups were 67.7 years (SD ± 6.546 years) and 66.15 years (SD ± 8.555 years), respectively. There was no significant difference between the mean ages of the 2 groups (P = .524). The same is true about mean volume of transition zone, mean weight of resected tissue, and mean Hb before and after TUR-P (Table 1). Operating time and volume of irrigation fluid were significantly different (50.55 minutes/42.65 minutes, P = .014; 8.03/13.10 L, P = .047). Two patients in the control group received blood transfusions. There was no case of TUR syndrome in the study group, whereas it was documented in 2 patients of the control group.
Slightly more patients of the study group were satisfied with the results of TUR-P, but this difference was not significant (81.8%/76.2%).

COMMENT

Previous studies have shown that finasteride, given preoperatively, decreases bleeding in patients undergoing transurethral prostate resection.3,4 This effect could be explained by its capability to decrease the expression of VEGF and significantly reduce microvessel density in prostatic suburethral tissue.2 The results of these studies led to other investigations to demonstrate reduction in prostate vascularity, using TRUS-CD for this purpose.6,7 In 1 study, dutasteride (types 1 and 2 isoenzymes of 5-alpha-reductase) was shown to be at least as good as finasteride in terms of improving symptoms and flow rates.8 The results of these studies demonstrated the qualitative reduction of prostatic blood flow after short-term oral therapy with dutasteride. The early changes already were observed after 7 days of treatment.5 The authors believed that this reduction is likely due to rapid short-term alterations in blood flow.

In our study, we first tried to standardize the CD preset to reduce artificial changes in the Doppler flow. To diminish inaccuracy in interpretation of TRUS-CD results, we decided to count every CD-spot. Cho et al.9 used this technique in their study in which they depicted and compared color flow in normal glands and in the cases of chronic prostatitis/pelvic pain syndrome. Our choice of a 6-week treatment was based on the previous studies with finasteride; the authors gave it from 2-12 weeks before TUR-P, and reported slightly different results.5,4 The results of the second phase of our study showed a significant reduction in CD-spots in 72% of the patients. It must be emphasized that the results in our study of Doppler flow reduction are comparable with the improvement of voiding symptoms reported by Desgrandchamps et al.10 These authors reported that in 72.5% of the patients who received dutasteride, the International Prostate Symptom Score (IPSS) decreased from 15.3 at baseline to 10.2 and 9.1 after 12 and 24 weeks, respectively. Based on the results of our studies, we propose that 6-week treatment with dutasteride reduces prostate vascularity in 72% of the patients with BPH and these patients may be good candidates for successful continued treatment with dutasteride. Alternatively, in patients without color flow changes, this treatment would be probably ineffective. However, at this point, this is only a proposal that must be verified in future study.

TUR-P is still the gold standard for the surgical treatment of symptomatic BPH. However, the associated morbidity and blood loss remain concerns.11,12 To prevent intraoperative bleeding in patients undergoing TURP, 5-alpha-reductase can be given preoperatively. Its ability to resolve this problem was supported by some studies3,4 and questioned by the other.13 Our study showed a significant reduction of operating time and volume of irrigation fluid in patients who received dutasteride preoperatively. As a result, there were no cases of TUR syndrome in the study group compared with 2 episodes in the controls. In our study, we failed to observe any significant reduction in blood loss during TURP; however, no patients in the study group needed a postoperative blood transfusion, in comparison with transfusions required by 2 patients in the control group. El Malik et al.14 in their study dedicated to the factors influencing TUR-P bleeding found a significant association between operating time and weight of resected prostate tissue, and the magnitude of blood loss caused by TUR-P. Because there was no significant difference in the mean weight of resected tissue (P = .433) in the 2 groups, we proposed that the low rate of postoperative transfusion in the study group is due to the significant reduction of operating time.

After the 6-week pretreatment with dutasteride, we observed a reduction in color flow mainly in the transitional zone adjacent to periurethral area. The latter could be explained by the vascular changes of BPH and possible capability of dutasteride to inhibit angiogenesis. As was demonstrated by Neumaier et al.15 in their comprehensive study, the urethral group of arteries become more numerous in the transitional zone and can be disarranged.

Slightly more patients of the study group were satisfied with the results of TUR-P, but this difference was not significant (81.8%/76.2%).

Figure 1. Color Doppler appearance of prostatic blood flow before (A) and 6 weeks after treatment with 0.5 mg dutasteride per day (B); less color spots are seen on the B.
and displaced along the cleft between the central bulk of the hyperplastic tissue and the peripheral gland. The authors also reported that venous flow signals were even more easily obtained in the periurethral zone. In our study, we failed to detect any significant difference in the amount of venous and arterial CD-spot signals in the periurethral area before dutasteride. Our spectroscopic analysis of color signals after dutasteride showed nearly

**Figure 2.** The decrease of blood flow (CD-spots) before (A) and 6 weeks after treatment with 0.5 mg dutasteride per day (B); these changes are more apparent in the transitional zone adjacent to periurethral area proximal to verumontanum (arrows).

**Table 1.** Clinical and statistical data of the 2 patient groups

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Age (y)</th>
<th>V-TZ</th>
<th>Resected tissue</th>
<th>Hb before TUR-P (g/dL)</th>
<th>Operating time (min)</th>
<th>V-irrigation (L)</th>
<th>Hb after TUR-P (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 22</td>
<td>67.7 ± 6.546</td>
<td>34.45 ± 7.688</td>
<td>24.10 ± 7.62</td>
<td>13.4 ± 0.91</td>
<td>42.65 ± 10.15</td>
<td>8.03 ± 3.58</td>
<td>12.3 ± 0.62</td>
</tr>
</tbody>
</table>

V-TZ = volume of transitional zone; Hb = hemoglobin; TUR-P = transurethral resection of prostate; V-irrigation = volume of irrigation fluids.
the same reduction in venous and arterial flow. So, we propose that after the 6-week pretreatment with dutasteride both arterial and venous microvascular blood flow are equally reduced.

Several limitations of this study should be acknowledged. All examinations were performed with the B&K Medical Diagnostic Ultrasound System and our results may not necessarily be valid for other instruments. As was demonstrated by Halpern et al., the lateral decubitus position may cause increased Doppler flow on the dependent side. However, the results of their consecutive study also revealed asymmetry in blood flow, despite lithotomy position. It must be also emphasized that even a slight compression on the rectal wall could obliterate color signals from small vessels. This problem can be overcome by shifting the probe laterally and using color capture to avoid excessive noise signals. All above-mentioned recommendations should be consider in the upcoming studies. In addition, all our patients made independent decisions on preoperative treatment with dutasteride, and this fact can cause bias. However, after 2 prestudy groups (dutasteride and alpha-blockers vs with alpha-blockers only) were formed, patients in both groups received sequentially numbered sealed envelopes and thus were randomly assigned into final control and study groups.

CONCLUSION

Based on the results of this study we confirm that 6-week pretreatment with dutasteride reduces prostatic vascularity, especially in the periurethral area proximal to verumontanum. This change plays a part in reduction in both venous and arterial microvascular blood flow. Six-week pretreatment with dutasteride can optimize TUR-P performance and results.

References