Reduced Intraoperative Bleeding During Transurethral Resection of the Prostate: Evaluation of Finasteride, Vascular Endothelial Growth Factor, and CD34

Ettore De Berardinis, MD, Gabriele Antonini, MD, Gian Maria Busetto, MD, Vincenzo Gentile, MD, Franco Di Silverio, MD, and Antonella Rossi, MD

Corresponding author
Vincenzo Gentile, MD
Department of Urology, University "La Sapienza" Policlinico Umberto I, Viale del Policlinico 155, 00161 Rome, Italy.
E-mail: vincenzo.gentile@uniroma1.it

Current Prostate Reports 2008, **6:**123–127
Current Medicine Group LLC ISSN 1544-1865

Finasteride is an antiandrogen that inhibits 5-α-reductase, an enzyme that converts testosterone to dihydrotestosterone. Finasteride significantly reduces intraoperative bleeding when 10 mg/d is administered for 60 days before transurethral resection of the prostate. Our double-blind, randomized, placebo-controlled study evaluated 200 patients with benign prostatic hyperplasia who underwent transurethral resection of the prostate. We compared a placebo group (n = 100) with a group (n = 100) administered 5 mg of finasteride twice a day for 8 weeks. We intended to demonstrate the mechanisms and effects of finasteride compared with those of vascular endothelial growth factor, and to evaluate CD34, an immunohistochemical marker of blood vessel density in the prostate. Our results indicated a lower average microvascular density and vascular endothelial growth factor index for hypertrophic prostate in the finasteride group than in the placebo group.

Introduction

Finasteride is an antiandrogen that inhibits 5-α-reductase, an enzyme that converts testosterone to dihydrotestosterone (DHT). The efficacy, safety, and ability of 5-α-reductase inhibitors (5ARIs) to reverse the natural progression of benign prostatic hyperplasia (BPH) have been convincingly demonstrated and established. Given the multifactorial etiology of BPH, the usefulness of 5ARIs in combination with α-adrenergic blockers has also been investigated and justified in select patients. Wider applications for 5ARIs are also emerging, though their important new role as chemopreventive agents remains unclear [1].

Finasteride prevents episodes of urothelial bleeding in men with BPH [2]. Some studies have demonstrated that finasteride has a role in the cascade of associated effects with the androgen-controlled vascular endothelial growth factor (VEGF). Suppression of VEGF leads to decreased angiogenesis, a possible mechanism for the observed effect with finasteride [3••]. The uptake of finasteride before transurethral resection of the prostate (TURP) has reduced surgical blood loss [4•], but studies have not shown a consistent effect [5].

Study Objectives and Design

We examined whether finasteride decreases blood loss and complications during TURP when provided as an 8-week treatment before surgery. We intended to demonstrate the mechanisms and effects of finasteride compared with VEGF. We also evaluated CD34, an immunohistochemical marker of the microvascular density (MVD) in the prostate.

Our double-blind, randomized, placebo-controlled study evaluated 200 BPH-affected patients who underwent TURP from 2004 to 2006. Placebo was compared with 10 mg/d of finasteride administered 8 weeks before TURP. All patients were selected according to age, hematic total prostate-specific antigen (PSA) level, and prostate volume measured by transrectal ultrasound (TRUS) (Table 1).

Our study included exclusion criteria such as a history of prostate disease different from BPH, any other prostate surgery, different administration scheme with any 5ARI within 12 months, treatment with aspirin or ticlopidine during the study period, and severe medical conditions, such as liver disease, bleeding disorders (eg, hemophilia), and unstable cardiovascular concerns.

Table 1. Patient characteristics

	Placebo group (twice daily for 8 wk)	Finasteride group (5 mg twice daily for 8 wk)	*P* value
Patients, *n*	100	100	–
Age, *y*	69 (65–71)	68 (64–70)	0.46
PSA, *ng/mL ± SD*	9.26 ± 4.54	8.67 ± 4.05	0.37
Prostate volume, *mL ± SD*	80.33 ± 35.32	90.25 ± 39.87	0.25
Volume cutted, *mL ± SD*	27.22 ± 8.21	34.83 ± 10.25	0.38
Operating time, *min*	30	35	–
Histologic prostate hypertrophy, %	100	100	–

PSA—prostate-specific antigen; SD—standard deviation.

We randomly assigned 200 patients to two treatment groups. Group 1 (n = 100) received placebo twice a day for 8 weeks before TURP, whereas group 2 (n = 100) received 5 mg of finasteride twice a day for 8 weeks before surgery. Daily administration of a 5-mg tablet of finasteride is the therapeutic dosage approved to treat symptomatic BPH. We measured surgical blood loss with a hemoglobin photometer, and postoperative adverse events were also recorded [6].

VEGF and CD34

Our study also evaluated VEGF and CD34, analyzing materials from the prostate. We histologically evaluated resected prostate chips from the TURP, ensuring that they were separated from those extracted from the urethra. Afterwards, the material was stained by monoclonal antibodies directed against CD34 and VEGF.

VEGF is a homodimeric glycoprotein for which four different isoforms have been described. It stimulates proliferation and migration of endothelial cells and plays a pivotal role in physiologic and pathologic angiogenesis. Although VEGF is produced by many different cells, its mitogenic activity mainly focuses on endothelial cells. Its effects are mediated through several receptors, including tyrosine kinase receptors. We performed VEGF immunostaining on diagnostic sections using antibody anti-VEGF.

CD34 (or myeloid progenitor cell antigen) is a heavily glycosylated type I transmembrane protein, 110 kDa. It is detected in bone marrow precursor cells and found in most endothelia, expressed on the luminal surface and membrane processes interdigitating between endothelial cells, but is absent from large veins and arteries. In smooth muscle cells, a variable CD34 staining is found. Intraprostatic microvessels were identified by immunostaining with anti-CD34 antihuman antibody.

Methods

Tissue specimens were fixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin. BPH was morphologically confirmed in all patients. Sections were cut from representative formalin-fixed, paraffin-embedded tumor blocks. The slides were dewaxed in xylene and rehydrated through a graded series of ethanols. Heat-induced epitope retrieval was carried out by immersing the slides in citrate buffer (pH 6) and microwaving at 600 W for 20 minutes before cooling and rinsing with phosphate-buffered saline (PBS). Endogenous peroxidase activity was quenched by incubating the sections in 1% hydrogen peroxide. Nonspecific binding sites were then blocked by preincubating with 20% normal serum and 1% bovine serum albumin (BSA) in PBS/0.3% Triton X-100 (Union Carbide, Dow Corporation, Midland, MI) for 20 minutes at room temperature. Sections were incubated with polyclonal rabbit anti-VEGF antibody at a concentration of 1:50, as well as monoclonal murine anti-CD34 at a concentration of 1:20.

After washing with 0.25% BSA and 0.05% polysorbate 20 in PBS, sections were incubated with biotinylated secondary pan-specific antibody at 1:500 for 1 hour at room temperature. Sections were again washed in PBS with 0.05% polysorbate 20, then incubated with horse radish peroxidase and conjugated streptavidin-biotin complex for 45 minutes. All sections were again washed in PBS with 0.05% polysorbate 20. Immunoreactivity was then visualized by adding hydrogen peroxide as an enzyme substrate, in the presence of 0.05% 3,3'-diaminobenzidine. Nuclei were then lightly counterstained with Harris's hematoxylin.

The area of most intense neovascularization was selected by scanning on low magnification (10–100×), avoiding areas with lymphocytic infiltration or fibrosis. Only the vascularity of hypertrophic areas considered viable (ie, nonnecrotic) was taken into account. Subsequently, individual microvessels were counted on a 400× field. Any brown-staining endothelial cell (CD34-positive) containing a visible nucleus and clearly separate from adjacent microvessels, epithelial cells, and other connective tissue elements, was considered a single, countable microvessel, without requirement for a lumen or the presence of erythrocytes. The microvessels were counted in a 0.74-mm^2 area (ie, a 400× field).

VEGF immunoreactivity was scored for the percentage of stained epithelial glandular and endothelial cells,

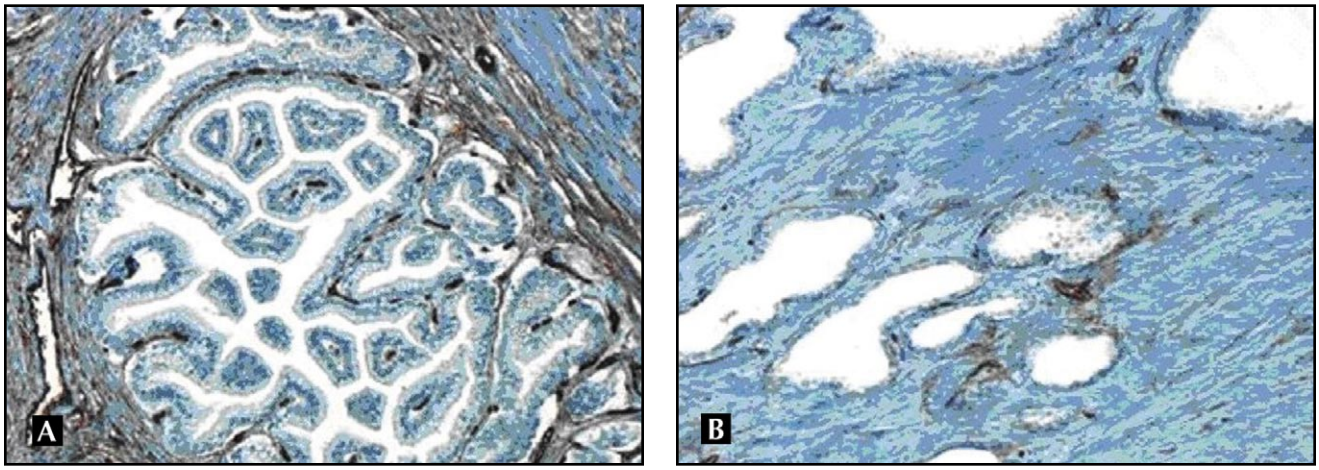

Figure 1. Intraprostatic microvessels with anti-CD34 antibodies. **A,** Placebo group, with high expression of microvascular density (CD34). **B,** Finasteride group, with low expression of microvascular density (CD34).

as 0, 1+, 2+, or 3+, according to staining intensity [7]. A hypertrophic area with any degree of staining was scored as VEGF-positive. Hyperplastic areas that were VEGF-positive and VEGF-negative were assigned the score of the area with strongest staining.

For the statistical analysis, we used the "tStudent" test to compare MVD and VEGF expression from treated patients and the placebo group. All results were reported as standard deviation ± significant differences ($P < 0.05$).

All 200 patients enrolled underwent TURP and completed the study. The surgical treatment duration was about 30 minutes. During this time, we resected 27.22 ± 8.21 g of prostatic tissue in the placebo group and 34.83 ± 10.25 g of prostatic tissue in the finasteride group ($P = 0.38$).

Results

In 8 weeks, 10 mg/d of finasteride reduced serum DHT by 90%, with intraprostatic DHT about 20 times lower than in the placebo group. A difference in perioperative bleeding was observed between the finasteride group (1.0–1.2 g Hb resected) and the placebo group (2.0–2.3 g Hb resected). Average MVD of the hypertrophic prostate, calculated by CD34 evaluation, was lower in patients treated with finasteride 10 mg/d for 8 weeks (16.08 ± 0.41; $P < 0.05$) than placebo (19.17 ± 1.15; $P < 0.05$) (Fig. 1A, Fig. 1B). The average VEGF index of the hypertrophic prostate was lower in patients treated with finasteride (1.68 ± 0.41; $P < 0.05$) than placebo (4.58 ± 0.50; $P < 0.05$).

Discussion

Finasteride was well tolerated at a dosage of 10 mg/d for 8 weeks before TURP. In our study, the primary end point was hemoglobin expressed in grams and in relation to the weight of the prostate resected, also expressed in grams. A significant difference was seen in intraoperative bleeding between the finasteride and placebo groups.

5ARIs reduce blood loss during TURP, shrinking the prostate by decreasing the number of blood vessels, which is similar to the effect achieved with androgen ablation. The entire prostate gland may then be less vascular, with potential bleeding reduced during surgery [8,9]. In many studies, 5ARIs reduce hematuria secondary to prostatic bleeding from the urothelium [10,11]. Of four double-blind, placebo-controlled studies, two studies administered finasteride and two administered dutasteride in patients in whom 3 months of finasteride did not reduce preoperative bleeding [3••,4•,5,7–11,12••]. Donohue et al. [13] randomly allocated 70 patients to receive 5 mg of finasteride or placebo for 2 weeks before TURP, noting a positive effect in a short pretreatment period (14 days), with reported losses of 2.7 g Hb in the resected tissue for the finasteride group and 4.7 g Hb in the resected tissue of the placebo group. Boccon-Gibod et al. [14•] randomly allocated 59 patients to receive 4 weeks of placebo or dutasteride (0.5 mg) before TURP, showing that blood loss during the operation was 1.4 g Hb and 1.9 g Hb in the resected tissue, respectively, with no significant difference between the two groups.

Other studies demonstrated different results. Crea et al. [15] analyzed 30 patients treated with finasteride for 8–10 weeks before TURP and revealed less blood loss than in untreated patients. The resected tissue was about 45 g and the blood loss was valued by the decrease in blood hemoglobin. The transfusion rate in the untreated patients was very high, at approximately 12%. Lund et al. [12••] reported a small difference in blood loss before the main operation between patients treated for 12 weeks with finasteride and placebo. Hagerty et al. [16] compared 12 patients who received finasteride 2–4 months before TURP with 19 patients who received placebo. In the finasteride group, patients needed fewer blood transfusions, with a lower incidence of clot retention, whereas patients in the placebo group needed more transfusions and had more clot retention.

VEGF and MVD have been independently evaluated in terms of mechanisms related to decreased bleeding in patients treated with finasteride. Pareek et al. [17] evaluated VEGF expression and suburethral prostatic MVD in patients with BPH treated with finasteride. The study included 24 patients undergoing surgery for BPH, of whom 12 patients received finasteride for a minimum of 6 weeks before surgery and the remaining 12 patients served as controls. Sections from the prostatic urothelium and hypertrophic prostate were individually stained for CD34 specific for nascent blood vessels and VEGF. Analysis of each specimen was performed in a blinded fashion. MVD was calculated by counting the number of positively stained blood vessels on 10 consecutive, nonoverlapping, high-power fields within the suburethral and hypertrophic prostate compartments. VEGF expression was examined by immunohistochemistry. Prostatic suburethral VEGF expression and MVD were significantly lower in the finasteride group than in the control group ($P < 0.05$). Differences in VEGF expression and MVD at the level of the hypertrophic prostate were not significantly different between the two groups. Therefore, decreased expression of VEGF with finasteride inhibits angiogenesis and significantly decreases MVD in prostatic suburethral tissue. This sequential relationship provides histochemical insight into mechanisms by which finasteride reduces prostatic urethral bleeding.

Donohue et al. [18••] measured the expression of VEGF and MVD in prostate glands after TURP following 2 weeks of treatment with finasteride. Sixty-four men scheduled to undergo TURP were randomly allocated to receive 5 mg of finasteride or placebo daily for 2 weeks before surgery. Sections of prostatic urothelium were stained for VEGF expression and for CD34 to assess MVD. Ten consecutive, nonoverlapping, high-power fields were analyzed in a blinded fashion. In all, 31 men received finasteride and 33 received placebo; the groups were similar in patient age, resected prostate weight, preoperative catheterization, PSA level, aspirin use, spinal anesthesia, and postoperative diagnosis of prostate cancer. A mean (95% CI) MVD of 60 (range, 55–65; $P < 0.01$) was significantly lower in the finasteride group than the MVD of 71 (range, 64–78; $P < 0.01$) in the placebo group. Similarly, the mean VEGF expression was significantly lower in the finasteride group (47; range, 43–52; $P < 0.01$) than in the placebo group (61; range, 54–67; $P < 0.01$). Therefore, finasteride inhibits angiogenic growth factors, leading to reduced vascularity, which is the basis of its action in reducing hematuria of prostatic origin.

Conclusions

Our study used VEGF and CD34 antibodies, starting from preclinical study in rats [19••], to determine microvessel density in patients with BPH. We pretreated half of the patients ($n = 200$) with 5 mg of finasteride twice a day for 8 weeks, intending to demonstrate a correlation between finasteride action and the vascularization of hypertrophic prostate tissue [20]. We clearly demonstrated that VEGF and CD34 values were firmly lower in patients pretreated with finasteride than placebo; therefore, a correlation exists. We used a higher 5ARI dose (10 mg vs 5 mg) for a longer period (8 weeks vs 4 weeks) than other studies. The 10 mg/d dosage (5 mg twice a day) was well tolerated by all patients; in fact, we did not observe any adverse effects.

Our results suggest that 10 mg of finasteride for 8 weeks reduces intraoperative TURP bleeding, as demonstrated by MVD reduction in hypertrophic prostatic tissue [21].

Disclosures

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Foley CL, Bott SR, Shergill IS, Kirby RS: **An update on the use of 5-alpha-reductase inhibitors.** *Drugs Today* 2004, **40:**213.
2. Delakas D, Lianos E, Karyotis I, Cranidis A: **Finasteride: a long-term follow-up in the treatment of recurrent hematuria associated with benign prostatic hyperplasia.** *Urol Int* 2001, **67:**69–72.
3.•• Hahn RG, Fagerstrom T, Tammela TLJ, et al.: **Blood loss and postoperative complications associated with TURP after pretreatment with dutasteride.** *BJU Int* 2007, **99:**587–594.

A discussion of dutasteride's efficacy in complications after TURP.

4.• Özdal ÖL, Özden C, Benli K, et al.: **Effect of short-term finasteride therapy on preoperative bleeding in patients who were candidates for transurethral resection of the prostate (TUR-P): a randomized controlled study.** *Prostate Cancer Prostatic Dis* 2005, **8:**215–218.

A report on finasteride's efficacy in TURP bleeding.

5. Sandfeldt L, Bailey DM, Hahn RG: **Blood loss during transurethral resection of the prostate after 3 months of treatment with finasteride.** *Urology* 2001, **58:**972–976.
6. Ekengren J, Hahn RG: **Blood loss during transurethral resection of the prostate as measured with the HemoCue photometer.** *Scand J Urol Nephrol* 1993, **27:**501–503.
7. Toi M, Hoshina S, Takayanagi T, Tominaga T: **Association of vascular endothelial growth factor expression with tumor angiogenesis and with early relapse in primary breast cancer.** *Cancer Science* 1994, **85:**1045–1049.
8. Lekas E, Bergh A, Damber JE: **Effects of finasteride and bicalutamide on prostatic blood flow in the rat.** *BJU Int* 2000, **85:**962–965.
9. Marshall S, Narayan P: **Treatment of prostatic bleeding: suppression of angiogenesis by androgen deprivation.** *J Urol* 1993, **149:**1553–1554.
10. Carlin BI, Bodner DR, Spirnak JP, Resnick MI: **Role of finasteride in the treatment of recurrent hematuria secondary to benign prostatic hyperplasia.** *Prostate* 1997, **31:**180–182.
11. Miller MI, Puchner PJ: **Effects of finasteride on hematuria associated with benign prostatic hyperplasia: long-term follow-up.** *Urology* 1998, **51:**237–240.

12.•• Lund L, Möller Ernst-Jensen K, Torring N, Erik Nielsen J: **Impact of finasteride treatment on perioperative bleeding before transurethral resection of the prostate: a prospective randomized study.** *Scand J Urol Nephrol* 2005, **39:**160–162.
This prospective randomized study is numerically important.
13. Donohue JF, Sharma H, Abraham R, et al.: **Transurethral prostate resection and bleeding: a randomized, placebo controlled trial of the role of finasteride for decreasing operative blood loss.** *J Urol* 2002, **168:**2024–2026.
14.• Boccon-Gibod L, Valton M, Ibrahim H, et al.: **Effect of dutasteride on reduction of intraoperative bleeding related to transurethral resection of the prostate** [in French]**.** *Prog Urol* 2005, **15:**1085–1089.
A study showing dutasteride's efficacy in TURP bleeding.
15. Crea G, Sanfilippo G, Anastasi G, et al.: **Presurgical finasteride therapy in patients treated endoscopically for benign prostatic hyperplasia.** *Urol Int* 2005, **74:**51–53.
16. Hagerty JA, Ginsberg PC, Harmon JD, Harkaway RC: **Pretreatment with finasteride decreases perioperative bleeding associated with transurethral resection of the prostate.** *Urology* 2000, **55:**684–689.
17. Pareek G, Shevchuk M, Armenakas NA, et al.: **The effect of finasteride on the expression of vascular endothelial growth factor and microvessel density: a possible mechanism for decreased prostatic bleeding in treated patients.** *J Urol* 2003, **169:**20–23.
18.•• Donohue JF, Hayne D, Karnik U, et al.: **Randomized, placebo-controlled trial showing that finasteride reduces prostatic vascularity rapidly within 2 weeks.** *BJU Int* 2005, **96:**1319–1322.
This study proves that finasteride reduces prostatic vascularity in 2 weeks.
19.•• Canda AE, Mungan MU, Yilmaz O, et al.: **Effects of finasteride on vascular surface density, number of microvessels and vascular endothelial growth factor expression of the rat prostate.** *Int Urol Nephrol* 2006, **38:**275–280.
Basic research shows finasteride's action on microvascular density and VEGF expression.
20. Haggstrom S, Torring N, Moller K, et al.: **Effects of finasteride on vascular endothelial growth factor.** *Scand J Urol Nephrol* 2002, **36:**182–187.
21. Foley SJ, Bailey DM: **Microvessel density in prostatic hyperplasia.** *BJU Int* 2000, **85:**70–73.