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Original Article

The Effect of Two Weeks of Treatment with Dutasteride on Bleeding after Transurethral Resection of the Prostate

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Purpose: Dutasteride affects the prostate by reducing intraprostatic dihydrotestosterone and prostate tissue vascularity. We evaluated the effect of pretreatment with dutasteride for two weeks on perioperative and postoperative bleeding during transurethral resection of the prostate (TURP).

Materials and Methods: Eighty-three patients who had benign prostatic hyperplasia together with the criteria for eligibility for TURP were included. The dutasteride group consisted of 40 patients who were treated with dutasteride (0.5 mg/d) for two weeks before surgery, and the control group consisted of 43 patients who did not receive dutasteride. Blood loss was evaluated in terms of reduction in serum hemoglobin (Hb) and hematocrit (Hct) levels, which were measured before, immediately after, and 24 hours after surgery. We also measured the durations of indwelling urethral catheter use, continuous saline bladder irrigation, and hospitalization.

Results: Lower mean blood loss was observed in the dutasteride group than the control group immediately after and 24 hours after surgery (ΔHb=0.65±1.27 g/dL vs. 1.16±0.73 g/dL, 1.30±1.00 g/dL vs. 1.86±1.05 g/dL respectively, p=0.019, p=0.011; ΔHct=1.89%±3.83% vs. 3.47%±2.09%, 3.69%±2.95% vs. 5.39%±3.23% respectively, p=0.016, p=0.011). In addition, there were fewer days of indwelling urethral catheter use (2.95 ±1.02 d vs. 3.92 ±1.14 d, p=0.000), continuous saline bladder irrigation (1.81 ±1.08 d vs. 2.36 ±1.06 d, p=0.016), and hospitalization after TURP (3.95 ±1.09 d vs. 4.76 ±1.19 d, p=0.001) in the dutasteride group.

Conclusions: Preoperative treatment with dutasteride for two weeks before TURP reduces surgical bleeding and length of hospitalization after TURP. This pretreatment can be used to decrease surgical bleeding associated with TURP.

Key Words: Dutasteride; Prostatic hyperplasia; Transurethral resection of prostate

INTRODUCTION

Patients with benign prostatic hyperplasia (BPH) who do not respond to medical treatment often undergo transurethral resection of the prostate (TURP), the gold standard for surgical treatment [1]. The safety and efficacy of TURP have been proven and validated [2]. However, it can result in perioperative bleeding, urinary incon-

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tinence, retrograde ejaculation, transurethral resection (TUR) syndrome, and erectile dysfunction [3]. These complications undoubtedly increase the suffering of patients.

The histologic diagnosis of BPH is based on the observation of proliferation of smooth muscle and epithelial cells in the transition zone. Dihydrotestosterone (DHT) is the primary androgen responsible for this proliferation in elderly men [4]. It is synthesized from testosterone by type 1 and type 2 5-α-reductases (5-AR), which are isoenzymes active in the prostate. The dual 5-α-reductase inhibitor (5-ARI), dutasteride, as well as α-adrenergic blocking agents (alpha blockers), are both approved for the treatment of BPH. Five-ARIs inhibit 5-AR and reduce the volume of the prostate over a period of six months, and thus can prevent complications of BPH such as acute urinary retention and the need for surgical treatment, and improve quality of life (QoL) by preventing voiding difficulties. Five -ARI treatment also decreases the expression of vascular endothelial growth factor (VEGF), reduces microvessel density in prostatic suburethral tissue, and inhibits angiogenesis [5]. There have been several studies of the effect of dutasteride on prostate vascularity. Zaitsu et al [6] showed that artery/arteriole and vein/venule density and area were reduced, and others reported that dutasteride treatment for six weeks before TURP reduced blood loss [7,8]. A change in vascularity was also observed by Doppler sonography [5]. However, taking dutasteride for short duration reduced vascularity as observed by Doppler transrectal prostatic ultrasonography [9]. In this study, we investigated whether pretreatment with dutasteride for two weeks before TURP reduced perioperative and postoperative bleeding and/or improved postoperative care.

MATERIALS AND METHODS

Patients who underwent TURP for symptomatic BPH between January 2008 and December 2012 were enrolled in the study. All patients whose voiding symptoms did not improve after two months of treatment with an alpha blocker (tamsulosin) underwent TURP. Subjects were excluded if they had renal failure, a history of using finasteride or dutasteride, pathologic findings after TURP other than BPH, previous invasive procedures of the prostate, urinary tract infection, bladder stones, urinary retention, a prostate volume of <30 mL, an age <55 years, or were using aspirin or antiplatelet or non-steroidal anti-inflammatory drugs.

Nine patients (four in group 1 and five in group 2) had high prostate-specific antigen (PSA) levels (>4). TRUS (transrectal ultrasonography) biopsies were carried out before TURP, and none of these patients had tumors.

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Hanyang University Hospital (GURI 2014-05-002-001). Transrectal prostatic ultrasonography was performed to evaluate prostate volume within 2 to 3 months before surgery. A routine hematologic analysis, including PSA, prothrombin time (PT), activated partial thromboplastin time (aPTT), bleeding time (BT), and international normalized ratio (INR) was also performed. Resected prostate volume was measured after surgery.

Eighty-three patients who were scheduled to undergo TURP were enrolled and divided into two groups. Forty patients (group 1) received dutasteride for two weeks before surgery and 43 patients (group 2) served as controls (Table 1).

TURP was performed under general anesthesia with a Storz continuous flow 26 Fr. resectoscope. One surgeon with 11 years of experience performed all the operations. Normal saline (0.9%) was used for irrigation during the surgery, whichz was performed with an Olympus Gyrus ACMI G400 ESU (Olympus, Tokyo, Japan). The prostate was resected between the bladder neck and the verumontanum, and between the middle lobe and the two side lobes that protrude into the bladder. The depth of resection extended as far as the prostatic capsule. Hemoglobin (Hb) and hematocrit (Hct) were checked one hour after the surgery and during the first postoperative days.

Postoperative care was carried out via an indwelling 18 Fr. Foley three-way catheter with a 30 mL urethral catheter balloon and continuous 0.9% normal saline bladder irrigation until the hematuria disappeared. The catheters were removed and the patients were discharged if they could void with clear urine when checked. We also investigated the length of hospitalization and the number of days of continuous bladder irrigation with normal saline and with an indwelling Foley catheter.

The results are presented as arithmetic means $\pm$ stand-

ard deviations. The Student's t-test was used to compare categorical variables. We used PASW Statistics for Windows, version 18.0 (IBM Co., Armonk, NY, USA) for statistical analysis, and a p value of <0.05 was considered statistically significant.

RESULTS

None of the patients in this study suffered side effects due to dutasteride. There were no significant differences in age, prostate volume, resected prostate volume, and PSA between the two groups. In addition, no postoperative side effects occurred, such as TUR syndrome, acute urinary retention due to blood clot, transfusion due to massive bleeding, etc. The two groups had similar PT, aPTT, BT, and INR when checked the day before surgery (Table 1). The mean operation time was almost two hours, and all the patients had continuous bladder irrigation im-

Table 1. Characteristics of the two study groups

Variable	Total	Dutasteride group (n=40)	Control group (n=43)	p value[a]
Age (yr)	71.98±6.40	71.16±6.53	72.16±6.33	0.47
PSA (ng/mL)	6.51±17.14	6.47±8.96	6.07±21.27	0.91
Prostate volume (g)	60.32±33.32	61.01±29.52	59.18±35.09	0.79
Hb (before TURP)	13.86±1.53	13.84±1.57	13.88±1.57	0.89
Hct (before TURP)	40.71±4.62	40.59±4.47	40.83±4.84	0.81
PT (s)	11.40±0.99	11.35±1.00	11.42±1.00	0.76
Bleeding time (s)	119.88±4.56	119.77±6.36	117.68±16.41	0.44
INR	0.93±0.08	0.92±0.81	0.94±0.73	0.46
aPTT (s)	30.92±3.76	30.60±4.26	31.26±3.06	0.39
IPSS	21.04±7.69	21.88±7.30	20.26±8.04	0.34
QoL	3.67±1.01	3.83±0.84	3.53±1.14	0.19
Qmax (mL/s)	7.04±4.91	6.73±4.97	7.34±4.92	0.57
Residual urine (mL)	73.60±59.33	84.15±61.86	63.79±55.78	0.12

Values are presented as mean±standard deviation.
PSA: prostate speciantigen, Hb: hemoglobin, Hct: hematocrit, TURP: transurethral resection of prostate, PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin time, IPSS: international prostate symptom score, QoL: quality of life, Qmax: maximum urinary flow rate.
[a]Student's t-test ($p<0.05$).

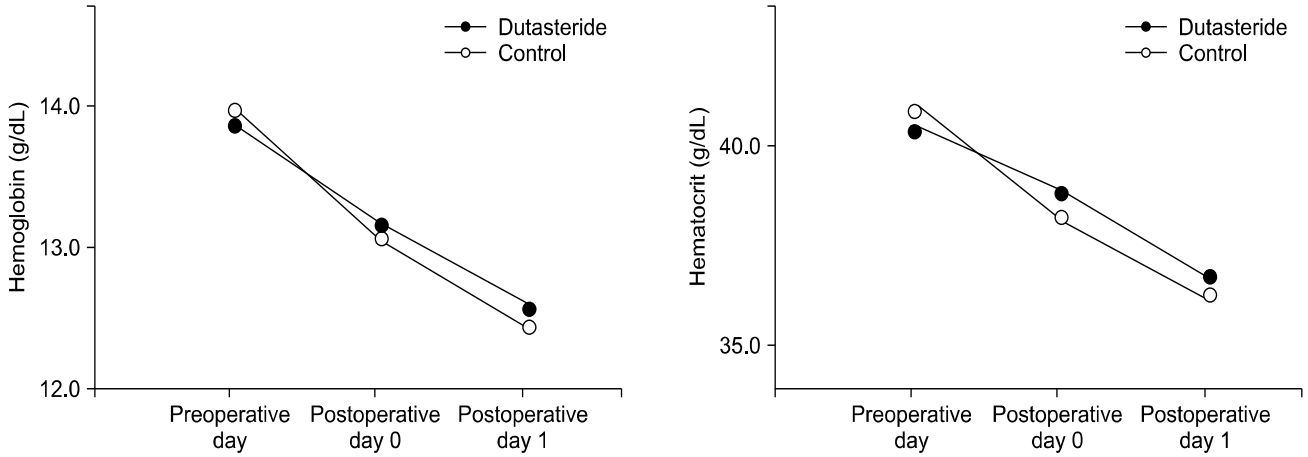

Fig. 1. Mean (standard deviation) hemoglobin and hematocrit levels over the peri-operative period in men taking dutasteride before transurethral resection of the prostate vs. controls. Changes in hemoglobin and hematocrit were statistically significant.

mediately after TURP.

Hb and Hct levels are shown in Fig. 1. After the two-week treatment period the dutasteride group had higher levels of both Hb and Hct than the controls ($p<0.05$).

Hb and Hct declined less in group 1 (dutasteride) than in group 2 (controls) immediately after surgery (⊿Hb 0.65±1.27 g/dL vs. 1.16±0.73 g/dL, respectively, $p=0.019$; ⊿Hct 1.89%±3.83% vs. 3.47%±2.09%, respectively, $p=0.016$) as well as one day later (⊿Hb 1.30±0.99 g/dL vs. 3.69±2.95 g/dL, respectively, $p=0.011$; ⊿Hct 3.69%±2.95% vs. 5.39%±3.23%, respectively, $p=0.011$; Table 2). The mean hospital stay was shorter in group 1, as were the durations of indwelling urethral Foley catheters and continuous saline bladder irrigation (2.95±1.02 d vs. 3.92±1.14 d, $p=0.000$, 1.81 d±1.06 d vs. 2.36 d±1.06 d, $p=0.016$, respectively).

Both groups had improved maximum urinary flow rate, volume of residual urine, International Prostate Symptom Score, and QoL.

DISCUSSION

TURP has long been the gold standard for surgical treatment of symptomatic BPH. Bleeding is the most common complication during TURP and in the postoperative period. Sometimes uncontrolled bleeding makes voiding difficult due to acute urinary retention of blood clots.

BPH is characterized by increased proliferation of stromal and acinar cells around the urethra, prolonged by increased gland angiogenesis. The increased vascularity can result in massive bleeding during and after TURP. Finasteride, a BPH medication, is a 5-ARI. It inhibits the conversion of testosterone to DHT and the resulting activation of androgen-controlled growth factor, which stimulates angiogenesis. Preoperative finasteride treatment has been reported to reduce this bleeding [10,11]. It reduced the expression of VEGF and lowered the suburethral microvessel density of the prostate [12].

Boccon-Gibod et al [13] examined whether dutasteride could be used to reduce bleeding after TURP in the same way as finasteride, and others have shown that it decreased artery/arteriole and vein/venule densities, and the extent of the vein/venule area of the prostate in BPH [6]. However, Hahn et al [8] found that a 2 to 4 week pretreatment with dutasteride did not significantly reduce blood loss in TURP, and others have reported similar findings and have recommended that dutasteride be taken for a longer duration [14].

Martov and Ergakov [15] found a significant reduction in blood loss when dutasteride was taken for over a month before surgery and Kravchick et al [5] found that the vascu-

Table 2. Results of the two study groups

Variable	Dutasteride group (n=40)	Control group (n=43)	p value[a]
⊿Hb (after TURP)	0.65±1.27	1.16±0.73	0.02
⊿Hct (after TURP)	1.89±3.83	3.47±2.09	0.02
⊿Hb (POD 1)	1.30±0.99	1.86±1.05	0.01
⊿Hct (POD 1)	3.69±2.95	5.39±3.23	0.01
Operative time (min)	116.56±27.52	119.74±29.51	0.11
Resected prostate volume (g)	24.9±16.78	23.80±14.20	0.74
Hospital days (d)	3.95±1.09	4.76±1.19	0.01
Continuous bladder irrigation (d)	1.81±1.08	2.36±1.06	0.02
Time of indwelling catheter (d)	2.95±1.02	3.92±1.14	0.01
IPSS (after TURP)	9.13±4.70	9.37±5.50	0.83
QoL (after TURP)	1.78±0.89	1.91±1.15	0.56
Qmax (after TURP)	17.65±6.53	16.09±8.91	0.37
Residual urine (after TURP)	18.08±15.49	11.49±24.67	0.15

Values are presented as mean±standard deviation.
⊿Hb: delta hemoglobin, TURP: transurethral resection of prostate, ⊿Hct: delta hematocrit, POD: postoperative day, IPSS: international prostate symptom score, QoL: quality of life, Qmax: maximum urinary flow rate.
[a]Student's t-test ($p<0.05$).

larity of the prostate, especially in the periurethral area, was reduced after taking dutasteride for six weeks. Pastore et al [16] observed that pretreatment with dutasteride for six weeks before TURP reduced surgical bleeding, prostate volume, and the weight of the resected prostate. Another study found that after taking dutasteride for only seven days, blood flow to the prostate was reduced as observed by Doppler transrectal prostatic ultrasonography, indicating that vascularity was changed during the short treatment time [9]. Woo et al [17] observed that dutasteride treatment for two weeks before TURP reduced microvessel density in the suburethral region.

In the present study, perioperative and postoperative bleeding were significantly reduced in the group taking dutasteride for 2 weeks before TURP. There were no significant effects on prostate volumes or resected prostate volumes. We analyzed the level of coagulation factors before TURP to assess the effect of dutasteride on bleeding control. Statistically meaningful differences were not detected between the two groups in PT, aPTT, INR, and bleeding time, and, based on these results, dutasteride may only affect vascularity-related bleeding during TURP.

Postoperative care of TURP involves continuous bladder irrigation and maintenance of a urethral Foley catheter until hematuria ceases. In this study, we examined the duration of continuous bladder irrigation, indwelling urethral Foley catheter use, and hospitalization after TURP, all three of which were lower in group 1 (dutasteride). We conclude that taking dutasteride before surgery is sufficient to reduce prostate tissue vascularity. Changes in Hb and Hct were also lower in group 1 than in group 2, demonstrating that preoperative dutasteride prevents TURP-related blood loss. Short-term dutasteride preceding scheduled TURP may also be suitable for patients taking aspirin or antiplatelet therapy.

Many other surgical treatments are being developed for BPH, but TURP is the gold standard treatment. However, morbidity and blood loss are major potential complications, and taking dutasteride before TURP could be effective in reducing these complications.

Several limitations of this study should be acknowledged. A longer period of taking dutasteride should be compared with short-term treatment in terms of effects on vascularity. In addition, a prospective study should be carried out with a large number of enrolled patients to ensure the collection of meaningful data.

CONCLUSIONS

Preoperative treatment with dutasteride for two weeks before TURP reduces surgical bleeding and hospitalization days after TURP. This pretreatment can be used to decrease surgical bleeding associated with TURP, although a prospective study is needed to confirm this conclusion.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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