Does Preoperative Use of Dutasteride Decrease Bleeding During Open Prostatectomy?

Arif Demirbas[1]*, Berkan Resorlu[1], Murat Tolga Gulpinar[2], Sina Kardas[3], Omer Gokhan Doluoglu[1], ,Abdulkadir Tepeler[3], Muhammet Fatih Kilinc[1], Tolga Karakan[1], Serkan Ozcan[1]

Purpose: To investigate whether use of dutasteride, a 5-alpha reductase inhibitor, for at least four weeks preoperatively affected the blood loss during open prostatectomy (OP).

Materials and methods: Retrospective analysis was made of the data of 110 patients who had undergone OP. Group I comprised 50 patients that used dutasteride for 4 weeks preoperatively, and Group II comprised 60 patients that did not use the drug. The groups were compared in respect of age, total prostate specific antigen (TPSA) levels, prostate volumes, preoperative hemoglobin (Hgb) and hematocrit (Hct) levels, postoperative reduction of Hgb and Hct, percentage reduction in Hgb and Hct, and the administration of postoperative blood products.

Results: No differences were determined between the two groups in respect of prostate volumes, TPSA, preoperative Hgb and Hct levels (P = .813, P = .978, P = .422, P =.183, respectively). Postoperative Hgb reduction was 2.19 ± 1.36 g/dL in Group I, and 2.5 ± 1.47 g/dL in Group II (P = .260). Hgb reduction was calculated as 16.4 ± 9.7% in Group I and 17.6 ± 9.7% in Group II (P = .505). Reductions in Hct were 5.8 ± 3.7% in Group I, and 7.3 ± 4.4% in Group II, and percent reductions were 14.8 ± 9.4% in Group I and 17.3 ± 10.2% in Group II (P = .068, P = .182, respectively).

Conclusion: The use of dutasteride before OP did not affect blood loss during surgery, therefore surgery should not be delayed for the administration of dutasteride to patients.

Keywords: prostate; open prostatectomy; dutasteride; bleeding

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a histopathological condition that causes lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO) in elderly males. Although BPH is evident histologically in most males aged > 40 years, it does not always cause symptoms or BOO[1-4]. The etiology of BPH consists of an increase of glandular-epithelial and stromal cells, and a decrease in apoptosis resulting from various factors, including androgens[4].

Dihydrotestosterone (DHT) is the main androgen of prostate. It is produced in the prostate from free testosterone by 5-alpha reductase (5aR) enzyme, and free testosterone is taken into the prostate cells through diffusion from plasma. 5aR has two isoforms, and type 2-5aR is the major one found in the prostate[1]. Finasteride inhibits only type 2-5aR, but dutasteride inhibits both type 1 and type 2-5aR, and the guidelines of the European Association of Urology have recommended it for patients with a prostate volume of > 40 ml and moderate or severe LUTS, with an evidence level of 1b[5].

Transurethral prostatectomy (TUR-P) is the gold standard treatment method for patients with a prostate volume of 30-80 milliliters (ml), when there are concomitant conditions of benign prostatic obstruction (BPO) requiring surgery, such as significant LUTS unresponsive to medical treatment, recurrent urine retention and urinary infection, persistent hematuria, renal dysfunction due to BOO and similar upper urinary tract alterations, and bladder stones secondary to obstruction. In cases of prostate volume >75-80 ml, the recommended surgical options are open prostatectomy (OP), and holmium laser enucleation of prostatectomy (HOLEP). OP is the most invasive treatment method of BPO. Even though OP may be thought to be rarely performed nowadays, in developing countries it is still a frequently applied operation (14%-40%), even for prostates <80mL in volume[5,6,7].

There are a number of studies that have investigated dutasteride, a type 1 and type 2 5aR inhibitor causing reduction in prostate vascularity and volume, and its effect on bleeding during surgery when used in the preoperative period, particularly before TUR-P procedure. In this study, an investigation was made of the use of dutasteride before OP, and its effect on bleeding during surgery.

METHODS

After obtaining Institutional Review Board approval for the study, the data of the patients with BOO due to BPH, and had OP because of prostate volume in three centers in Turkey between 2013 and 2014 were analyzed retrospectively. Use of preoperative dutasteride was searched for in the hospital records, and confirmed

[1]Department of Urology, Ankara Training and Research Hospital, Ankara, Turkey.

[2]Department of Urology, Çanakkale 18 Mart University, Canakkale, Turkey.

[3]Department of Urology, Bezmialem University, Istanbul, Turkey.

*Correspondence: Ankara Training and Research Hospital, Ankara, Turkey.

Phone: +905322500072

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Table 1. The descriptive characteristics of the patients that had open prostatectomy due to BPH.

	Group I (n=50)	Group II (n=60)	*p*-value
Mean age	74.64 ± 5.25	65.48 ± 7.27	< 0.001
Prostate volume (mL)	129.22 ± 40.40	127.51 ± 34.86	0.813
Total PSA (ng/dL)	8.1 ± 6	8.14 ± 6.78	0.978
Preoperative Hgb (g/dL)	13.25 ± 1.8	13.91 ± 1.5	0.422
Preoperative Hct (%)	39.4 ± 5.2	41.66 ± 4.5	0.183

by examining the patients' records in the National Pharmacy Database. Group I comprised 50 patients administered with dutasteride for at least 4 weeks preoperatively. Group II comprised 60 patients with no dutasteride use. For each patient, a record was made of age, total prostate specific antigen (TPSA) levels, prostate volumes measured transrectally, pre- and postoperative hemoglobin (Hgb) and hematocrit (Hct) levels, postoperative transfusion of blood products, and the histopathological results of the OP specimens. Patients with serum TPSA levels > 4 ng/ml had transrectal ultrasonography guided (TRUSG) prostate biopsies, and a benign result was obtained (31 in Group I, 33 in Group II). OP was applied directly, without any biopsies, to 10 patients between the ages of 78 and 86 years, taking the 10-year life expectancy into consideration. It was noted that all OP specimens were reported as benign. Postoperative Hgb and Hct levels were obtained from peripheral blood samples collected within 2 hours after surgery, in all three clinics. Preoperative Hgb and Hct levels were obtained from the complete blood counts ordered preoperatively, when consulting the patient to the anesthesiologist. OP was performed using a suprapubic prostatectomy approach (Freyer procedure) in all three clinics, and none of the patients had a retropubic prostatectomy procedure. No antiaggregants or anticoagulants were used on any patient during the surgical procedure, or within 1 week preoperatively.

The patients in Groups I and II were compared in respect of age, TPSA levels, prostate volumes, the difference between preoperative and postoperative Hgb and Hct levels (reduction of Hgb and Hct) used to determine bleeding, the ratio of reduction in Hgb and Hct to preoperative Hgb and Hct (reduction percentage), and postoperative transfusion of blood products. In addition, the correlation between age and bleeding parameters was investigated, independently of the other parameters.

Statistical analysis

The data analysis was performed using SPSS for Windows, version 11.5 software (SPSS Inc., Chicago, IL, United States). The normality of the distribution of data was tested with P-P plot and Kolmogorov-Smirnov tests. All data were determined to conform to normal distribution. Descriptive statistics were shown as mean ± standard deviation for the variables with normal distribution. The Student's-t test was used for the intergroup analysis of continuous variables. Data were analyzed with ANCOVA, corrected for age and bleeding parameters. A value of $P < .05$ was considered statistically significant.

RESULTS

The mean age of the patients was 74.64 ± 5.25 years in Group I and 65.48 ± 7.27 years in Group II ($P < .001$). The mean preoperative prostate volume as measured with TRUSG was 129.22 ± 40.40 mL in Group I, and 127.51 ± 34.86 mL in Group II. The difference between the two groups was not significant ($P = .813$) (**Table 1**). The mean TPSA levels were 8.1 ± 6 ng/dL and 8.14 ± 6.78 ng/dL in Groups I and II, respectively ($P = .978$) (**Table 1**). Preoperative Hgb was 13.25 ± 1.8 g/dL and Hct was 39.4 ± 5.2% in Group I, and those values were 13.91 ± 1.5 g/dL and 41.66 ± 4.5%, respectively in Group II. No significant difference was seen between the groups in respect of Hgb and Hct levels ($P = .422$ and $P = .183$, respectively) (**Table 1**). Postoperative Hgb was 11.05 ± 1.8 g/dL and Hct was 33.52 ± 5.5% in Group I, and those levels were 11.41 ± 1.5 g/dl and 34.31 ± 4.9%, respectively in Group II.

Analysis of the parameters used to determine the amount of bleeding during surgery showed Hgb reduction of 2.19 ± 1.36 g/dL in Group I and 2.5 ± 1.47 g/dL in Group II, with no significant difference between the groups ($P = .260$) (**Table 2**). Hct reduction was 5.8 ± 3.7% in Group I, and 7.3 ± 4.4% in Group II ($P = .068$). No significant differences were determined between the groups in respect of Hgb and Hct reduction ($P = .505$, $P = .182$, respectively) (**Table 2**).

The correlation between age and Hgb and Hct reduction percentages were analyzed with SPSS-ANCOVA test since there was a statistically significant difference between the groups for age ($P < .001$). Age was not correlated with Hgb reduction ($P = .599$) or Hct reduction ($P = .309$) or with Hgb reduction percentage ($P = .757$) or Hct reduction percentage ($P = .627$). Thus, no correlation was found between age and the parameters indicating bleeding amount during surgery.

Postoperative transfusion of blood products was necessary in 11 (10%) of 110 patients that had OP. Each patient was administered 1 unit of erythrocyte suspension (ES). The distribution of the 11 patients that had ES transfusion was equal in Groups I and II [5 patients (10%) in group I, and 6 patients (10%) in Group II].

DISCUSSION

Benign prostatic hyperplasia (BPH) is a frequently seen histopathological condition in males, and epidemiolog-

Table 2. The parameters measured to determine the amount of blood loss in the groups.

	Group I (n=50)	Group II (n=60)	*p*-value
Hgb reduction (g/dL)	2.19 ± 1.36	2.5 ± 1.47	0.260
Hct reduction (%)	5.8 ± 3.7	7.3 ± 4.4	0.068
Hgb reduction percentage	16.4 ± 9.7	17.6 ± 9.7	0.505
Hct reduction percentage	14.8 ± 9.4	17.3 ± 10.2	0.182

ical studies have reported that its prevalence increases with aging. It is histopathologically evident in 50% of cases at 50 years of age, and in 88% of cases after the age of 80 years. Autopsy studies have shown that the increasing prevalence was not associated with race or geographic characteristics, but only with age [8-10]. Other than the histopathological changes, the main problem is enlargement of the prostate, which has been specified as the natural course of the disease, resulting in BOO and related to a decrease in urine flow rate, and decreased quality of life [11,12].

BOO related to BPH needs treatment after the development of complications. OP is a safe treatment option when non-invasive or minimally invasive and endoscopic treatment options are not suitable due to the volume of the prostate[13-15]. Although the OP procedure has low morbidity and mortality, perioperative bleeding and urinary retention that develop due to clots in the early postoperative period are important problems [13,16].

There have been some randomized, controlled studies and a meta-analysis on bleeding during TUR-P and type 1 and type 2 5aR inhibitors that were supposed to decrease this bleeding, but there have been few studies on OP, which is a more invasive procedure[17].

The hypothesis that the use of 5aR inhibitors before TUR-P could cause less bleeding is based on histopathological studies showing interaction of DHT with some factors such as vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), and transforming growth factor (TGF-beta), and decrease of arterial and venous microvessels in prostate tissue in patients who have been administered those agents[4,18,19]. Some other studies have claimed the opposite, and reported that the use of dutasteride did not result in any difference in prostatic microvessel density when compared with the control groups[20, 21].

Pastore et al.[22] performed a randomized controlled study on 142 patients that had TUR-P, and reported that dutasteride use for 6 weeks decreased bleeding significantly. The authors found Hgb reduction to be 1.29 ± 0.81 g/dL in the dutasteride group and 1.83 ± 1.25 g/dL in the control group ($p < .0027$), Hct reduction was determined as 5.67 ± 2.58% in the dutasteride group, and 6.50 ± 2.40% in the control group ($P = .0491$). In 2015, a study from Korea conducted on 83 patients reported similar findings, and Hgb reduction was found to be 0.65 ± 1.27 g/dL in the dutasteride group despite use of the drug for 2 weeks, and Hgb reduction was found to be 1.16 ± 0.73 g/dL in the control group ($P = .019$). In the same study, Hct reduction was 1.89 ± 3.83% in the dutasteride group, and 3.47 ± 2.09% in the control group ($P = .016$). The authors recommended preoperative use of dutasteride for 2 weeks before TUR-P to decrease bleeding. The authors also reported that the duration of urethral catheter and hospital stay were shorter due to less bleeding in patients that used dutasteride[23].

In 2007, Hahn et al.[20] conducted a randomized, controlled study on 213 patients from 6 countries scheduled for TUR-P. Use of dusteride preoperatively for 28-32 days resulted in 88% reduction in DHT compared to the placebo group, although the groups did not show any significant differences in respect of the amount of Hgb determined in the irrigation fluid, clot retention, need for transfusion, or development of acute urinary retention. In a meta-analysis of all randomized controlled studies performed before 2015, the effect of 5aR inhibitors on bleeding during TUR-P was analysed, and no difference was found between the dutasteride and control groups in respect of calculated blood loss, Hgb reduction, removed tissue weight, prostate volume, need for transfusion, or duration of surgery[17]. Only one study performed on a small number of patients reported less bleeding in relation to the removed tissue/grams in the dutasteride group[24].

To date, only one study has investigated the use of dutasteride before OP. That retrospective study was performed in 2015, included a total of 218 patients, 46 of whom used dutasteride. The effect of dutasteride was investigated by taking only Hgb reduction into consideration. The patients were administered dutasteride preoperatively for 6 weeks, and the difference between the study and the control groups for Hgb reduction was found to be significant (2.72 g/dL vs. 1.93 g/dL, $P = .01$). However, there was a significant difference between the preoperative Hgb levels of the groups ($P = .002$). In addition, the Hct value that shows the ratio of total erythrocyte volume to total blood volume was not taken into consideration when comparing the blood loss between the groups[25].

The descriptive statistics of the current study groups are presented in **Table 1**. Taking those data into consideration, prostate volume ($P = .813$), TPSA ($P = .978$), preoperative Hgb ($P = .422$), and preoperative Hct ($P = .183$) were similar in both groups, but there was a significant difference between Group I and Group II for age ($P < .001$). However, the 'SPSS-ANCOVA' test was applied to analyze the hypothesis that age could have an effect on bleeding. It was determined that age and Hgb reduction, Hct reduction, and Hgb and Hct reduction percentages were not correlated, independently of the other parameters ($P = .599$, $P = .309$, $P = .757$, $P = .627$, respectively).

Hemoglobin reduction, Hct reduction, and Hgb and Hct reduction percentages that show a proportional decrease postoperatively compared to the preoperative levels, were used as the parameters to determine blood loss during OP in the current study, and these were compared between the two groups (**Table 2**). No significant differences were determined between the dutasteride and control groups in respect of those four parameters ($P = .260$, $P = .068$, $P = .505$, $P = .182$, respectively) (**Table 2**). There was a need for blood transfusion after the surgical procedure in 11 (10%) patients, and each patient was transfused 1 unit erythrocyte suspension. Of those patients 5 (10%) were in the dutasteride group, and 6 (10%) were in the control group. There was no significant difference between the groups.

Limitations of this study are that it was retrospective in nature and different surgeons performed the surgical procedures. However, as there are only a few studies in literature, that more parameters were examined in this study, and comparisons were made of similar groups can be considered to be the strengths of this research.

CONCLUSIONS

In conclusion, the data obtained in this study showed that the use of preoperative dutasteride by patients planned to undergo OP did not reduce the amount of bleeding caused by OP. Although there are many randomized, controlled studies and meta-analyses related to a reduced amount of bleeding with the use of

dutasteride before TUR-P, there has been no previous study on this subject related to OP. Therefore, there is a need for further studies to support the evidence-based medical requirement of the opinions determined in this study.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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