

## Impact of statin use on perioperative bleeding in patients with benign prostatic hyperplasia who underwent monopolar TURP

Benign prostat hiperplazi nedeniyle transüretal prostat rezeksiyonu uygulanan hastalarda statin kullanımının perioperatif kanamaya etkisi

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### ÖZET

**Amaç:** Transüretal prostat rezeksiyonu (TURP) uygulanan benign prostat hiperplazisi (BPH) hastalarında statin kullanımının kanama komplikasyonu üzerine etkisini değerlendirmeyi amaçladık.

**Gereç ve Yöntemler:** Bu çalışma TURP ameliyatı geçirmiş BPH hastalarını içeren prospektif bir vaka-kontrol çalışmasıdır. Çalışmaya yetmiş altı hasta dahil edildi (30 statin kullanıcısı ve 74 statin kullanmayan). Hasta yaşı, ameliyat öncesi laboratuvar değerleri (tam kan sayımı, prostat spesifik antijen (PSA) seviyeleri, prostat hacmi, uluslararası normleştirilmiş oran (INR), aktif parsiyel tromboplastin zamanı (aPTT)), intraoperatif özellikler (rezeke edilen prostat dokusu miktarı, kan transfüzyonu, ameliyat süresi, üriner kateterizasyon süresi) ve ameliyat sonrası özellikler (serum tam kan sayımı ve hastanede kalış süresi) değerlendirildi. Statin kullanan ve kullanmayan TURP yapılan hastalar hematokrit değerleri ve kanama komplikasyonları açısından karşılaştırıldı.

**Bulgular:** Hematokrit ve trombosit sayısındaki azalma düzeyi açısından gruplar arasında fark yoktu. Her iki grupta da ameliyat sonrası hematokrit ve trombosit sayıları ameliyat öncesi değerlere göre anlamlı derecede düşüktü. Gruplar arasında yaş, PSA, prostat hacmi, histopatolojik tanı, transüretal rezeksiyon (TUR) hacmi, INR, PT, aPTT, transfüze edilen kan miktarı, ameliyat süresi, irrigasyon süresi, hematokrit ve trombosit sayısı açısından anlamlı fark yoktu. Statin kullanan grupta TUR hacmi, antikoagülan kullanım sıklığı, kateterizasyon süresi ve hastanede kalış süresi istatistiksel olarak daha yüksekti.

**Sonuç:** Sonuçlarımız, TURP uygulanan BPH'lı hastalarda statin kullanımının kanamayı etkilemediğini gösterdi. Statinlerin yaygın kullanımı göz önüne alındığında, ameliyat sırasında kanama üzerindeki etkilerine ışık tutacak daha fazla çalışmaya ihtiyaç vardır.

**Anahtar Kelimeler:** benign prostat hiperplazisi, kanama, prostatın transüretal rezeksiyonu, statin

This study was approved by the Ethics Committee of Ankara Türkiye Yüksek İhtisas Training and Research Hospital (Approval Number: 30. Date: December 28, 2021). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

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## ABSTRACT

**Objective:** We aimed to evaluate the effect of statin use on bleeding complications in benign prostatic hyperplasia (BPH) patients who underwent transurethral resection of the prostate (TURP).

**Material and Methods:** This prospective case-control study included patients with benign prostatic hyperplasia (BPH) who underwent TURP surgery. Seventy-six patients were included (30 statin users and 46 statin non-users). Data including patient age, preoperative laboratory values (complete blood count, prostate-specific antigen (PSA) levels, prostate volume, international normalized ratio (INR), activated partial thromboplastin time (aPTT)), intraoperative characteristics (amount of resected prostate tissue, blood transfusion, duration of surgery, duration of urinary catheterization) and postoperative features (serum complete blood count, and length of hospital stay) were collected. Patients who underwent TURP with or without statin use were compared with hematocrit and bleeding complications.

**Results:** There was no difference between the groups regarding the degree of reduction in hematocrit and platelet count. In both groups, postoperative hematocrit and platelet counts were significantly lower than preoperative values. There was no significant difference between the groups regarding age, PSA, prostate volume, histopathological diagnosis, transurethral resection (TUR) volume, INR, PT, aPTT, number of red blood cell (RBC) units transfused, duration of surgery, irrigation time, hematocrit, and platelet count. TUR volume, frequency of anticoagulant use, duration, and length of hospital stay were statistically higher in the statin user group.

**Conclusion:** Our results showed that statin use did not impact bleeding in patients with BPH who underwent TURP. Considering the widespread use of statins, during surgery the effects of bleeding, we need more information on further studies to light.

**Keywords:** *benign prostatic hyperplasia, bleeding, statin, transurethral resection of the prostate*

## INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common prostatic disease that negatively affects the quality of life in aging men (1). After a certain threshold, the enlargement of the prostate causes some obstructive and irritative lower urinary tract symptoms (LUTS) (2). Surgical treatment is indicated in patients who develop complications due to BPH or do not benefit from medical treatment (3). Transurethral resection of the prostate (TURP) is the standard gold treatment for symptomatic BPH, but with serious side effects such as bleeding, ejaculatory dysfunction, bladder neck contracture, urethral stricture, and TUR syndrome (3-5). Bleeding is a problematic complication that may cause a need for re-hospitalization, re-catheterization, and blood transfusion.

Statins, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are the most commonly used drugs in treating hyperlipidemia (6,7). Some experimental studies have shown that statins can reduce thrombus formation by affecting the coagulation cascade (8-11). Data is ascertaining the literature regarding the effects of statins on bleeding complications after surgical operations. To the best of our knowledge, only two studies reported increased bleeding complications in patients who underwent surgery while using statins (12,13). Since patients with BPH are often elderly, dyslipidemia and heart diseases are common, increasing the probability of statin use among patients with BPH. Thus, we aimed to evaluate the effect of statin use on bleeding complications in BPH patients who underwent TURP.

## MATERIAL AND METHODS

This prospective case-control study aimed to investigate the effect of statin use on the hemostasis during TURP operation. Turkey Health Sciences University Ethics Committee approved the study protocol (29620911-929). All patients gave written informed consent.

### Patients

We prospectively included 154 consecutive patients with benign prostatic hyperplasia (BPH) who underwent TURP surgery between January 2018 and June 2019. According to the European As-

sociation of Urology (EAU) guideline (14). As part of the routine preoperative practice, acetylsalicylic acid was stopped seven days before the surgery. Patients who previously underwent TURP and transurethral resection of bladder tumor (TURBT) procedures, those receiving enoxaparin or other anticoagulant medications, subjects that had been diagnosed with prostate cancer, those that were found to have bladder neck stenosis intraoperatively, and patients with urethral stricture and stenosis were excluded from the study. A total of 50 patients were excluded due to these exclusion criteria. All patients underwent transrectal ultrasound evaluation during the initial diagnosis of BPH preoperatively. The same radiologist performed all examinations. The height (H), width (W), and length (L) of the prostate were used to calculate prostate volume with the ellipsoid estimation formula " $H \times W \times L \times 0.523$ " (15). The whole study cohort was divided into two groups: group 1 comprised patients who received a statin drug, and group 2 comprised patients who were not receiving statins at the time of the surgery. Since no common complication of statin has been reported during the TURP operation, it is not recommended to stop statins before the operation in our hospital.

### **Data Collection**

Data, including age, preoperative laboratory parameters including serum hemoglobin, platelet (thrombocyte) count, prostate-specific antigen (PSA) levels, prostate volume, prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), routine biochemistry, urinalysis, and urine culture, were recorded for each study participant.

Intra and postoperative features include the amount of resected prostate tissue, irrigation time, TUR volume, number of blood transfusions, duration of surgery, duration of urinary catheterization, length of hospital stay, and complete blood count (six hours after the surgery) were collected.

Patients who underwent TURP due to BPH were observed during operation and after the surgery, until discharge to develop any bleeding complication, hematoma formation, need for red blood cell transfusion, and reoperation to provide hemostasis.

### **Surgical Procedure**

The same surgical team operated on all patients. Urethrocystoscopy and cystoscopy inserted a Karl Storz 26F monopolar resectoscope 30° optics through external urethral meatus at the lithotomy position and under general anesthesia. Unless pathologic conditions such as stricture, tumors, or stones were detected, resection was started from the 6 o'clock position with 1.5% glycine solution. Afterward, the median lobe, if any, right lobe, and left lobe were resected in respective order from bladder neck up to the verumontanum. A space sufficient for urination was created at the prostatic lodge, and the resectoscope was forwarded to the prostatic capsule. Hemostasis was provided via coherization in bleeding areas followed by a 22F 3-way Foley catheter placement through the urethra. Finally, the catheter's balloon was inflated, left to traction, and a 0.9% saline irrigation fluid was connected.

### **Statistical Analysis**

Statistical analysis was carried out using SPSS version 21 (SPSS Inc., Chicago, IL, USA). The normality check was performed via the Shapiro-Wilk test. Data are presented as mean  $\pm$  standard deviation or median (minimum-maximum) for continuous variables with regard to the normality of distribution and frequency (percentage) for qualitative variables. Age was analyzed with the independent samples t-test. Hematocrit values were analyzed with two-way repeated-measures analysis of variances (ANOVA). Non-normally distributed variables were analyzed with the Mann-Whitney U test. Platelet values were analyzed with the Wilcoxon Signed Ranks test for repeated measurements. The comparison of the groups in terms of platelets was performed by analyzing differences between the measurements with the Mann-Whitney U test. Categorical variables were evaluated using the Chi-square test or Fisher's exact test for comparisons. Since some of the variables significantly differed between groups and to be able to determine other possible significant factors on bleeding amounts, linear regression analysis (stepwise selection method) was performed with hematocrit differences between before and after the operation as the dependent variable. P-value  $< 0.05$  was accepted as statistically significant.

We performed linear regression analysis (stepwise selection method) with hematocrit differences be-

tween preoperative and postoperative results as the dependent variable for determining independent associates of hematocrit reduction during operation and also the effect of statins by controlling the variables that demonstrated significant differences between groups (TUR volume, anticoagulant use, and duration of catheterization).

**RESULTS**

Overall, 104 patients, 30 of whom were statin users, and 74 were non-users, were available for analysis. According to statin use, patients’ characteristics are summarized in tables 1 and 2. There was no significant difference between the groups (statin user and non-user) regarding age, serum PSA level, prostate volume, histopathological diagnosis, TUR volume, INR, PT, aPTT, and the number of RBCs units transfused, TUR volume, hematocrit, and platelet count. On the other hand, irrigation time, duration of surgery, frequency of acetylsalicylic acid use, duration of catheterization, and length of hospital stay were statistically higher in the statin user group than in the non-users. Furthermore, postoperative hematocrit and platelet counts in both groups were significantly lower than preoperative values. However, there was no difference between the groups regarding the degree of reduction in hematocrit and platelet counts. We performed linear regression analysis (stepwise selection method) with hematocrit differences between before and after the operation as the dependent variable for determining significant factors on bleeding amounts during operation and also the effect of statin medication by controlling the variables significantly differs between groups (TUR volume, anticoagulant usage, irrigation time and duration of catheterization). We found that higher surgery durations are a significant risk factor for higher bleeding amounts. Other variables included in the model statin usage (p=0.683), age (p=0.937), TUR volume (p=0.446), platelet (p=0.243), INR (p=0.055), anticoagulant usage (p=0.925), irrigation time (p=0.429), duration of catheterization (p=0.570) found as non-significant (Table 3). The difference between preoperative and postoperative serum hematocrit levels, according to groups, is depicted in Figure 1.

**Table 1.** Summary of patient characteristics according to statin medication

	Statin		Total	p-value
	User (n=30)	Nonuser (n=74)		
<b>Pre-operative parameters</b>				
Age (years)	69.97 ± 7.43	66.55 ± 8.41	67.54 ± 8.26	0.056
PSA (mg/dl)	3.29 (0 - 21.13)	2.47 (0.30 - 31.21)	2.69 (0 - 31.21)	0.613
Prostate Volume (ml)	58 (20 - 140)	55.5 (15 - 230)	56 (15 - 230)	0.549
<b>Diagnosis</b>				
Adenomyomatous hyperplasia	19 (63.33%)	49 (66.22%)	68 (65.38%)	0.594
Adenomyomatous hyperplasia + Chronic prostatitis	11 (36.67%)	23 (31.08%)	34 (32.69%)	
Prostate cancer	0 (0.00%)	2 (2.70%)	2 (1.92%)	
<b>Operative parameters</b>				
TUR Volume (ml)	20 (10 - 80)	19 (10 - 70)	20 (10 - 80)	0.132
INR	1.08 (0.89 - 1.29)	1.07 (0.93 - 1.45)	1.07 (0.89 - 1.45)	0.682
PT (seconds)	11.9 (10.5 - 14.9)	12 (10.5 - 16.7)	12.0 (10.5 - 16.7)	0.760
aPTT (seconds)	30.1 (24.1 - 45.1)	29.2 (19.8 - 41.0)	29.5 (19.8 - 45.1)	0.771
Acetylsalicylic acid user	26 (86.67%)	20 (27.03%)	46 (44.23%)	<0.001
Number of Blood Transfusions	1 (3.33%)	0 (0.00%)	1 (0.96%)	0.288
Duration of Surgery (minute)	60 (30 - 90)	50 (20 - 95)	50 (20 - 95)	0.017
Irrigation Time (hour)	6 (4 - 10)	5 (4 - 10)	5 (4 - 10)	0.011
Duration of Catheterization (hour)	36 (30 - 48)	36 (24 - 48)	36 (24 - 48)	0.011
Length of Stay in Hospital (hours)	48 (42 - 60)	48 (36 - 60)	48 (36 - 60)	0.001
<i>aPTT: activated partial thromboplastin time, INR: international normalized ratio, PSA: prostate specific antigen, PT:prothrombin time, TUR: Transurethral Resection. Data are given as mean ± standard deviation or median (minimum - maximum) for continuous variables with regard to normality and frequency (percentage) for categorical variables</i>				

**Table 2.** Comparison of the groups in terms of hematocrit and platelet count

	Statin		Total	p-value
	User (n=30)	Nonuser (n=74)		
<b>Hematocrit (%)</b>				
Pre-operative	42.80 ± 5.12	43.01 ± 5.09	42.95 ± 5.08	0.945
Post-operative	38.85 ± 5.35	39.11 ± 4.23	39.04 ± 4.55	
p (within variables)	<0.001	<0.001	<0.001	
<b>Platelet (x1000/mm<sup>3</sup>)</b>				
Pre-operative	216.5 (163 - 479)	238.5 (154 - 388)	236 (154 - 479)	0.261
Post-operative	199 (134 - 327)	199 (66 - 391)	199 (66 - 391)	
p (within variables)	0.001	<0.001	<0.001	

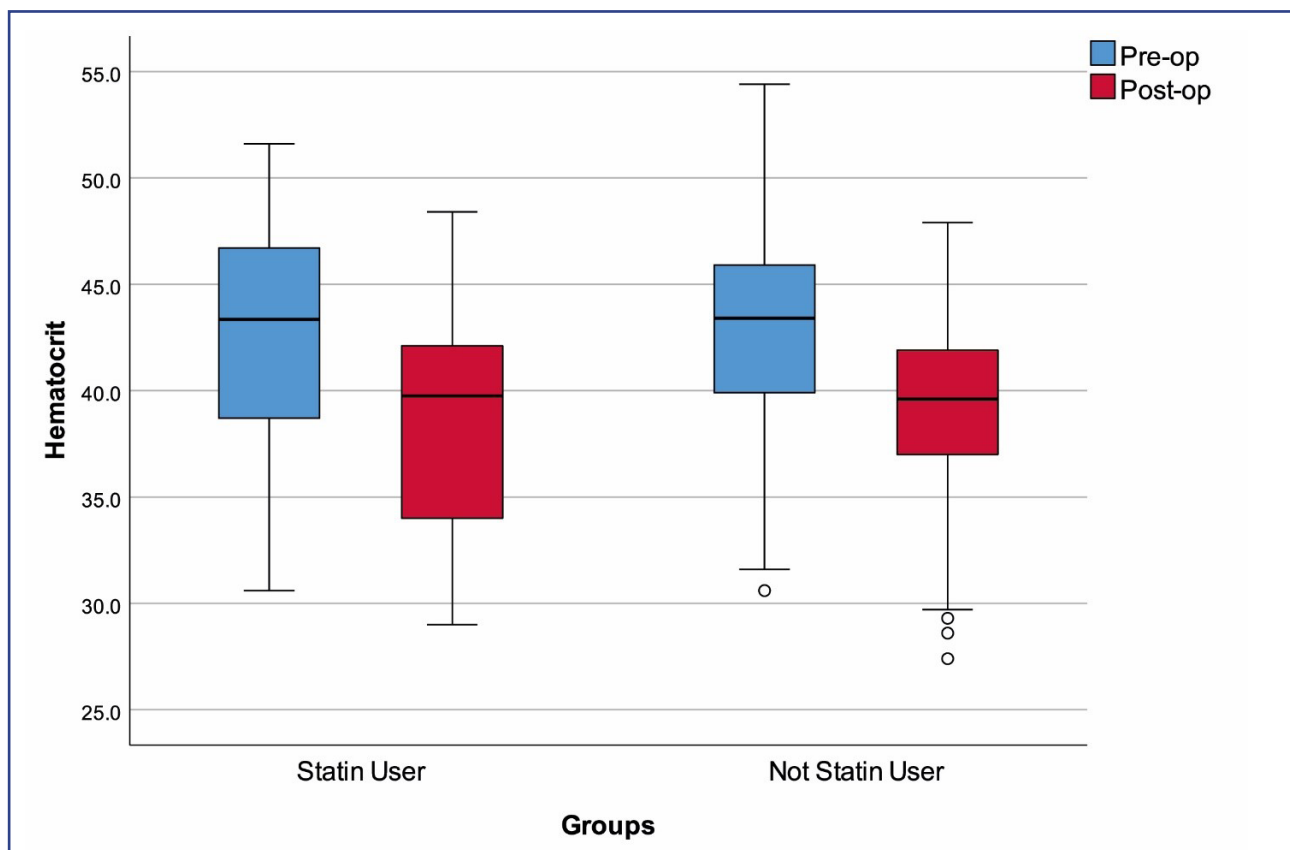
Data are given as mean ± standard deviation or median (minimum - maximum) for continuous variables with regard to normality and frequency (percentage) for categorical variables.

**Table 3.** Linear regression analysis results for determining independent associates of hematocrit reduction during operation

	Unstandardized Beta	Std. Error	Standardized Beta	t	p	95% Confidence Interval for Beta	
						Lower	Upper
(Constant)	1.875	0.963		1.947	0.054	-0.035	3.784
Duration of Surgery	0.038	0.017	0.215	2.226	0.028	0.004	0.072

**Dependent Variable:** Hematocrit Differences; R<sup>2</sup>=0.046; F=4.597; p=0.028

**Figure 1.** Hematocrit Values Before and After Operation According to Statin Medication



## DISCUSSION

It is the first study in the literature evaluating the effect of statin use on bleeding in patients undergoing TURP operation due to BPH. The present study showed no difference in the effect of statins on hemorrhage in patients with BPH who underwent the TURP procedure.

Heart diseases are among the leading causes of death globally (16). Coronary artery diseases are the most common heart diseases, and hyperlipidemia is considered one of the major risk factors of CAD. Statin group drugs have an important success in the treatment of hyperlipidemia. Therefore, it has widespread use in the world. It is more common in patients over 60 years of age, diagnosed with CAD and hyperlipidemia.

In several experimental studies, it has been demonstrated that statins might reduce fibrin formation and thrombus development through the downregulation of the coagulation cascade (8-10); however, the exact mechanism is yet to be elucidated, and research has shown that statins might reduce tissue factor expression, therefore decreasing thrombin formation (8,17,18). It has been shown that statins increase tissue plasminogen activator (tPA) and decrease plasminogen activator inhibitor-1 (PAI-1) expression in vascular endothelial cells (10). These mechanisms might account for the observed unfavorable effect of statins on hemostasis.

Besides this, the antithrombotic effect of statins was associated with reducing inducible nitric oxide synthase (iNOS) expression and consequently inhibiting nitrite accumulation and TNF-alpha release (19). A systematic review stated that statins might decrease the incidence and recurrence of venous thromboembolism; the authors claimed that statins could be instrumental in treating post-thrombotic syndrome (9). A meta-analysis showed that statins could decrease the plasma level of von Willebrand factor (VWF) antigen, which carries factor VIII (20).

Several lines of clinical evidence pointed to the antithrombotic role of statins. A randomized, double-blind, placebo-controlled study (referred to as JUPITER) showed that rosuvastatin reduced the risk of venous thromboembolism in asymptomatic subjects (21). Statins have also been shown to prevent venous thromboembolism in some high-risk populations, such as individuals with nephrotic syndrome or active cancer (22,23).

It has been demonstrated that statin use does not increase bleeding risk in the general population (24). The discordance of the mechanistic effects of statins on hemostasis and observed clinical outcomes might partly be because statin-associated changes in the coagulation system are not the main pathways and can be maintained by alternative pathways.

Hauer-Jensen et al. investigated the effect of statins on wound complications after inguinal or ventral hernia and showed that statin use was an independent predictor of postoperative hemorrhage and hematoma development. The authors reported that statins caused a relative increase in the risk for postoperative hemorrhage or wound hematoma by 60% (12). Truesdale et al. evaluated the effect of statin use on postoperative blood hematocrit values in patients who underwent open radical prostatectomy. The study results showed that blood hematocrit reduction was significantly higher in statin users than non-users (20.7% vs. 8.6%, respectively,  $p < 0.001$ ). Moreover, the multivariable analysis revealed a moderate association between postoperative hemorrhage and statin use, despite being technically insignificant ( $p = 0.06$ ) (13). Our results were not in agreement with the two studies mentioned earlier. The studies by Hauer-Jensen and Truesdale et al. were retrospective. Hence, some potential factors promoting bleeding might not have been controlled adequately. Besides, differences in study cohorts and surgical procedures might have contributed to conflicting results.

Some limitations of our study must be mentioned. First, our sample size was relatively small to detect a subtle potential relationship between statin use and bleeding events. Second, we did not study detailed coagulation parameters, which might be affected despite the lack of clinically significant bleeding complications and patients' hematocrit values. Despite the shortcomings, this is the first prospective study in the literature investigating the effect of statins on bleeding in patients undergoing the TURP procedure.

## CONCLUSION

In conclusion, in contrast to previous studies, our results showed that statin use did not impact bleeding in patients with BPH that underwent TURP. As we stated above, this result might be due to alternative pathways that compensate statin disrupted coagulation reactions. Considering the widespread use of statins, further studies are needed to shed more light on the effect of statins on bleeding during surgery.

**Conflict of Interest:** The authors declare to have no conflicts of interest.

**Financial Disclosure:** The authors declared that this study had received no financial support.

**Informed Consent:** Informed consent was obtained from all individual participants included in the study.

**Ethical Approval:** The study was approved by the Ethics Committee of Ankara Türkiye Yüksek İhtisas Training and Research Hospital (No: 30, Date: December 28, 2021). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

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