Preoperative aspirin and anticoagulants do not affect partial nephrectomy bleeding

Muqsit Buchh,[1] Courtney Yong, MD,[2] Fezaan Kazi,[1] Ali Sualeh,[1]
James Slaven, MD,[3] Ronald S. Boris, MD,[2] Chandru P. Sundaram, MD[2]

[1]Indiana University School of Medicine, Indianapolis, Indiana, USA
[2]Department of Urology, Indiana University, Indianapolis, Indiana, USA
[3]Department of Biostatistics and Health Data Science, Indiana University, Indianapolis, Indiana, USA

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Introduction: *Studies have reached mixed conclusions on the role of antiplatelet and anticoagulant agents on postoperative complications of partial nephrectomies. This study examines whether preoperative anticoagulation use affected the risk of hemorrhagic complications after partial nephrectomy.*

Materials and methods: *This is a retrospective chart review of all partial nephrectomies performed between 2017 and 2022 at a single institution. For each operation, preoperative data was gathered on whether the patient was on anticoagulation, the type and dose of anticoagulation, and how many days the anticoagulation was held preoperatively. Bivariate analyses for continuous measures were performed using Student's t-tests when there were two comparison groups and ANOVA models when there were more than two comparison groups and Chi-Square tests were used for categorical variables, with Fisher's Exact being used when expected cell counts were small.*

Results: *In this study, warfarin was held for an average of 5.43 days, clopidogrel was held for an average of 6.60 days, aspirin was held for an average of 7.65 days, and direct oral anticoagulants (DOACs) were held for an average of 4.00 days. There was no significant difference in hemoglobin (Hb) change, rate of intraoperative transfusion, postoperative transfusion, bleeding complication, pseudoaneurysm rate, or additional bleeding processes between patients on prior anticoagulation therapy and those not on therapy. There was no significant difference in intraoperative or postoperative outcomes based on history of aspirin use and continuation of aspirin through the surgery. While estimated blood loss appeared statistically significant initially, this difference was accounted for by the covariates of comorbidities, RENAL score, surgical approach, and type of renorrhaphy. Overall, there was no difference in complication rate based solely on aspirin use or continuation of aspirin through surgery.*

Conclusions: *No difference in complication rate of partial nephrectomy was determined to be solely due to prior use of anticoagulation or aspirin use alone with appropriate cessation of anticoagulation preoperatively. Overall, patients on anticoagulation are not at a higher risk of intraoperative or postoperative bleeding complications when undergoing partial nephrectomy.*

Key Words: nephrectomy, anticoagulants, platelet aggregation inhibitors, surgical blood loss, blood transfusion

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Address correspondence to Dr. Chandru P. Sundaram, Department of Urology, Indiana University, 535 N Barnhill Drive, Indianapolis, IN 46202 USA

Introduction

The balance between bleeding and thrombosis in the operating room is a delicate one requiring input from surgeons, pharmacists, cardiologists,

hematologists, and patients. While guidelines exist to model proper handling of anticoagulation for many operations, newer procedures require a reevaluation of risks of preoperative, perioperative, and postoperative complications. For example, studies have shown that perioperative aspirin is safe during radical nephrectomy.[1] Within the last decade, however, the standard of management for cT1 renal masses has changed from radical to robot-assisted partial nephrectomies, but this is not without an increase in blood loss and complications.[2,3] Studies have reached mixed conclusions on the role of antiplatelet and anticoagulant agents on postoperative complications of partial nephrectomies. More research is needed to determine the true relationship between anticoagulation discontinuation and partial nephrectomy complications, with the goal of determining guidelines for different anticoagulant agents. In this study, we examined whether preoperative anticoagulation use affected the risk of hemorrhagic complications after partial nephrectomy.

Materials and methods

We performed a retrospective chart review of all partial nephrectomies performed between 2017 and 2022 at a single institution. For each operation, preoperative data was gathered on whether the patient was on anticoagulation, the type and dose of anticoagulation, and how many days the anticoagulation was held preoperatively. Reasons for anticoagulation use were documented and can be seen in Table 1. Preoperative and postoperative day 1 (POD1) hemoglobin levels were collected. Intraoperative data collected include type of renorrhaphy (single layer vs two layer), estimated blood loss (EBL), and amount of blood

TABLE 1. **Anticoagulated vs. non-anticoagulated patient demographics**

	Anticoagulation n = 175	**Not on anticoagulation n = 310**	**p value**
Male (n, %)	104 (59.4)	188 (60.7)	.7926
Age (avg, st dev)	63.9 (9.0)	55.5 (12.4)	< .0001
Type of anticoagulation (n, %)			
Warfarin	13 (7.4)	n/a	n/a
Antiplatelet	15 (8.6)		
DOAC	22 (12.6)		
Aspirin	144 (82.3)		
• 81 mg	131 (74.9)		
• 162 mg	2 (1.1)		
• 325 mg	11 (6.3)		
NSAID	11 (6.3)		
Comorbidities requiring anticoagulation (n, %)			
Afib/flutter	31 (17.7)	12 (3.9)	< .0001
Stroke	11 (6.3)	6 (1.9)	.0124
CAD/MI	54 (30.9)	5 (1.6)	< .0001
CABG	15 (8.6)	0 (0)	< .0001
DVT/PE	17 (9.7)	8 (2.6)	.0006
Cardiac stent	29 (16.6)	2 (0.7)	< .0001
RENAL score (median, IQR)	7 (6-9)	7 (6-8)	.0862
Robotic (n, %)	143 (81.7)	260 (83.9)	.5428
Unclamped (n, %)	43 (24.5)	93 (30)	.2012
Type of renorrhaphy (n, %)			
1 layer (1)	37 (21.1)	64 (20.7)	.8969
2 layer (2)	138 (78.9)	246 (79.4)	

products transfused. Postoperative data included whether a transfusion was required, the presence of a bleeding complication, pseudoaneurysm, and whether an intervention needed to be performed for hemostasis.

For statistical analysis, bivariate analyses for continuous measures were performed using Student's t-tests when there were two comparison groups and ANOVA models when there were more than two comparison groups and Chi-Square tests were used for categorical variables, with Fisher's Exact being used when expected cell counts were small. Multivariable models were then performed to account for confounding variables by adjusting for any differences due to covariates such as comorbidities, RENAL score, surgical approach (open vs. robot), and type of renorrhaphy (single layer vs. two layer). All analytic assumptions were verified with transformations being used when necessary and non-parametric tests being performed if necessary. All statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA).

Results

There were 485 partial nephrectomies performed during the study period by 11 urologists at our center. Demographic characteristics are shown in Table 1. There was no significant difference in gender between the anticoagulation groups. Patients who were on anticoagulation preoperatively tended to be older, with a mean age of 63.9 years as compared to 55.5 years in the group not on anticoagulation ($p < .0001$). Breakdown of pharmacotherapy used for anticoagulation included warfarin (7.4%), antiplatelet therapy (8.6%), direct oral anticoagulants (DOACs) (12.6%), and aspirin (82.3%). RENAL score, robotic procedure, and type of renorrhaphy used for hemostasis did not differ between the two groups.

The complication rates between the anticoagulated and non-anticoagulated groups are shown in Table 2. In this study, warfarin was held for an average of 5.43 days, clopidogrel was held for an average of 6.60 days, aspirin was held for an average of 7.65 days, and DOACs were held for an average of 4.00 days prior to surgery. After surgery, the median number of days anticoagulation was held was 3 (range 0-21, IQR 1-7). There was no significant difference in hemoglobin (Hb) change, rate of intraoperative transfusion, postoperative transfusion, bleeding complication, pseudoaneurysm rate, or additional bleeding processes between patients on prior anticoagulation therapy and those not on therapy, Table 2. There was a statistically significant difference in estimated blood loss (EBL) between the two groups ($p = .0003$). Adjusting for covariates, however, found that this difference was no longer significant and likely not a result of coagulation status alone, Table 2. Thus, there were no differences in outcomes when patients had a history of anticoagulation use.

TABLE 2. **Anticoagulated vs. non-anticoagulated complication rates**

	Anticoagulation n = 175	**Not on anticoagulation n = 310**	**p value**	**Adjusted p value**
Hb preop	14.0 (12.9, 15.0)	14.1 (13.1, 14.8)	.8738	.1674
Hb POD1	12.0 (10.9, 13.3)	12.2 (11.1, 13.1)	.6735	.8924
Hb change	1.9 (1.2, 2.6)	1.8 (1.0, 2.6)	.4180	.1001
EBL	150 (100, 300)	100 (50, 200)	.0003	.3345
Intraop transfusion	5 (2.9)	12 (3.9)	.5599	.2968
Intraop transfusion units	1.0 (0.6, 1.5)	1.0 (0.7, 2.0)	.9155	n/a
Postop transfusion	6 (3.4)	10 (3.2)	.9044	.9751
Postop transfusion units	1.5 (1.0, 4.0)	2.0 (1.0, 3.0)	.9088	n/a
Bleeding complication	3 (1.7)	4 (1.3)	.7073	.3180
Pseudoaneurysm	2 (1.1)	4 (1.3)	> .9999	.2624
Additional procedure for bleeding complication	1 (0.6)	3 (1.0)	> .9999	.3018

TABLE 3. **Aspirin duration and complication rates**

	No aspirin n = 341	**Aspirin, discontinued before surgery n = 87**	**Aspirin, continued through surgery n = 55**	**p value**	**Adjusted p value**
Hb preop	14.1 (13.1, 14.8)	14.2 (13.4, 15.4)	13.7 (12.8, 14.6)	.0761	.3406
Hb POD	12.2 (11.0, 13.1)	12.1 (11.3, 13.3)	11.7 (10.5, 12.9)	.2874	.7304
Hb change	1.8 (1.1, 2.6)	2.0 (1.4, 2.6)	1.8 (0.9, 3.4)	.2805	.1293
EBL	100 (50, 200)	150 (100, 300)	100 (50, 300)	.0054	.5183
Intraop transfusion	14 (4.1)	1 (1.2)	2 (3.6)	.4094	.0979
Intraop transfusion units	1.0 (0.7, 1.5)	1.5 (1.5, 1.5)	2.1 (0.6, 3.5)	.7220	n/a
Postop transfusion	11 (3.2)	2 (2.3)	2 (3.6)	.8798	.9766
Postop transfusion units	2.0 (1.0, 3.0)	2.5 (1.0, 4.0)	2.5 (1.0, 4.0)	.9907	n/a
Bleeding complication	4 (1.2)	1 (1.2)	1 (1.8)	.8105	.8913
Pseudoaneurysm	4 (1.2)	1 (1.2)	0 (0)	>.9999	.9975
Additional procedure for bleeding complication	3 (0.9)	1 (1.2)	0 (0)	>.9999	.9958

We additionally analyzed differences in outcomes for patients specifically on aspirin prior to partial nephrectomy. There was no significant difference in intraoperative or postoperative outcomes based on history of aspirin use and continuation of aspirin through the surgery, Table 3. While estimated blood loss appeared statistically significant initially, this difference was accounted for by the covariates of comorbidities, RENAL score, surgical approach, and type of renorrhaphy. The need for intraoperative transfusion was higher, although not significantly so, in those who continued aspirin through surgery as compared to those who did not (2 transfusions vs. 1, p = .0979). Overall, there was no difference in complication rate based solely on aspirin use or continuation of aspirin through surgery.

It is also important to address possible thrombotic complications which may have occurred secondary to holding anticoagulants and antiplatelets. Of the patients included in this study, there was one occurrence of pulmonary embolism which occurred on POD 5 when the patient was readmitted for dyspnea. At the time, he was holding his clopidogrel but had continued his home aspirin (325 mg) through the surgery. This patient had no previous history of known pulmonary embolism or deep vein thrombosis.

Discussion

In this retrospective study from 2017 to 2022, no difference in complication rate of partial nephrectomy was determined to be solely due to prior use of anticoagulation or aspirin use alone with appropriate cessation of anticoagulation preoperatively. Overall, patients on anticoagulation are not at a higher risk of intraoperative or postoperative bleeding complications when undergoing partial nephrectomy. Some past multi-center analyses found that perioperative dose of aspirin 81 mg led to a heightened risk of blood transfusions, pseudoaneurysms, and overall postoperative complications.[4,5] Other studies, however, found no difference in overall perioperative complication rate between those on anticoagulant/antiplatelet therapy and those not on it, showing that tumor size was the only significant predictor of significant bleeding outcomes.[6,7] Of note, patients on daily aspirin within these studies tended to be older and have greater comorbidities, so analysis of aspirin independent of other factors is an important consideration.[8] One study found that even when anticoagulation was stopped preoperatively, the use of therapeutic anticoagulation was a major determinant of postoperative complications in robot-assisted partial nephrectomies.[9]

The findings from this study about anticoagulation status not significantly impacting complication rate of partial nephrectomies are in concordance with several papers previously documented.[6,7] It is important to consider that even while several studies conclude statistically significant differences in bleeding outcomes, nearly all deny any clinically significant outcomes in terms of length of stay or higher-grade complications.[8] Indeed, in our study, although estimated blood loss was significantly different between groups on univariate analysis, the actual amount of difference was only 50 mL, which is clinically insignificant. This was additionally found to be insignificant once controlling for potential confounding variables.

The findings of this study contrast with other studies which supported a negative effect of anticoagulation, even when stopped preoperatively, on postoperative complications of partial nephrectomies.[4,9] One possible reason for this may be that different institutions have different recommendations for the duration anticoagulants need to be held prior to surgery. For example, aspirin was held for 5 days prior to surgery in the Pradere et al study whereas it was held for an average of 7.65 days prior to surgery in this study. The recommended duration of time to hold aspirin is 7-10 days, which is a potential explanation for the findings of the Pradere study.[10] Differences in holding period length may have also played a role for other anticoagulant agents between studies.

Regarding aspirin use specifically, there was a slightly higher risk of intraoperative transfusion in patients who continued aspirin through surgery compared to those who stopped aspirin, but this only approached significance ($p = 0.098$). Additionally, the rate of intraoperative transfusion was similar between patients who continued aspirin through surgery (3.6%) and those who were not on aspirin at all (4.1%), suggesting no true difference in transfusion rates between the groups. Since some papers agree with our finding that there is no difference in intraoperative transfusion rate with antiplatelet therapies[1,6,7] and some disagree with that finding,[4,5] a larger meta-analysis with greater sample size may be needed to come to a definite conclusion on whether aspirin should be held preoperatively or not. It is important to remember that clinical decision-making lies at the heart of this data. Clinicians may have a lower threshold for transfusing blood intraoperatively if a patient is on aspirin perioperatively compared to one whose aspirin was discontinued. Additionally, the presence of coronary artery disease lowers the threshold for administering blood transfusions, potentially confounding the transfusion rate.

Limitations of our study include its single-center, retrospective nature, which limits its generalizability and subjects the data to selection bias. To limit the study to a contemporary cohort from 2017 to 2022, the study also has a smaller sample size than other comparable studies in the literature, and there were few bleeding events, which limits our analysis. The rate of documented bleeding complications requiring procedures (1% vs. 1%-10%)[4,7] and transfusions (6% vs. 2%-20%)[4,5,7] was slightly lower in our series. Finally, although our typical practice at our institution is to restart anticoagulation within 5 to 7 days, we did not have data on when anticoagulation was restarted postoperatively, which may affect the postoperative risk of bleeding complications.[9]

Improved modern medicine has led to aging patient populations with more comorbidities, necessitating the use of long term anticoagulation therapy. Minimizing bleeding complications for these populations is a challenging yet worthwhile endeavor to improve outcomes of partial nephrectomies. This paper provides evidence that the duration of preoperative holding of anticoagulation therapy used in this study is sufficient to prevent bleeding outcomes around partial nephrectomies with no adverse risk to these patients on anticoagulation. Whether to hold aspirin use perioperatively is a widely debated topic with studies supporting both sides, but this paper provides evidence that bleeding outcomes will likely not be affected if aspirin is continued through surgery. Cardiological consultation should be considered in cases where risks and benefits of anticoagulation are less clearly defined. □

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