Aspirin and clopidogrel during robotic partial nephrectomy, is it safe?

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Introduction: *Continuation of antiplatelet medications through major urologic surgery may increase the risk of intraoperative and postoperative bleeding complications. However, withdrawal of antiplatelet therapy may place some patients at high risk of serious cardiovascular or cerebrovascular complications. We assess the feasibility of performing robotic partial nephrectomy (RPN) in patients maintained on aspirin or dual antiplatelet therapy with aspirin and clopidogrel.*

Material and methods: *Perioperative data was collected prospectively on 230 subjects undergoing RPN enrolled in an IRB approved quality of life study. We analyzed subjects who were maintained on either aspirin alone or both aspirin and clopidogrel throughout the operative and perioperative period.*

Results: *Of the 230 patients, six were identified who continued antiplatelet medication throughout the perioperative period. Four patients were maintained on 81 mg of aspirin and two patients continued aspirin and clopidogrel. Average RENAL score was 7 with mean tumor size of 4.1 cm. There were no intraoperative complications and no conversions to open surgery. Average estimated blood loss was 242 mL. Ninety day complication rate was 33%. One patient had postoperative bleeding on day 14 after restarting coumadin in addition to their aspirin.*

Conclusions: *We present a case series demonstrating that in carefully selected patients, RPN on aspirin and clopidogrel is feasible and safe. This is the first report of patients who underwent RPN while on both aspirin and clopidogrel.*

Key Words: aspirin, clopidogrel, robotic surgery, nephrectomy

Introduction

Patients who undergo percutaneous coronary intervention (PCI) with intracoronary stent placement for coronary artery disease (CAD) are commonly placed on dual antiplatelet therapy with aspirin and clopidogrel for a minimum of 12 months following placement of drug-eluting stents (DES), and for 1 month following bare-metal stents (BMS) to decrease risk of stent thrombosis.[1] This poses a challenge in patients who are diagnosed with a renal mass during this time frame. The standard of care for treatment of a renal mass is surgical excision by radical nephrectomy (RN) or partial nephrectomy (PN). Continuation of dual antiplatelet therapy throughout PN and RN may increase intraoperative and postoperative bleeding risk. However, premature withdrawal of clopidogrel for noncardiac surgery has been associated with a 31% rate of coronary stent thrombosis and death.[2] Some renal masses can be monitored with serial imaging to allow adequate time for coronary stent endothelialization at which point antiplatelet medications can be held for surgical intervention. However, some renal masses may not be appropriate for surveillance or they may display aggressive growth characteristics on serial imaging. Delaying intervention may place the patient at risk for tumor progression and/or metastatic disease.[3] Minimal data is currently available on the safety of continued antiplatelet therapy through major urologic surgery. We assess the feasibility of performing robotic partial nephrectomy (RPN) in patients maintained on aspirin or dual antiplatelet therapy with aspirin and clopidogrel.

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Materials and methods

Beginning in July 2009, perioperative data was collected prospectively on 230 patients undergoing RPN enrolled in an IRB approved quality of life study. Study data were collected and managed using REDCap electronic data capture tools hosted at Beth Israel Deaconess Medical Center. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies.[4] We performed a retrospective analysis of patients who were maintained on aspirin alone or aspirin and clopidogrel throughout the perioperative period, including the day of surgery. Baseline patient demographic and clinical data were recorded, including age, sex, race, body mass index (BMI), and Charlson Comorbidity Index. All renal masses were assigned a RENAL score.[5] In all cases, a single surgeon performed a standard transperitoneal RPN with an early unclamping technique.[6] Briefly, during resection of the tumor using endoshears, intra-renal vessels are ligated with the assistance of biopolar cautery when visualized. After removal of the tumor, we close the open venous sinuses, end arteries, and collecting system at the base of the resection defect using a single layer of running 3-0 absorbable barbed suture. The hilar bulldog clamps are than removed allowing for visualization of any active bleeding in the defect, which if present is oversewn with additional figure of eight 3-0 barbed sutures. The renorrhaphy is then completed "off clamp" using a sliding clip renorrhaphy technique using 0 braided absorbable suture. No tissue sealant or cellulose bolsters are used. Patients are placed on a 2-day partial nephrectomy hospital pathway that includes ambulation on postoperative day 1. Patients are asked to avoid heavy lifting or exercise for 6 weeks. Operative variables included warm ischemia time, estimated blood loss (EBL), blood transfusions and intraoperative complications. Postoperatively, hospital length of stay was recorded as well as 90-day complication rates.

Results

Of the 230 patients, six were identified who continued antiplatelet therapy throughout the perioperative

TABLE 1. **Patient demographics and clinical summary**

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**Average**
Age	35	54	88	63	71	67	63
Sex	M	F	F	M	F	M	-
BMI	26.1	27.6	28	27	25.5	34.7	28.2
Charlson Comorbidity Index	3	5	7	4	6	7	5.3
Anticoagulation	Aspirin/ clopidogrel	Aspirin/ clopidogrel	Aspirin	Aspirin	Aspirin	Aspirin	-
Tumor size	4.3 cm	3.5 cm	5.5 cm	4.8 cm	2 cm	4.3 cm	4.1 cm
RENAL score	10x	4x	8a	8x	5x	7x	7
WIT	16 min	11 min	18 min	20 min	11 min	12 min	14.7 min
EBL	150 cc	200 cc	250 cc	100 cc	250 cc	500 cc	241.7 cc
Transfusions (Y/N)	N	N	Y	N	N	N	-
LOS	2 days	2 days	6 days	3 days	2 days	3 days	3 days
Complications	None	None	Ileus (POD0) Bleeding (POD14)	None	Nausea (POD10)	None	
Pathology subtype of RCC	Clear cell	Chromophobe	Clear cell	Clear cell	Papillary	Clear cell	-

BMI = body mass index; WIT = warm ischemia time; EBL = estimated blood loss; LOS = length of stay; RCC = renal cell carcinoma

period, and were analyzed. Four patients were maintained on 81 mg of aspirin during surgery for high risk cardiovascular disease or cerebrovascular disease. Two patients were incidentally found to have renal masses within 1 month following PCI with DES. Due to concerning imaging characteristics of the masses, as well as the concern for stent thrombosis with cessation of antiplatelet therapy, the operating surgeon and cardiology teams made a joint decision to perform RPN while continuing both antiplatelet medications. Baseline demographic and clinical information is presented in Table 1. There were five Caucasian patients and one Asian patient. One patient with atrial fibrillation was on aspirin and chronically anticoagulated with warfarin, which was held prior to surgery while the patient continued aspirin. One patient with CAD was instructed to continue aspirin but held clopidogrel through the perioperative period. Average RENAL score was 7 with mean tumor size of 4.1 cm. There were no intraoperative complications and no conversion to open surgery. Average EBL was 242 mL.

Perioperative details for each patient is presented in Table 1. Overall 90-day complication rate was 33%. There were no major complications in the two patients maintained on dual antiplatelet therapy through the perioperative period. One patient experienced a Clavien grade I complication with nausea on postoperative day 10. One patient, on aspirin only, developed an ileus postoperatively and was discharged on postoperative day 6 after conservative management. The same patient developed a postoperative bleed on day 14 after restarting warfarin requiring readmission and blood transfusion. Angiography showed no evidence of ongoing bleeding and patient was discharged without additional intervention. This patient had a 6.5 cm mass with RENAL score 8. All other patients were discharged home on postoperative day 2-3.

Discussion

The diagnosis of incidental renal masses is increasing as a result of more widespread use of cross-sectional imaging.[7] With roughly 1.8 million Americans undergoing PCI with intracoronary stent placement each year, urologists are seeing more patients who require major urologic surgery who are on chronic anticoagulation.[8] Common practice, based on published guidelines, is to discontinue aspirin and other forms of anticoagulation prior to major urologic surgery.[9] However, for some high risk patients, holding anticoagulation, specifically antiplatelet medications, places them at high risk for cardiovascular and cerebrovascular complications.[10,11] Furthermore, guidelines from the American College of Cardiology state dual antiplatelet therapy must be maintained for 1 month following BMS placement and 1 year following DES placement.[1] Thus, urologists are required to balance the risks of thrombotic complications with the increased risk of bleeding when performing surgery on patients after PCI. We present a case series of medically complex patients maintained on antiplatelet therapy during RPN. Notably, this is the first report of patients who underwent RPN whilst continuing both aspirin and clopidogrel throughout the perioperative period, including the day of surgery.

A growing body of literature suggests that continuing aspirin during low and intermediate risk urologic surgery is safe.[12-14] Additionally, small retrospective studies have shown aspirin to be safe during robotic prostatectomy and radical nephrectomy, Table 2.[15-19] Partial nephrectomy is a technically challenging procedure that poses a serious bleeding risk, particularly with larger, endophytic masses that require complex renorrhaphy.[20] To our knowledge there are no reports of continuing aspirin and/or clopidogrel through this surgery. In our series, four patients underwent RPN while on aspirin therapy and two others while on both aspirin and clopidogrel. One patient was readmitted on POD14 for a delayed bleed requiring blood transfusion. However this patient developed the complication after restarting warfarin.

Several retrospective studies have shown renal surgery to be safe in patients on chronic anticoagulation, Table 2.[21-24] It is important to note that contrary to this series, anticoagulation was held in the perioperative period in these studies. Some patients were bridged with short-acting alternatives, which were also held perioperatively. Kefer et al published a case-control study on 47 patients who underwent open or laparoscopic partial nephrectomy on chronic warfarin, cilostazol, or clopidogrel compared to a contemporary matched cohort showing no increase in bleeding complication or transfusion after restarting these medicines in the postoperative period.[21] Varkarakis et al reviewed 25 patients taking warfarin who underwent laparoscopic renal and adrenal surgery.[22] They showed chronic anticoagulation is associated with higher rates of postoperative bleeding and transfusion when compared to controls. Sfakianos et al published an analysis of 172 patients taking warfarin, enoxaparin sodium, tinzaparin sodium, or clopidogrel, and 695 patients taking aspirin who subsequently underwent partial or radical nephrectomy.[23] They found that patients restarting their anticoagulation had higher postoperative transfusion rates as well as higher overall complication rates when compared to patients not

TABLE 2. **Literature review of major urologic surgery on anticoagulation**

Studies	N (pts)	Anticoagulation	Procedures	Anticoagulation continued during surgery	Average EBL	Blood transfusions (%)	Overall complications (%)
Nowfar et al	6	Aspirin	RP	Yes	180 cc	0	1 (16.7%)
Parikh et al	Prostatectomy: 51 Nephrectomy: 14	Aspirin	RP and RN	Yes	100 cc 50 cc	0	Not reported
Binhas et al	54	Aspirin	LAP and RP	Yes	450 cc (median EBL)	4 (7.4%)	8 (14.8%)
Mortezavi et al	38	Aspirin	RP	Yes	271 cc	2 (5.3%)	8 (21.1%)
Leyh-Bannurah at al	19	Aspirin	RP	Yes	250 cc	0 (0)	3 (15.8%)
Leyh-Bannurah at al	118	Aspirin	Open prostatectomy	Yes	887 cc	25 (21%)*	21 (17.8%)
Kefer et al	47	Warfarin, clopidogrel, cilostazol, aspirin	LAP and open PN	No	241 cc	7 (14.9%)	14 (29.8%)
Varkarakis et al	25	Warfarin	LAP-RN, PN, pyeloplasty, adrenalectomy	No	303 cc	6 (24%)*	Overall complications not reported Bleeding complications 2 (8.0%)*
Sfakianos et al	172	Warfarin, clopidogrel, enoxaparin, tinzaparin	LAP and open RN and PN	No	265 cc	39 (22.7%)*	30 (17.4%)*
Sfakianos et al	695	Aspirin	LAP and open RN and PN	No	250 cc	53 (7.6%)	50 (7.2%)

*statistically significant difference from control group. EBL = estimated blood loss; RRP = robotic prostatectomy; RN = robotic nephrectomy; LAP = laparoscopic; PN = partial nephrectomy

on anticoagulation. They also found higher rates of transfusion and complications in patients on warfarin, enoxapirin, tinzaparin, or clopidogrel when compared to patients on aspirin. While these studies suggest an increase in postoperative transfusion requirements and complications in patients on chronic anticoagulation, each author deemed renal surgery to be safe in the setting of chronic anticoagulation. It should be noted that, of the 47 patients analyzed in Kefer et al, five patients experienced thromboembolic complications within the 30-day follow up period compared to zero patients in the control group, while this difference

was not statistically significant it underscores the risk of holding chronic anticoagulants in this patient population.

There are no published studies for patients maintained on clopidogrel through partial nephrectomy, however by extrapolating available data, few would question an increased risk of bleeding complications for these patients. A survey of 297 urologists in 2009 found that 97.1% stop clopidogrel prior to major urologic surgery.[25] In most instances it is safe to hold clopidogrel for surgery, but for patients with recently placed intracoronary stents, premature withdrawal of dual antiplatelet therapy places them at high risk for stent thrombosis.[2,26] This may pose a significant problem for patients with recent DES who are diagnosed with urgent or emergent surgical conditions. We describe two cases where renal masses concerning for RCC were incidentally diagnosed within one month of DES placement and who were both relatively young (ages 35 and 54 respectively). Diagnosis of a renal mass usually does not require urgent surgery and in many cases active surveillance is a safe option until the patient is able to hold clopidogrel. Multiple studies demonstrate the safety of active surveillance for patients with small renal masses based on the observations that the vast majority of renal masses grow in a slow and predictable fashion.[3,27-29] Our two patients required more urgent resection based on their young age and tumor size greater than 3 cm. Radiofrequency ablation or cryoablation are alternative therapies for small renal masses and despite their higher recurrence rates, there is a lower side-effect profile compared to partial nephrectomy.[3] However, chronic anticoagulation places patients at higher risk for bleeding after ablation[30] and there is little data describing bleeding risk in ablative therapies while patients continue antiplatelet medication. Moreover, ablative therapies are only indicated for exophytic masses smaller than 3 cm, and post treatment surgery after ablation can result in a high rate of complications.[31] Thus, these small masses appropriate for ablation can be safely followed in anticoagulated patients with active surveillance. If there is significant growth over the short term, as occurred in one of our patients, we have shown robotic partial nephrectomy is an appropriate treatment choice.

Major limitations to this paper include its retrospective nature, small sample size, and lack of a control group. Additionally, all surgeries were performed by a single, fellowship-trained minimally invasive surgeon with 10 years of robotic surgery experience.

In conclusion, we present a case series demonstrating, in carefully selected patients, RPN on aspirin and plavix is feasible and safe. A multidisciplinary approach which includes close communication between the surgical and cardiology teams is vital. Additional prospective, multi-center studies are needed to further define risks of surgery in this complex patient population. □

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