Impact of anticoagulant and antiplatelet drugs on perioperative outcomes of robotic assisted partial nephrectomy

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ABSTRACT

Objective:

To evaluate the impact of therapeutic anticoagulant or antiplatelet on the morbidity of robot assisted partial nephrectomy (RAPN).

Material and methods:

From 2011 to 2015, we retrospectively analysed a prospectively maintained institutional review board-approved database of RAPN from two academic departments of urology. We evaluated the occurrence of overall complications and hemorrhagic complications (pseudoaneurysm, arterio-venous fistula, hematoma, transfusion). Patients with therapeutic anticoagulant (AC) or antiplatelet (AP), stopped or not before surgery, were compared with patients without therapeutic AC or AP. A logistic regression model was used to identify predictors of complications.

Results:

Out of 533 RAPN patients, 70 had AC or AP (50% aspirin, 25% clopidogrel, 28% AC, 8% new oral anticoagulant (DOAC)). Clopidogrel, AC and DOAC were always stopped preoperatively. Aspirin was continued in 25% of the cases. In univariate analysis, overall complications (39.2% vs. 17.4%; $p=0.001$) and hemorrhagic complications (32.7% vs. 9.6%; $p<0.001$) were higher in AC/AP patients. Hospital stay was longer in the AC/AP group (5.1 vs. 3.9 days ; $p<0.001$). In multivariate analysis, predictors of complications were: therapeutic AC intake (OR =4.3, IC95% [1.2-15.9], $p=0.03$) and tumour size (OR=1.8, IC95% [1.3-7.2], $p=0.03$). Patients on aspirin tended to have more complications (OR= 2.4 ; IC95% [0.4-9.3] ; $p=0.15$).

Conclusion:

Antiplatelet and therapeutic anticoagulant increase the morbidity of RAPN. These treatments should be taken into account in treatment decision-making algorithm of small renal masses.

Key words: robot; partial nephrectomy; renal tumour ; anticoagulant; antiplatelet

Conflicts of interest: none

- All the authors who contribute to this study have no conflicts of interest with this study.

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INTRODUCTION

With the aging of the population, many people with cardiovascular conditions are being treated with oral anticoagulants (AC) and/or antiplatelet (AP) drugs¹. These medications can be difficult to handle in case of a surgical intervention. They usually have to be stopped before the operation, which can increase the risk of thrombosis and/or embolism. Furthermore, when resumed in the post-operative period, they can increase the risk of post-operative bleeding.

Hemorrhagic complications (HC) (bleeding, hematoma, arterio-venous fistula, pseudo-aneurysm) can occur during or after partial nephrectomy (PN) in up to 5-10% of the cases^{2,34}. When patients are taking AP or therapeutic AC, the risk of haemorrhage is supposedly higher, although data on this topic is very limited⁵. For that reason, the optimal management of therapeutic AC/AP before and after PN remains unknown.

Robot assisted PN (RAPN) has spread significantly worldwide and is now the most popular mini-invasive technique to perform PN. It has been reported that RAPN could be associated with a decreased risk of bleeding compared to open PN^{6,7}, possibly because of enhanced vision and better quality of renal parenchyma repair.

Our primary objective was to evaluate the impact of therapeutic AC/AP on RAPN perioperative morbidity. We hypothesized that patients with therapeutic AC or AP would have an increased risk of HC. Our secondary objective was to try and discern whether the timing of resumption of therapeutic AC/AP after RAPN had any influence on the occurrence of an HC.

Materials and Methods

Study population

We made a retrospective analysis of two prospectively maintained, institutional review board-approved databases. These databases included all RAPN performed between January 2010 and June 2015 at two academic departments of urology. Patients were divided into two groups: patients taking therapeutic AC and/or AP before surgery (group A), and patients without AP or therapeutic AC (group B).

We precisely looked at whether therapeutic AC/AP had been stopped before surgery, and the exact moment when it had been restarted postoperatively.

The following data were collected: surgeon's experience (categorized as < 20 procedures, between 20 and 50 procedures and > 50 procedures for each single surgeon), operative time, warm ischemia time, pedicle clamping technique (off-clamp, early unclamping or standard unclamping⁸), estimated blood loss (EBL), blood transfusion, and length of hospital stay. Estimated GFR (eGFR) was evaluated using the Modification of Diet in Renal Disease (MDRD)⁹. Tumour complexity was assessed using the RENAL nephrometry score¹⁰. Complications were reported according to the EAU guidelines¹¹ and classified using the Clavien Dindo score¹². Major complications were defined as a Clavien score ≥ 3 . HC were defined as the occurrence of an arterio-venous fistula, a pseudoaneurysm, or an hematoma requiring transfusion. All post-operative thrombotic or embolism events were recorded including: pulmonary embolism, thrombophlebitis, acute coronary syndrome, and stroke.

Perioperative management of AC/AP

Perioperative management of AC/AP was not standardized and was left at the anaesthesiologist and surgeon's discretion based on estimated cardiovascular risk of the patient. All patients taking therapeutic AC were switched to a low molecular weight

heparin (LMWH) before surgery; international normalized ratio was measured on the day of surgery to ensure normalization. In patients taking clopidogrel, the drug was either stopped preoperatively or switched to aspirin (75mg daily). For patients taking aspirin (75mg daily), the drug was either stopped or continued perioperatively at the same dosage. Therapeutic AC and AP were resumed postoperatively according to surgeon's decision. All patients who were not under therapeutic anticoagulation underwent prophylaxis of venous thromboembolism using LMWH (enoxaparin 40 mg once per day for 30 days post-operatively) according to the American College of Chest Physician guidelines¹³, even when they were under antiplatelet therapy.

Criteria for blood transfusions were a haemoglobin level below 9 g/dl and/or persistent hypotension.

Statistical analysis

Means and standard deviations were reported for continuous variables and proportions were used for nominal variables. Comparisons between groups were performed using χ^2 test and Fisher exact test for discrete variables and Mann-Whitney test for continuous variables. Subgroup analyses were performed to assess the impact of each independent AC or AP on RAPN outcomes. Multiple linear regression analysis was applied to define clinical parameters associated with estimated blood loss. A logistic regression model was used to assess predictors of hemorrhagic and overall complications. A sensitivity analysis was performed by matching patients under AC and/or AP with patients without AC or AP in a 1:1 fashion according to RENAL score, tumour size and ASA score.

For continuous variables, odd ratios were expressed as a range (per change in regressor over entire range). Statistical analyses were performed using JMP v.10.0 software (SAS institute Inc, Cary, NC, USA). All tests were two sided with a significance level set at $p < 0.05$.

Results

Patients' demographics

There were 530 patients who underwent RAPN. Among them, 70 (13.2%) were taking therapeutic AC and/or AP before surgery (group A). Patients' characteristics are summarized in table 1. Most patients' characteristics were similar on both institutions (supplementary table 1). Tumour size and RENAL score were comparable in both groups. Distribution of therapeutic AC and AP treatments in group A was as follows: 50% aspirin, 25% clopidogrel, 28% oral AC (coumadin or warfarin) and 8% direct oral AC (DOAC) (apixaban, dabigatran or rivaroxaban). Indications of AC/AP are summarized in supplementary table 2.

AC, DOAC and clopidogrel were stopped in 100% of the cases. Clopidogrel and AC were stopped seven and six days before surgery, respectively. 27% of the patients taking clopidogrel were switched to aspirin. Nine patients (26%) taking aspirin had their treatment continued peri-operatively. In the other cases, aspirin was stopped on average four days before surgery.

After RAPN, treatments were resumed on average on day one, eight, 12 and 20 for aspirin, clopidogrel, oral AC and DOAC, respectively. In the AC group, therapeutic doses of LMWH were given on day one in 50% of cases and on day 2 to 5 in the other 50% of cases, then continued until usual AC treatment was resumed.

Perioperative outcomes (table 2)

Operative time was similar in both groups (143.4 min vs. 136.3 min; $p=0.35$). EBL was slightly higher in the AC/AP group although not significant (339 ml vs. 282 ml; $p=0.29$). Use of haemostatic agents was similar between both groups (35.2% vs. 37.6%; $p=0.74$). Overall complications rate was higher in the AC/AP group (39.2% vs. 17.4%; $p<0.001$) including an increased rate of major complications (19.2% vs. 9.6%; $p=0.01$). HC and transfusions occurred more frequently in the AC/AP group (32.7% vs. 9.6%,

$p<0.001$, and 25% vs. 10%, $p=0.008$, respectively). There was no difference regarding thromboembolic complications (0.9% vs. 0%; $p=0.9$) between patients with or without AC/AP. HC were treated either by interventional radiology in case of pseudoaneurysm and arterio-venous fistula (7.6%) or surgically to drain perirenal hematomas (2.9%). Urinary fistulas were all treated endoscopically (2.2%). Finally, hospital stay was longer in AC/AP patients (5.1 vs. 3.9 days; $p<0.001$).

Subgroup analyses

Perioperative outcomes were compared in various subgroups: aspirin ($n=35$) vs. no aspirin ($n=497$), clopidogrel ($n=18$) vs. no clopidogrel ($n=515$), AC ($n=20$) vs. no AC ($n=513$) (supplementary table 3). When considered independently, each treatment was associated with increased overall complications (45% vs. 19%; 43% vs. 20%, and 41% vs. 20%, respectively) and more haemorrhagic complications (24% vs. 13%; 31% vs. 13%; and 40% vs. 13% respectively). Most of the HC occurred in the first 10 days after RAPN: at that time 62% of AC patients and 100% of AP patients had resumed their treatment.

In the AC/AP group, three patients had an acute coronary syndrome: one patient with a coronary stent, had clopidogrel stopped seven days before surgery without discontinuation of aspirin. The two other patients (under aspirin for coronary stents) had aspirin stopped 5 days before RAPN and resumed on day one. No patients developed any DVP or EP.

We performed a subgroup analysis in patients under aspirin to evaluate the impact of perioperative management of aspirin. Among 35 patients under aspirin, precise data concerning the management of aspirin was available in 28: nine had their treatment continued and 19 had aspirin stopped before surgery and resumed on day one. EBL was similar in both groups (413 vs. 328 ml; $p=0.3$) but there was a non-significant trend

towards higher complications rate (66% vs. 36%; $p=0.13$), increased major complications (33% vs. 15%; $p=0.3$), and increased hemorrhagic complications (33% vs. 21%; $p=0.4$) when aspirin was not interrupted. Hospital stay also tended to be longer when aspirin was continued (6.8 vs. 5.1 days; $p=0.25$).

Match-paired analysis

There were 70 patients in both groups with a mean RENAL score of 6.7 (see table 3). Mean age and BMI did not differ. Estimated blood loss was higher in patients without AC/AP but it did not reach statistical significance (419 ml vs. 339 ml; $p=0.17$). In this matched population, patients without AC/AP had lower complication rate (21.4% vs. 38.6%; $p=0.03$), lower HC (4.2% vs. 31.4%; $p<0.001$) and decreased transfusions (8.6% vs. 24.3%).

Predictors of complications

In multivariate analysis that adjusted for age, ASA score, Body Mass Index, surgeon's experience, aspirin, clopidogrel, AC, opening of the upper urinary tract, RENAL score and tumour size, AC (OR=4.3; IC95% [1.2-15.9]; $p=0.03$) and tumour size (OR=1.8; IC95% [1.3-7.2]; $p=0.03$) were the only predictors of complications. Aspirin (OR=2.4; IC95% [0.4-9.3]; $p=0.15$) or clopidogrel (OR=1.6; IC95% [0.4-9.3]; $p=0.58$) had no impact on the occurrence of a complication (table 4).

Discussion

With the aging of the population, many patients are being treated with AC or AP for various cardio-vascular conditions. These treatments can be difficult to handle when planning a surgical procedure. This is particularly true in the case of PN where the risk of peri and post-operative bleeding is the most feared complication¹⁴.

Our study confirmed that patients treated with AC or AP had an increased rate of HC after RAPN. Studies on the subject are very limited. In one of the largest published series (47 patients with AC undergoing open or laparoscopic PN), Kefer reported a four times higher blood loss but similar transfusion rates compared to patients without AC¹⁵. However time period between AC discontinuation and resumption was longer than in our series (aspirin and clopidogrel were stopped ten days before and resumed seven days after PN). In a cohort of 1,005 RPN, Kara et al found no impact of prophylactic AC on the occurrence of haemorrhagic events¹⁶. Our findings suggest that therapeutic AC increase the risk of HC compared to prophylactic AC.

We also found that therapeutic AC was a major determinant of perioperative morbidity. It was associated with a significant increase of global complications and was one of the two only significant predictive factors in multivariate analysis. We believe this is an important finding that can help counsel the patients regarding the risks of surgery. Clear information should be delivered to patients taking AC or AP to emphasize the increased risk of complications. Indeed, the risk of bleeding after cryoablation or radiofrequency ablation in patients with AC is much lower^{16,17}.

AP was also associated with the risk of bleeding during or after PN. This is in line with the findings of previous series¹⁶. Moreover, we observed a more important risk of bleeding (although not significant) in the small group of patients in whom aspirin had not been discontinued compared to those in whom it had been stopped. To date only two series have aimed to determine the impact of continuing aspirin during the perioperative period of PN. Althaus reported a series of six RAPN performed under aspirin concluding that in selected cases RAPN was safe and feasible, but it is difficult to draw any conclusion from such a small case series⁵. More recently, Leavitt reported similar postoperative complications in patients « on-aspirin » and « off-aspirin » undergoing

laparoscopic PN implying that it was safe to maintain during PN¹⁸. Conversely, we found a clear trend towards higher complications in patients in whom aspirin was continued. One explication could be that tumours were more complex in our series.

Peri-operative blood loss was similar in both groups even after match-paired analysis, which means that AP/ therapeutic AC treatments have an impact mainly on the post-operative period and do not make surgery harder.

Patients under AC and/or AP have a significantly higher risk of complications after RAPN. We believe this finding can be helpful to counsel patients regarding the options to treat localized renal masses. Patients under AC/AP with a small renal mass might be advised to consider ablative treatments rather than surgery.

Our study has some limitations inherent to its retrospective design. Suspension and resumption of AC/AP were not standardized. Also, we did not differentiate AC and AP patients in our analysis, which could be a matter of debate. We arbitrarily defined HC as hematoma requiring transfusion, pseudo-aneurysm or arterio-venous fistula but there is no consensus in the literature. The relatively limited number of patient under AP/therapeutic AC is another limitation of our study that must be confirmed by publications from other institutions. Finally, there were some minor differences between both groups, which could have biased our results despite the use of multivariate and match-paired analyses.

Conclusion

In this series therapeutic AC increased the risk of overall complications and HC after RAPN whereas AP only increased the risk of HC. Although always stopped pre-operatively, AC was a major determinant of post-operative complications. Although additional data is needed, we believe our findings should be taken into consideration when counselling patients with AP/AC on the management of a renal tumour.

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Table 1. Patients' characteristics

	Patients under AC/AP N=70	Patients without AC/AP N=463	P value
Mean (SD) age, years	66.6 $\pm$ 0.5	59.7 $\pm$ 1.4	0.001*
Mean (SD) BMI	27.03 $\pm$ 1.5	27.07 $\pm$ 0.6	0.98
Mean (SD) ASA score	2.5 $\pm$ 0.5	1.7 $\pm$ 0.6	0.001*
Number of patients under AC	20 (28%)	-	-
Number of patients under NOAC	6 (8%)	-	-
Number of patients under Aspirin	35 (50%)	-	-
Number of patients under Clopidogrel	18 (25%)	-	-
Mean (SD) Tumour complexity according to RENAL nephrometry score	6.6	7.2	0.07
Mean (SD) tumour size, mm	32.1 $\pm$ 1.8	32.8 $\pm$ 0.7	0.70
Pathological subtype			0.96
Renal cell carcinoma	36 (60%)	224 (60.5%)	
Others	24 (40%)	46 (39.5%)	

Patients under anticoagulant (AC), NOAC or antiplatelet (AP) and patients without AC, NOAC or AP

*: statistically significant

Table 2. Perioperative outcomes between patients with AC or AP and without AC or AP

	Patients under AC/AP (n=70)	Patients without AC/AP (n=463)	P value
Operative time $\pm$ SD (min)	142.9 $\pm$ 55	136.6 $\pm$ 50	0.35
Warm ischemia time $\pm$ SD (min)	14.3 $\pm$ 6.3	15.1 $\pm$ 8.1	0.45
Early unclamping (%)	45 (71.4%)	244 (81%)	0.09
Opening of upper urinary tracts (%)	21 (36.2 %)	166 (39.1%)	0.66
Conversion to open surgery (%)	3 (5.3%)	4 (0.9%)	0.19
Estimated blood loss $\pm$ SD (ml)	339 $\pm$ 308	282 $\pm$ 405	0.29
Hemostatic agents use (%)	19 (35.2%)	64 (37.6%)	0.74
Complications (%)	22 (39.2%)	51 (17.4%)	<0.001*
Major complications (Clavien $\geq$ 3)	10 (19.2%)	18 (9.6%)	0.01*
<i>Surgical complications</i>	6 (60%)	10 (55%)	
<i>Medical complications</i>	4 (40%)	4 (20%)	
Hemorrhagic complications	17 (32.7%)	18 (9.6%)	<0.001*
<i>Hematoma</i>	4 (23.5%)	8 (44.4%)	
<i>Pseudoaneurysm</i>	7 (41.2%)	9 (50.0%)	
<i>Arterio-veinous fistula</i>	6 (35.3%)	-	
Transfusion rate (%)	13 (25%)	19 (10%)	0.008*
Length of hospital stay (days)	5.1 $\pm$ 0.2	3.9 $\pm$ 0.1	<0.001*

*: statistically significant

Table 3: match-paired analysis

	Patients under AC/AP N=70	Patients without AC/AP N=70	p-value
Mean RENAL score	6.6 ± 0.3	6.6 ± 0.3	0.99
ASA score : 1 2 3	34 (48.6%) 34 (48.6%) 2 (2.8%)	34 (48.6%) 34 (48.6%) 2 (2.8%)	1
Mean tumor size (mm)	32.1 ± 1.8	32.1 ± 1.8	0.99
Mean age (years)	66.6 ± 1.1	64.6 ± 1.1	0.26
Mean Body Mass index (kg/m²)	27.0 ± 0.7	27.5 ± 0.7	0.65
Estimated blood loss (ml)	339 ± 41	419 ± 40	0.17
Operative time (min)	142.9 ± 7.4	172.2 ± 7.4	0.006*
Complication	27 (38.6%)	15 (21.4%)	0.03*
Hemorrhagic complication	22 (31.4%)	3 (4.2%)	<0.001*
Major complication	13 (18.6%)	7 (10%)	0.15

Transfusion	17 (24.3%)	6 (8.6%)	0.01*
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* : statistically significant

Table 4: Multivariate analysis: predictors of complications

Variable	Odds ratio (95% CI)	p
Aspirin	2.4 (0.7-7.7)	0.15
Clopidogrel	1.6 (0.4-9.3)	0.58
Anticoagulant	4.3 (1.2-15.9)	0.03*
Opening of upper urinary tracts	1.3 (0.5-3.3)	0.52
Surgeon's experience		
< 20 cases	1 (Ref)	
20-50 cases	0.7 (0.2-1.9)	0.46
> 50 cases	0.9 (0.4-2.3)	0.92
ASA		
1	1 (Ref)	
2	0.7 (0.2-2.1)	0.50
3	1.3 (0.3-5.3)	0.71
RENAL Score	1.9 (0.3-11)	0.48
Tumour size	1.8 (1.3-7.2)	0.03*
Age	1.9 (0.2-18.6)	0.57
BMI	7.2 (0.4-137)	0.17

*Statistically significant