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Urothelial Cancer

Impact of Antiaggregant and Anticoagulant Medications on Perioperative Complications in Upper Tract Urothelial Carcinoma

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Abstract

Background and objective: Contemporary data are limited regarding the clinical practice of administering anticoagulant and antiplatelet medications (AA) perioperatively for patients with upper tract urothelial carcinoma (UTUC). Our aim was to investigate real-world AA perioperative management among patients with UTUC who underwent radical nephroureterectomy (RNU) and the impact on perioperative complications.

Methods: We conducted a retrospective analysis of data from the Clinical Research Office of the Endourology Society UTUC registry. Patients were stratified into two groups according to perioperative AA use in the RNU cohort. Baseline characteristics were compared between the control and AA groups and intraoperative and postoperative complications were analyzed. We also conducted subgroup analysis for patients who discontinued AA use in comparison to those who continued AA therapy. Univariable and multivariable analyses were performed to identify predictors of perioperative complications.

Key findings and limitations: A total of 1264 patients who underwent RNU were included in the analysis. Of these, 393 (31%) had AA treatment before RNU and 871 (69%) did not. Intraoperative complications occurred in 23 patients (5.9%) in the AA group and 41 (4.7%) in the control group. Postoperative complications occurred in 101 patients (26%) in the AA group and 182 (21%) in the control group. Multivariable logistic regression demonstrated that AA was not an independent risk factor for either intraoperative complications (odds ratio 0.93, 95% confidence interval [CI] 0.48–1.83; p = 0.84) or postoperative complications (odds ratio 0.93, 95% CI 0.66–1.30; p = 0.66).

Conclusions and clinical implications: Anticoagulant and antiaggregant therapy in patients undergoing RNU is safe, with no difference in the incidence of intraoperative and postoperative complications.

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Patient summary: Our analysis for patients with cancer in the upper urinary tract showed that taking drugs to prevent blood clots before surgery to remove a kidney is safe. We found no significant differences in complication rates in comparison to patients not taking these drugs.

The Clinical Research Office of the Endourology Society UTUC registry study is registered on ClinicalTrials.gov as NCT02281188.

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1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) is a rare cancer, accounting for only 5–10% of urothelial carcinoma [1]. Radical nephroureterectomy (RNU) is the standard treatment for UTUC, whereas kidney-sparing surgery is an option for localized low-risk disease or patients with imperative indications [2]. Preoperative management is crucial for the best patient outcomes.

Anticoagulant and antiaggregant medications are widely used for the treatment and secondary prevention of atherothrombotic events and other thrombotic disorders [3,4]. Anticoagulants inhibit the coagulation cascade and prevent the formation of blood clots, while antiaggregants work by inhibiting platelet aggregation and reducing the risk of arterial thrombosis [5]. Although anticoagulants and antiaggregants are necessary for patients with atrial fibrillation or previous venous thromboembolism, preoperative management remains a challenge in urology [6,7]. Contemporary data are limited regarding clinical practice for continuation of anticoagulant and antiaggregant therapy in the perioperative period for patients with UTUC for whom surgery is planned. Therefore, we investigated realworld preoperative management of anticoagulant and/or antiaggregant (AA) therapy and the impact on perioperative complications using data from the Clinical Research Office of the Endourology Society (CROES) UTUC registry.

2. Patients and methods

2.1. Study design and population

The CROES-UTUC registry, one of the largest real-world prospective global data sets on the management of UTUC, was established in 2014. Data were collected for patients aged ≥ 18 yr with suspected UTUC who were undergoing any diagnostic or surgical intervention at 101 centers in 29 countries [8]. The study criteria were wide-ranging to provide comprehensive real-world data. The registry follows the recommendations of the Agency for Healthcare Research and Quality for the design and use of patient registries for scientific, clinical, and health policy purposes [9] and is registered on ClinicalTrials.gov as NCT02281188.

The CROES-UTUC registry collected clinical data on baseline characteristics, risk factors, clinical assessment, intervention received, and survival outcomes for the target population. Data from all participating centers were collected using an online web-based data management system located and maintained at the CROES office.

2.2. Cohort information

Patient data collection started in December 2014 and ended in March 2019. Patients aged \geq 18 yr undergoing RNU for pathologically confirmed UTUC were included. The exclusion criteria were as follows: (1) patients without information for surgical treatment, intraoperative or postoperative complications, or AA use; and (2) patients who did not undergo RNU as planned or who underwent RNU during follow-up. Baseline patient characteristics, disease information, treatment details, and postoperative data were extracted from the database. AA use included antiplatelet medications, conventional anticoagulants (warfarin), and novel anticoagulation agents. The cohort was dichotomized into the AA group and the control group (no AA use).

2.3. Study outcomes

The primary outcomes for this study were overall intraoperative and postoperative complications. Intraoperative events were categorized into four types: inadvertent ureteric rupture (avulsion or ureter injury); bleeding requiring transfusion; bowel injury; and other. Postoperative complications were categorized into six types: major adverse cardiac events; significant hematuria requiring intervention or transfusion; sepsis; major cerebrovascular events; pulmonary complications; and other. The Clavien-Dindo classification of postoperative complications was applied when assessing the results.

2.4. Statistical analysis

Data were analyzed using SPSS v25.0 (IBM Corp., Armonk, NY, USA). Primary outcomes are summarized using descriptive statistics in terms of the frequency and proportion for categorical variables, and the median and interquartile range (IQR) for continuous variables. No comparison of baseline characteristics was conducted for this registry study, as this would not contribute to reducing potential confounding factors. Logistic regression analyses were used to estimate the odds ratio (OR) and 95% confidence interval (CI) for effects. Univariable logistic analysis was used to select significant factors (p < 0.2) for further multivariable logistic analysis. Subgroup analyses were performed for stratification by AA continuation status, and for anticoagulant versus antiaggregant use.

3. Results

3.1. Patient demographics

A total of 1264 patients who underwent RNU and had information on perioperative complications and AA use from December 12, 2014 to March 11, 2019 were included in this analysis. Of these, 393 patients (31%) received AA therapy before RNU and the other 871 (69%) did not (Supplementary Fig. 1).

Table 1 summarizes the clinicopathologic characteristics of the study population. Median age was higher in the AA group than in the control group (74 vs 69 yr). The AA group had a greater proportion of male patients (81% vs 69%) and former (39% vs 31%), while the control group had better ASA and CCI scores.

3.2. Intraoperative and postoperative complications

3.2.1. Complications in the AA and control groups

Intraoperative complications occurred in 23 patients (5.9%) in the AA group and 41 (4.7%) in the control group. Postoperative complications occurred in 101 patients (26%) in the AA group and 182 (21%) in the control group. Table 2 lists the numbers of events for the intraoperative and postoperative complication categories. Detailed information for complications in the "other" categories is listed in Supple-

Table 1 – Baseline characteristics of the study population by gro

Parameter	AA group (<i>n</i> = 393)	Control group (n = 871)		
Median age, yr (IQR)	74 (68-80)	69 (62-77)		
Male, n (%)	318 (81)	602 (69)		
Median BMI, kg/m ² (IQR)	25 (24–29)	25 (23–28)		
Smoking status, <i>n</i> (%)	100 (25)	200 (24)		
No	100 (25)	298 (34)		
Yes, present	106 (27)	224 (26)		
Yes, past	153 (39)	266 (31)		
ASA score, n (%)				
I–II	140 (36)	637 (73)		
III-IV	249 (63)	223 (26)		
CCI, n (%)				
0	69 (18)	237 (27)		
1–2	156 (40)	229 (26)		
3-4	103 (26)	75 (8.6)		
>4	47 (12)	26 (3.0)		
Surgical approach, n (%)				
Open	133 (34)	295 (34)		
Laparoscopic	205 (52)	486 (56)		
Robotic	49 (13)	80 (9.2)		
pT stage, n (%) ^a				
<pt2< td=""><td>175 (45)</td><td>339 (39)</td></pt2<>	175 (45)	339 (39)		
≥pT2	201 (51)	485 (56)		
Tumor grade, n (%)				
Grade 1	44 (11)	106 (12)		
Grade 2	89 (23)	206 (24)		
Grade 3	227 (58)	477 (55)		
Tumor size, n (%)				
<2 cm	80 (20)	170 (20)		
≥2 cm	302 (77)	656 (75)		
Multifocal tumor, n (%)				
No	253 (64)	611 (70)		
Yes	89 (23)	152 (18)		

AA = anticoagulant and/or antiaggregant use; BMI = body mass index; ASA = American Society of Anesthesiologists; CCI = Charlson comorbidity index; IQR = interquartile range.

^a TNM 2009 staging scheme.

Table 2 – Complications in the control and AA groups

Complication	AA group (n = 393)	Control group (n = 871)
Intraoperative complications, n (%)	23 (5.9)	41 (4.7)
Inadvertent rupture of ureter	1 (0.30)	2 (0.20)
Bleeding requiring transfusion	7 (1.8)	21 (2.4)
Bowel injury	2 (0.50)	7 (0.80)
Other	14 (3.6)	16 (1.8)
Postoperative complications, n (%)	101 (26)	182 (21)
Major adverse cardiac event	14 (3.6)	10 (1.1)
Significant hematuria	5 (1.3)	11 (1.3)
Sepsis	26 (6.6)	47 (5.4)
Major cerebrovascular event	4 (1.0)	2 (0.20)
Pulmonary complications	12 (3.1)	10 (1.1)
Other	43 (11)	71 (8.2)
AA = anticoagulant and/or antiaggrega	ant use.	

mentary Table 1. Classification of postoperative complications by Clavien-Dindo grade revealed a higher proportion of patients with Clavien-Dindo grade II postoperative complications in the AA group (17% vs. 12%; Supplementary Table 2).

Univariable logistic regression analysis revealed that AA use was not a risk factor for either intraoperative (OR 1.26, 95% CI 0.74–2.13; p = 0.39) or postoperative complications (OR 1.31, 95% CI 0.99–1.73; p = 0.06). Multivariable logistic regression also demonstrated that AA use was not an independent risk factor for either intraoperative (OR 0.93, 95% CI 0.48–1.83; p = 0.84) or postoperative complications (OR 0.93, 95% CI 0.66–1.30; p = 0.66; Table 3).

3.2.2. Complications by AA continuation status

Of the 393 patients in the AA group, 280 (71%) stopped AA therapy before RNU and the remaining 79 (20%) continued AA use. Of the 79 patients in the AA continuation group, 72 used antiaggregants, two used anticoagulants, two used a combination (Persantin + Asasantin), and three did not have accurate information regarding their medications. Supplementary Table 3 lists baseline characteristics for the control, AA discontinuation, and AA continuation groups. Intraoperative complications occurred in 16 patients (5.7%) in the AA discontinuation group and five (6.9%) in the AA continuation group. Postoperative complications occurred in 69 patients (25%) in the AA discontinuation group and 19 (26%) in the AA continuation group. Supplementary Table 4 lists the numbers of events for the intraoperative and postoperative complication subtypes. Multivariable logistic regression indicated that AA discontinuation (OR 0.92, 95% CI 0.44–1.94; *p* = 0.83) and AA continuation (OR 1.12, 95% CI 0.32–3.95; p = 0.86) were not independent risk factors for intraoperative complications. AA discontinuation (OR 1.04, 95% CI 0.70–1.55; p = 0.86) and AA continuation (OR 0.79, 95% CI 0.39–1.63; *p* = 0.53) were also not associated with postoperative complications (Supplementary Table 5). Most patients in the AA continuation group were using aspirin (86% vs 54%; Supplementary Table 6).

3.2.3. Anticoagulant versus antiaggregant use

Supplementary Table 7 summarizes clinicopathologic characteristics of the anticoagulant and antiaggregant subgroups. Four patients (5.3%) in the anticoagulant group

Parameter	Intraoperative complications				Postoperative complications			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p valu
AA use	1.26 (0.74-2.13)	0.39	0.93 (0.48-1.83)	0.84	1.31 (0.99-1.73)	0.06	0.93 (0.66-1.30)	0.66
Age	1.02 (0.99-1.04)	0.20	1.02 (0.98-1.05)	0.37	1.01 (0.99-1.02)	0.18	1.00 (0.99-1.02)	0.72
Male sex	1.03 (0.58-1.82)	0.92			1.30 (0.95-1.76)	0.10	1.13 (0.77-1.68)	0.54
Body mass index	0.99 (0.93-1.06)	0.90			0.99 (0.96-1.03)	0.71		
Smoking status								
No	Reference				Reference		Reference	
Yes, present	0.95 (0.48-1.90)	0.88			1.21 (0.85-1.72)	0.29	1.15 (0.75-1.78)	0.52
Yes, past	1.21 (0.65-2.25)	0.54			1.33 (0.96-1.85)	0.09	1.18 (0.79-1.76)	0.41
ASA score								
I–II	Reference		Reference		Reference			
III-V	1.48 (0.90-2.46)	0.13	1.20 (0.63-2.29)	0.58	1.15 (0.88-1.51)	0.32		
CCI								
0	Reference				Reference		Reference	
1-2	1.26 (0.66-2.40)	0.49			0.98 (0.67-1.41)	0.90	0.98 (0.66-1.45)	0.92
3-4	0.85 (0.34-2.04)	0.72			1.74 (1.14-2.64)	0.01	1.78 (1.13-2.80)	0.01
>4	1.05 (0.34-3.24)	0.93			3.12 (1.82-5.34)	< 0.01	3.13 (1.75-5.57)	< 0.01
Surgical approach	, ,				. ,		. ,	
Open	Reference		Reference		Reference			
Laparoscopic	0.63 (0.36-1.11)	0.11	0.75 (0.40-1.38)	0.35	0.99 (0.74-1.33)	0.96		
Robotic	0.93 (0.39-2.19)	0.86	0.88 (0.29-2.66)	0.81	1.32 (0.84-2.08)	0.22		
TNM (2009) staging	, ,		· · · ·		. ,			
<pt2< td=""><td>Reference</td><td></td><td></td><td></td><td>Reference</td><td></td><td></td><td></td></pt2<>	Reference				Reference			
≥pT2	1.38 (0.80-2.38)	0.25			0.92 (0.70-1.21)	0.54		
Tumor grade								
G1	Reference		Reference		Reference			
G2	0.44 (0.18-1.11)	0.08	0.40 (0.14-1.10)	0.08	0.94 (0.58-1.53)	0.81		
G3	0.80 (0.39-1.64)	0.54	0.70 (0.31-1.57)	0.39	1.10 (0.72-1.69)	0.66		
Tumor size								
<2 cm	Reference				Reference			
>2 cm	1.09 (0.57-2.08)	0.79			1.04 (0.74–1.45)	0.83		
Multifocal tumor								
No	Reference		Reference		Reference			
Yes	1.56 (0.87–2.81)	0.14	1.38 (0.71-2.65)	0.34	0.79 (0.56–1.14)	0.21		

Table 3 – Logistic regression analyses for overall intraoperative and postoperative complications

and 17 (5.7%) in the antiaggregant group experienced intraoperative complications, while 19 (25%) in the anticoagulant group and 76 (26%) in the antiaggregant group had postoperative complications. The numbers of events for each subtype are presented in Supplementary Table 8. Multivariable logistic regression demonstrated that in comparison to anticoagulant use, antiaggregant use was not an independent risk factor for either intraoperative (OR 1.13, 95% CI 0.23–5.64; p = 0.88) or postoperative complications (OR 1.03, 95% CI 0.51–2.08; p = 0.95; Supplementary Table 9).

4. Discussion

Our study results reveal that AA use was not associated with statistically significant differences in intraoperative and postoperative complications for patients with UTUC undergoing RNU. Furthermore, AA discontinuation before RNU did not seem to increase or decrease the likelihood of intraoperative and postoperative complications. However, further studies are needed to confirm these findings.

Complications were categorized as four intraoperative types and six postoperative types. Incidence rates for inadvertent rupture of a ureter, bleeding, bowel lesions, and other intraoperative complications were comparable between the groups. Although the incidence of postoperative complications was similar between the AA and control groups overall, the AA group had higher rates for cardiac and pulmonary complications. However, subgroup analysis revealed that the incidence of postoperative complications in the "other" category was higher in the AA continuation group than in the AA discontinuation group (18% vs 8.9%; Supplementary Table 4). Given these findings, it is of utmost importance to closely monitor patients after RNU, particularly those who continue AA treatment throughout the entire perioperative period.

Clinicians face a predicament when considering cessation of AA for patients undergoing surgery procedures in weighing the hazard of hemorrhage during and after surgery against the potential threat of thrombosis that arises from AA discontinuation [10]. Surgeons must have a comprehensive knowledge of the AA agent in question, including its mode of operation, any counteracting agents available, and the duration required to regain the therapeutic effect [11]. The higher risk of cardiac and pulmonary complications following RNU observed in the AA group in our study might stem from a surge in platelet activation occurring as a rebound effect subsequent to AA discontinuation before the procedure [12,13]. Results from several modest-sized studies on administration of aspirin and warfarin during TRUS biopsy collectively suggest that low-dose aspirin, and possibly warfarin, is generally considered safe [14,15]. Our analysis of AA use in patients undergoing RNU also revealed that this practice is generally safe.

Patients with UTUC used different AA agents in the realworld setting, with acetylsalicylic acid (ASA; aspirin) the drug most frequently used. Albisinni et al [16] reported that maintenance of ASA therapy for patients undergoing radical cystectomy was safe and did not exacerbate postoperative bleeding complications. Furthermore, ASA continuation was correlated with lower risk of ischemic events, in contrast to ASA discontinuation before surgical intervention. This suggests that uninterrupted ASA therapy may offer a protective effect against cardiovascular events in patients undergoing robotic cystectomy. The authors concluded that, in line with any surgical decision-making process, surgeons have a duty to select the optimal treatment option for patients while minimizing the potential for adverse events in this specific setting [16]. Wessels et al [17] also evaluated surgical outcomes of radical cystectomy for patients on continuous ASA antiplatelet therapy and assessed its safety and potential advantages. Both univariate and multivariate analyses demonstrated that ongoing ASA therapy was not an independent predictor of transfusion requirement or the occurrence of severe postoperative complications [17]. To the best of our knowledge, the current study is the first to evaluate the impact of uninterrupted AA administration on both perioperative and postoperative complications for patients undergoing RNU.

Our study has several limitations that must be considered. First, despite the prospective and consecutive nature of data collection, the registry lacked predefined research objectives at inception, with potential for selection bias in the current comparative analysis because of missing or incomplete data. As the registry is now closed, validation of the outcomes is not feasible. However, given the rarity of UTUC, prospective multicenter registries represent a viable and valuable means of generating meaningful insights into this disease. Second, variations in clinical management and follow-up protocols across participating centers and within the cohort introduced heterogeneity. Despite these constraints, our findings offer valuable realworld insights for perioperative AA management in patients with UTUC.

5. Conclusions

AA therapy for patients undergoing RNU was not associated with statistically significant differences in intraoperative or postoperative complications in comparison to a control group not receiving AA therapy. However, the CIs for estimates of the effects of AA therapy on outcomes are compatible with both potential benefit and potential harm, highlighting the need for cautious interpretation and further investigation to confirm these findings.

Author contributions: Jeremy Yuen-Chun Teoh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: de la Rosette, Teoh, Ng. Acquisition of data: Liu, Zhao. Analysis and interpretation of data: Liu. Drafting of the manuscript: Liu, Wong. Critical revision of the manuscript for important intellectual content: de la Rosette, Laguna, Ng, Teoh. Statistical analysis: Liu, Zhao. Obtaining funding: de la Rosette. Administrative, technical, or material support: de la Rosette, Ng, Teoh. Supervision: de la Rosette, Ng, Teoh. Other: None.

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Ethics considerations: This study was approved by the institutional review board and informed consent was obtained from the study subjects.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2025.02.007.

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