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Continuing acetylsalicylic acid during Robotic-Assisted Radical Cystectomy with intracorporeal urinary diversion does not increase hemorrhagic complications: results from a large multicentric cohort

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Abstract

Objectives: To evaluate whether continuing the antiplatelet drug acetylsalicylic acid≤100mg (ASA) during Robotic-assisted radical cystectomy (RARC) with intracorporeal urinary diversion (ICUD) increases the risk of peri-and postoperative hemorrhagic complications and overall morbidity. Indeed, guidelines recommend interrupting antiplatelet therapy before radical cystectomy; however, RARC with ICUD is associated to reduced estimated blood loss and blood transfusions compared to its open counterpart.

Methods: Data from a multicentric European database were analyzed. All participating centers maintained a prospective database of patients undergoing RARC with ICUD. We identified patients receiving antiplatelet therapy by acetylsalicylic acid ≤100mg. Patients were divided into three groups: those not taking acetylsalicylic acid (no-ASA), those where ASA was continued perioperatively (c-ASA) and

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those where ASA was interrupted perioperatively (i-ASA). Estimated blood loss and peri-and post-operative transfusions were recorded. Hemorrhagic complications, ischemic, thrombotic and cardiac morbidity was recorded and classified using the Clavien-Dindo score by a senior urologist.

Results: 640 patients were analyzed. Patients on acetylsalicylic acid were significantly older and had more comorbidities. No significant difference was found for estimated blood loss between no-ASA, c-ASA and i-ASA (280 vs. 300 vs. 200ml respectively; $P = 0.09$). Similarly, no significant difference was found for intraoperative (5% vs. 9% vs. 11%; $P = 0.07$) and postoperative transfusion rate (11% vs. 13% vs. 18%; $P = 0.17$). Higher ischemic complications were noted in the i-ASA group compared to no-ASA and c-ASA (4% vs. 0.6% vs. 1.4%; $P = 0.03$). On uni and multivariate logistic regression, continuing acetylsalicylic acid was not significantly associated to either major complications or post-operative transfusions.

Conclusions: Peri-operative acetylsalicylic acid continuation in RARC with ICUD does not increase hemorrhagic complications. Interrupting acetylsalicylic acid peri-operatively may expose patients to a higher risk of ischemic events.

1. Introduction

Robotic-assisted radical cystectomy (RARC) with intracorporeal urinary diversion (ICUD) is gaining increasing acceptance across urology departments worldwide [1]. Although the guidelines still consider the open procedure as gold standard [2], randomized controlled trials [3,4] have assessed its non-inferiority in terms of oncologic results, associated with a reduction of intraoperative estimated blood loss (EBL) and blood transfusions. Although a significant reduction in post-operative complications has yet been demonstrated [5], many key opinion leaders support the reduced invasiveness of RARC and the multiple "unquantifiable" advantages of the technique over open radical cystectomy [6].

Patients admitted for radical cystectomy are frequently elderly with significant cardiovascular co-morbidities [7]. As such, chronic daily antiplatelet therapy with acetylsalicylic acid ≤100mg is commonly seen in this particular population. Studies have suggested that continuing antiplatelet therapy perioperatively, especially for patients with significant cardiovascular co-morbidities, can reduce the risk of postoperative acute myocardial infarction for non-cardiac surgery [8]. However, EAU guidelines recommend interrupting antiplatelet and anticoagulant therapy before radical cystectomy [9], as the procedure is associated to elevated intraoperative bleeding [10]. To date, no study has explored the impact of continuous acetylsalicylic acid therapy during RARC with ICUD.

Aim of this study is to evaluate whether continuing the antiplatelet drug acetylsalicylic acid during RARC with ICUD increases the risk of peri-and post-operative hemorrhagic complications, as well as overall morbidity.

2. Patients and methods

The current project was launched by the European Association of Urology - Young Academic Urologists (EAU-YAU), Urothelial carcinoma working group in October 2020. A large multicentric database (14 European centres) of patients undergoing RARC with ICUD was constructed, including patients operated between 2015 and 2020. Only centres maintaining a local prospective registry of patients undergoing RARC with ICUD were invited to participate, each centre providing ethics committee and institutional review board approval. Currently, the database encloses >900 patients.

RARC with ICUD was performed to treat MIBC or high-risk recurrent or refractory non-MIBC. No formal contraindications for RARC with ICUD were imposed. Neoadjuvant therapy was administered following multidisciplinary discussion according to the protocols or trials of each centre. American Society of Anaesthesiology score was evaluated by a senior anaesthesiologist. Patients with incomplete data regarding antiplatelet or anticoagulant use (n =111), estimated blood loss (EBL) (n =134) and with non-oncologic pathology (n =17) were excluded from final analysis. Patients ($n = 8$) receiving other types of antiplatelet drugs than acetylsalicylic acid ≤100mg, as clopidogrel or ticlopidine, were also excluded. Patients were then categorized in those not receiving acetylsalicylic acid ≤100mg (no-ASA), those receiving the drug and continuing it through surgery (c-ASA), and finally those receiving acetylsalicylic acid ≤100mg and interrupting the drug 5-7 days prior to cystectomy (i-ASA). For this latter group of patients, acetylsalicylic acid was generally reintroduced 3-7 days after surgery.

All RARC procedures were performed using DaVinci Si or Xi robotic platforms. No bowel preparation was performed prior to surgery. All centres implemented an enhanced recovery after surgery protocol, although this was not standardized across departments. All patients underwent complete ICUD, regardless of the type of urinary diversion performed (ileal conduit vs. neobladder vs ureterocutaneostomy). Haemostatic agents were used only in selected cases according to surgeons' intraoperative evaluation. Following the ERAS society recommendations [11], nasogastric tube was always removed at the end of the procedure; early mobilization and early oral feeding was encouraged for all patients, starting on post-op day (POD) 1; multimodal opioid-sparing pain control was always prescribed. Low-molecular weight heparin was prescribed for four weeks following guidelines [2]. Ureteral catheters were usually removed on

POD 7-14 and urethral catheter (in case of neobladder reconstruction) on POD 10-21.

30-day postoperative complications were noted in local prospective databases. Complications were reported according to the modified Clavien-Dindo classification [12] and further divided in minor (Clavien I-II) and major complications (Clavien III-V). Any deviation from the normal postoperative course occurring during the first 30 days after surgery was considered a complication. Any death following re-hospitalization for any post-surgical complication was attributed to bladder cancer and thus considered as Clavien V. Transfusions were administered in anaemic patients following local guidelines.

To detail cardiovascular morbidity, we specifically defined haemorrhagic, ischemic, thrombotic and cardiac complications. Haemorrhagic events included requiring a blood transfusion, hypovolemic shock, laparotomy/laparoscopy for postoperative bleeding and gastrointestinal bleeding requiring endoscopy. Ischemic complications included arterial embolism, ischemic stroke, critical limb ischemia and bowel ischemia. Thrombotic complications comprehended deep venous thrombosis and pulmonary embolism. Cardiac complications included acute myocardial infarction, arrythmias requiring pharmacologic intervention and cardiogenic shock.

The ten points of the Martin's criteria on surgical complications are respected in the present study [13].

Descriptive statistics were used to illustrate results. Difference across the three groups (non ASA, c-ASA and i-ASA) were tested using Kruskall-wallis test for continuous variables and McNemar's test for categoric variables. Uni and multivariate logistic regressions were performed to assess the association between antiplatelet therapy and major complications complications or post-operative transfusions. All statistical analyses were performed using Stata 14.1 (StataCorp, TX); a P-value$\leq$0.05 was considered statistically significant. The guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [14] were respected in the current study.

3. Results

A total of 640 patients were available for final analyses. Baseline characteristics, as well as pathologic data are shown in (Table 1).

Patients receiving acetylsalicylic acid $\leq$100mg (c-ASA and i-ASA) were significantly older and presented more comorbidities (measured via both the American Society of Anesthesiology score and the Charlson comorbidity score). However, when restricting analysis to these patients receiving acetyl salicylic acid (c-ASA and i-ASA), no significant difference was found in terms of age (*Mann-Whitney P = 0.60*) or Charlson comorbidity index (*Mann-Whitney P=0.84*). While the same rate of neobladders were reconstructed across patients not receiving antiplatelet drugs (no-ASA) and those continuing therapy through surgery (c-ASA) (43% vs. 44%), this rate was significantly lower in patients interrupting therapy before RARC (i-ASA) (22%). Overall, pathologic characteristics were comparable across the 3 groups and no significant difference in EBL was observed ($P = 0.09$). (Table 2) details all peri-operative and postoperative complications encountered in this study. Although higher in the group interrupting ASA (Table 2), the rate of intraoperative ($P = 0.07$) and postoperative ($P = 0.17$) transfusion was not significantly different across the three groups. Similarly, the overall and major complications rates were comparable. However, patients interrupting acetyl-salicylic acid experienced a significant increase in ischemic complications ($P = 0.03$) compared to those not receiving the drug and those continuing it through surgery.

On uni and multivariate logistic regression (Table 3), male patients and those receiving a neobladder reconstruction were more likely to experience major complications (Clavien $\geq$ III). Age and number of resected lymph nodes were significantly associated to postoperative blood transfusion on crude and adjusted logistic regressions. Continuing acetylsalicylic acid during surgery was not significantly associated either to major complication risk or to postoperative transfusions.

4. Discussion

Continuing or interrupting antiplatelet therapy perioperatively for patients with high cardiovascular risk profile remains a major dilemma in clinical practice. While withdrawal of antiplatelet therapy could increase the risk of major cardiovascular and thrombotic events, it may supposedly decrease the perioperative bleeding risk. These competing risks of ischemic and hemorrhagic events make antiplatelet perioperative management a crucial modifiable factor [10]. Although guidelines recommend interrupting antiplatelet therapy perioperatively, as it could possibly increase the bleeding risk in an already high-risk procedure, literature is sparse and there is no strong supporting evidence for such recommendation. While some data has been published for open radical cystectomy [15,16], this dilemma remains especially questionable in RARC, as no studies are yet published.

To our knowledge, this is the first study to assess the influence of continuing acetylsalicylic acid during RARC with ICUD on peri and postoperative hemorrhagic risk, as well as cardiovascular morbidity. The results on 640 patients have shown that acetylsalicylic acid should not be interrupted in patients undergoing RARC with ICUD for three main reasons: (1) no significant difference was found for estimated blood loss and transfusion rate between the groups no-ASA, i-ASA and c-ASA; (2) no significant difference in major complications were found between these groups; and (3) a higher rate of ischemic complications were noted when interrupting acetylsalicylic acid before surgery.

Table 1
Preoperative and pathologic data

Preoperative	Entire cohort ($n = 640$)	No-ASA ($n = 494$)	c-ASA ($n = 70$)	i-ASA ($n = 76$)	*P*-value
Age *(years)* median (IQR)	67 (60 −73)	66 (58 −72)	70 (66 −75)	71 (64 −77)	<0.0001
Mean ± SD	66±10	65±10	70±9	70±8	
Sex					0.06
M	535 (84%)	405 (82%)	65 (93%)	65 (86%)	
F	105 (16%)	89 (18%)	5 (7%)	11 (14%)	
BMI (kg/m^2). median (IQR)	25.9 (23.6 −28.4)	25.6 (23.4 −28.4)	27 (24.3 −28.5)	26.2 (24.2 −28.4)	0.07
Mean ± SD	26.2±4.1	26±4.3	26.8±3.6	26.6±3.4	
Smoking status					
Never	193 (30%)	149 (31%)	10 (14%)	34 (45%)	0.001
Active	205 (33%)	157 (32%)	32 (46%)	16 (21%)	
Former	228 (35%)	176 (36%)	26 (37%)	26 (34%)	
Unknown	14 (2%)	12 (3%)	2 (3%)	0	
Anticoagulant therapy	36/640 (6%)	31/494 (6%)	1/70 (1%)	4/76 (5%)	0.25
American Society of Anesthesiology score					<0.0001
1	65 (10%)	57 (12%)	4 (6%)	4 (5%)	
2	396 (62%)	326 (66%)	29 (41%)	41 (54%)	
3	177 (27.7%)	111 (22%)	37 (53%)	29 (38%)	
4	2 (0.3%)	0	0	2 (3%)	
Charlson comorbidity index					<0.0001
2	140 (22%)	128 (26%)	5 (7%)	7 (9%)	
3	172 (27%)	139 (28%)	16 (23%)	17 (22%)	
4	163 (25%)	127 (26%)	17 (25%)	18 (24%)	
5	98 (15%)	60 (12%)	16 (22%)	23 (30%)	
6	43 (7%)	29 (6%)	8 (12%)	6 (8%)	
7	13 (2%)	6 (1%)	4 (6%)	3 (4%)	
≥8	11 (2%)	5 (1%)	4 (6%)	2 (3%)	
Neoadjuvant chemo or immunotherapy					0.56
No	292 (46%)	222 (45%)	34 (49%)	38 (51%)	
Yes	348 (54%)	272 (55%)	36 (51%)	37 (49%)	
Urinary diversion					0.002
Ileal conduit	354 (55%)	267 (54%)	35 (50%)	52 (68%)	
Neobladder	260 (41%)	212 (43%)	31 (44%)	17 (22%)	
Ureterocutaneostomy	26 (4%)	15 (3%)	4 (6%)	7 (9%)	
Pathologic					
pT					0.71
pT0	192 (30%)	150 (30%)	21 (30%)	21 (27%)	
pTa; pTis; pT1	161 (25%)	125 (25%)	17 (24%)	19 (25%)	
pT2	104 (16%)	72 (15%)	14 (20%)	18 (24%)	
pT3	143 (22.7%)	116 (23.6%)	12 (17%)	15 (20%)	
pT4	38 (6%)	29 (6%)	6 (9%)	3 (4%)	
pTx	2 (0.3%)	2 (0.4%)	0	0	
pN					0.14
pN0	500 (78%)	389 (80%)	56 (80%)	55 (72%)	
pN1	60 (9%)	44 (9%)	8 (11%)	8 (12%)	
pN2	55 (9%)	46 (9%)	5 (8%)	4 (5%)	
pN3	11 (2%)	7 (1%)	0	4 (5%)	
pNx	14 (2%)	8 (1%)	1 (1%)	5 (6%)	
N resected lymph nodes median (IQR)	19 (14 −28)	20 (14 −29)	18 (12 −23)	19 (13 −27)	0.20
Mean ± SD	21±12	22±12	19±11	20±11	
Positive surgical margins	32/640 (5%)	24/494 (5%)	4/70 (6%)	4/76 (5%)	0.94
Locally advanced (pT3-4 or pN1-3)	223/640 (35%)	174/494 (35%)	23/70 (33%)	26/76 (34%)	0.92

c-ASA: Acetyl-salicilic acid continued throughout surgery. **i-ASA**: Acetyl-salicilic acid interrupted 5-7 days before surgery.

Perioperative acetylsalicylic acid continuation has been studied in high-risk patients undergoing non-cardiac surgery in general. In a randomized controlled trial performed by Oscarsson et al. [16], perioperative ASA use was demonstrated to reduce the risk of major cardiovascular events without increasing bleeding complications. This study included patients undergoing all types of surgery (abdominal, urologic, orthopedic and gynecological); among urologic surgeries were prostate surgery (open or transurethral), open cystectomy and open nephrectomy. Another

Table 2
Perioperative, postoperative and complication data

	Entire Cohort ($n = 640$)	No-ASA ($n = 494$)	Continued-ASA ($n = 70$)	Interrupted-ASA (n=76)	*P*-value
OR time *(mins)* median (IQR)	340 (294 −420)	345 (300 −420)	325 (285 −407)	318 (280-398)	0.07
Mean ± SD	349±94	353±95	328±97	335±87	
EBL *(ml)* median (IQR)	250 (200 −450)	280 (200 −450)	300 (200v484)	200 (110-425)	0.09
Mean ± SD	366±355	366±343	386±308	345±305	
Intraoperative transfusion	37/640 (6%)	23/494 (5%)	6/70 (9%)	8/76 (11%)	0.07
Number of intraop transfusions	2 (1 −2)	1 (1 −2)	2 (1 −2)	2(1 −2)	0.48
Postoperative transfusion	77/640 (12%)	54/494 (11%)	9/70 (13%)	14/76 (18%)	0.17
Number of post-op transfusions	2(2 −3)	2 (2 −3)	2(2 −4)	2 (2 −4)	0.12
Overall complications	364/640 (57%)	276/494 (56%)	37/70 (53%)	51/76 (67%)	0.13
Major complications (Clavien >III)	120/640 (19%)	91/494 (18%)	13/70 (19%)	16/76 (21%)	0.46
Bleeding complications	80/640 (12.5%)	58/494 (12%)	7/70 (10%)	15/76 (20%)	0.11
Ischemic complications	7/640 (1%)	3/494 (0.6%)	1/70 (1.4%)	3/76 (4%)	0.03
Thromboembolic complications	10/640 (1.5%)	8/494 (1.6%)	1/70 (1.4%)	1/76 (1.3%)	0.97
Cardiac complications	22/640	15/494 (3%)	2/70 (2.9%)	5/76 (6.6%)	0.277
Hospital stay *(days).* median (IQR)	11 (8 −16)	11 (8 −16)	11 (8 −14)	12 (8 −16)	0.95
Mean ± SD	13±7	13±7	14±10	13±6	
30-day Readmission rate	84/640	66/494	6/70	12/76	0.77

Table 3
Uni and multivariate logistic regressions exploring the risk of major complications (Clavien ≥III) or postoperative transfusion

	Univariate			Multivariate		
Risk of Major Complications	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	0.99	0.97 −1.01	0.40			
Sex (male vs. female)	3.75	1.69 −8.30	<0.001	3.27	1.54-6.96	0.002
BMI *(kg/m^2)*	0.99	0.94 −1.04	0.67			
American Society f Anesthesiology score (1 −2 vs. 3 −4)	0.74	0.47 −1.18	0.21			
Charlson Comorbidity Index	1.00	0.88 −1.14	0.97			
Acetylsalicilic therapy						
None	Ref	Ref	Ref	Ref	Ref	Ref
Continuous	1.01	0.53 −1.92	0.97	0.85	0.44 −1.68	0.65
Interrupted	1.18	0.65 −2.14	0.59	1.44	0.77 −2.66	0.25
pT stage (≤pT2 vs. ≥ pT3)	1.00	0.65 −1.54	0.99			
Continent urinary diversion	1.89	1.27 −2.82	0.002	1.68	1.12 −2.52	0.012
Number of resected Lymph nodes	1.02	1.001 −1.03	0.028	1.01	0.99 −1.03	0.16

	Univariate			Multivariate		
Risk of Postop Transfusion	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.04	1.009 −1.06	0.007	1.04	1.01 −1.07	0.007
Sex (male vs. female)	1.36	0.68 −2.73	0.39			
BMI *(kg/m^2)*	0.99	0.94 −1.05	0.86			
American Society f Anesthesiology score (1-2 vs. 3-4)	1.37	0.82 −2.27	0.23			
Charlson Comorbidity Index	1.16	0.99 −1.35	0.051			
Acetylsalicilic therapy						
None	Ref	Ref	Ref	Ref	Ref	Ref
Continuous	1.20	0.57 −2.56	0.63	1.14	0.53 −2.45	0.75
Interrupted	1.84	0.97 −3.51	0.064	1.72	0.89 −3.31	0.11
pT stage (≤pT2 vs. ≥ pT3)	1.40	0.84 −2.33	0.19			
Continent urinary diversion	0.71	0.43 −1.18	0.19			
Number of resected Lymph nodes	1.02	1.01 −1.04	0.017	1.03	1.01 −1.05	0.006

randomized controlled trial (POISE-2) done on 4998 patients (among which 16% underwent urologic "or" gynecologic procedures) has yet shown that continuing ASA had no significant effect on the rate of a composite of death or nonfatal myocardial infarction but increased the risk of major bleeding [17]. However, in these 2 studies, various confounding factors existed; subgroup analysis was not done regarding surgery type, and specific risk to each procedure was not evaluated.

Regarding urology, acetylsalicylic acid is usually continued throughout the perioperative period if there is no concern for active bleeding, such as in low-risk surgeries (endourological procedures, laser prostatectomy, etc.) [18]. However, for high-risk procedures such as radical cystectomy, guidelines and urological societies recommend interrupting a drug that theoretically increased the hemorragic risk.

Wessels et al. have assessed the impact of continuing antiplatelet therapy with acetylsalicylic acid on operative outcomes and cardiac morbidity in patients undergoing open radical cystectomy in a bicentric prospective study of 461 consecutive patients [15]. They have concluded that perioperative continuation of ASA in radical cystectomy is safe regarding blood loss, transfusion rate, and complication rate; increased ischemic complications were found in patients interrupting the antiplatelet drug before surgery [15]. These results were corroborated in our study in RARC with ICUD. Moreover, male sex and type of urinary diversion were prognostic factors for transfusion, while male sex and BMI were prognostic factors for complication rate. In our study (RARC with ICUD), only age and number of resected lymph nodes were significant predictors for transfusion rate, while male sex and type of urinary diversion were significantly associated to major complication rate.

RARC is known to be associated with lower blood loss and transfusion rates when compared with open radical cystectomy [19]. This reduction in blood loss can be partly explained by the pneumoperitoneum, which permits to minimize blood loss in laparoscopic and robot-assisted surgeries compared to open procedures. This has allowed the evaluation of acetylsalicylic acid continuation in many other laparoscopic and robot-assisted surgeries, in urology (robotic and laparoscopic radical prostatectomy, robotic partial nephrectomy) [20−23] as well as other specialties [24,25]. The majority of these studies concluded that perioperative continuation of antiplatelet therapy was demonstrated to decrease cardiovascular mobidity and mortality without increasing hemorrhagic complications, although a minority have concluded to a higher hemorrhagic risk and transfusion rate [26,27]. Assuming that continuing ASA is probably safe in open radical cystectomy, and considering that RARC is known to have less hemorrhagic complications when compared to open surgery, it is then logical that acetylsalicylic acid continuation should be also safe in RARC. This was confirmed by our study.

Finally, as in any decision in surgery, it is our responsibility to chose the best option for our patients with the least serious potential adverse events. Although we recognize the negative impact of blood transfusions on bladder cancer [28], we feel that taking the risk of increased EBL or transfusion is worth a while compared to risking postoperative ischemia or myocardial infarction [29], which we believe to have a greater impact on the overall morbidity of radical cystectomy. This is even more true for patients with cardiac stents [29].

Our study is not devoid of limitations. Its retrospective nature makes it difficult to draw genuine conclusions, first due to selection bias relative to the surgeon's preoperative decision about acetylsalicylic acid withdrawal based on personal preference and potential surgical complexity (e.g. rate of neobladder inferior in i-ASA group). However, it should be noted that no significnt difference was found in Charlson Comorbidity index (which includes cardiovacular disease) across the c-ASA and i-ASA groups. It should be highlighted that apart from three centers in which patients under acetyl-salicylic acid would either interrupt or continue the treatment through surgery, in eleven other centers the dichotomy was complete, with either all patients interrupting or all patients continuing therapy. This stresses the real weight if local habitudes on the peri-operative management of antiaggregant therapy, probably dictating the management of these drugs more than an actual analysis of patient and procedural risk factors. Also, the limited sample size with reagrds to patients receiving ASA before surgery can limit the interpretation of results, cosidering that ischemic complications are rare and thus may not be fully identified with the present sample size.

Moreover, we cannot account for other drugs which may have an impact on platelet function, such as serotonin reuptake inhibitors [30] and sevoflurane [31] which directly increase the risk of postoperative bleeding.

5. Conclusions

Although the habits that took years to build do not take a day to change, it is time to replace the old paradigms with real-life data. This study is the first to show that continuing acetylsalicylic acid peri-operatively in RARC with ICUD is not associated to increased hemorrhagic complications. Moreover, interrupting acetylsalycilic acid before surgery can increase the risk of post-operative ischaemic events. Further prospective and randomized trials are needed to confirm our findings.

Conflict of interest

The authors report no conflict of Interest.

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