

Effect of Perioperative Antiplatelet Management on Thromboembolic Complications after Liver Resection

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ABSTRACT

AIM: The aim of the study was to specify the effect of perioperative antiplatelet (APT) management on postoperative thromboembolism (TE) after liver resection.

METHODS: Consecutive 398 patients undergoing liver resection at our hospital from 2005 to 2017 were retrospectively reviewed. Our perioperative antithrombotic management protocol includes preoperative aspirin monotherapy for patients with high thromboembolic risks. Among them, 125 patients (31.4%) had atherosclerotic thromboembolic risk and received APT. The cohort was classified into three groups; patients without APT (N-APT group), APT-discontinued patients (D-APT group), and aspirin-continued patients (C-APT group). The predicted risk of each group

was assessed by CHADS₂ score, and the rates of TE were compared between the groups.

RESULTS: Significantly lower CHADS₂ score of N-APT group was observed compared to those of other groups, although the D-APT and C-APT groups had similar distribution of the scores. Among 398 patients, postoperative TE was found in 6 cases (1.5%). Three cases resulted in in-hospital death and other 3 patients were discharged with moderate to severe sequelae. More TE occurred in the D-APT group (4.2%), whereas only one case in the C-APT group (1.9%) and three cases in the N-APT group (0.7%) were observed ($p=0.038$). Although having high CHADS₂ scores, patients in C-APT group showed a relatively low rate of postoperative TE events, mainly due to the preventive effect of preoperative aspirin continuation against TE.

CONCLUSION: Liver resection should be performed under rigid perioperative antithrombotic management in order to avoid thromboembolic complications. Especially in patients with APT for thrombotic risks, it is suggested that management with continued preoperative single aspirin therapy should be considered regardless of TE risks.

Key words: Preoperative aspirin continuation; esophagogastrointestinal surgery; Hepatobiliary and pancreas surgery; Thromboembolic complication

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INTRODUCTION

Nowadays, the number of antiplatelet therapy (APT)-received patients with histories of cardio- and/or cerebro-vascular diseases has been increasing, and these patients often require digestive surgery. Perioperative antithrombotic management is difficult and often bothersome due to the potential risks of both bleeding and

thromboembolism (TE)^[1-3].

Regarding the bleeding risks, the safety of preoperative single APT continuation during various types of surgery has been reported^[4-10]. Although some studies including POISE-2 study have reported a slight increase in bleeding risks after non-cardiac surgery in patients with APT continuation^[4,5], most studies have shown that preoperative APT continuation is not associated with significant bleeding complications^[6-9]. Regarding the thromboembolic risks, the focus of recent updated guidelines concerning antithrombotic management during endoscopic procedures or non-cardiac surgery has shifted from the risk of bleeding to the risk of TE related to withdrawal of antithrombotics^[11-15]. However, there is no definite evidence to date concerning the efficacy of APT continuation on TE during major digestive surgery, including liver resection (LR), a relatively high invasive surgical procedure.

In our institution, We established our own risk stratification system and perioperative antithrombotic management protocol for APT-burdened patients (“Kokura Protocol”), including preoperative continuation of aspirin monotherapy in patients with high thromboembolic risks, and have demonstrated the safety and feasibility of both open and laparoscopic abdominal surgeries under the Kokura Protocol^[9,16-19]. In addition, we continue to manage APT-prescribed patients undergoing major digestive surgery using the same perioperative management protocol and operative policy, and the data of more additional patients receiving preoperative aspirin continuation have been accumulated. In the present study, we reviewed more than 398 consecutive patients receiving LR, and investigated the effect of discontinuation of APT on TE occurrence during LR.

PATIENTS AND METHODS

Our institutional review board approved the current study. Potentially relevant cases were searched from the single institution prospectively collected surgery database. After excluding cases with emergency surgery or surgery for benign diseases, a total of 398 consecutive major digestive surgery for malignancy, performed from 2005 to 2017, were included in the current study. All procedures were executed by or under the guidance of one of the board-certified attending surgeons in our institution.

The status of patients’ symptoms and functions regarding ambulatory status was reported according to the ECOG scale of performance status (PS)^[20]. Postoperative complications were assessed and categorized by Clavien-Dindo classification (CDC) and CDC class 2 or higher was considered significant^[21]. Postoperative TE and bleeding complications were defined as previously reported^[16,17]. Briefly, TE included cerebral infarction, myocardial infarction, mesenteric infarction, pulmonary thromboembolism, and acute arterial embolism; bleeding complication included luminal bleeding (e.g. gastrointestinal bleeding), abdominal bleeding, and abdominal wall hematoma. Operative mortality was defined as death within 30 d after surgery.

The primary outcome included TE. To analyze the background and surgical factors in the whole cohort, the patients were divided into three groups according to the preoperative status of antiplatelets; 273 patients who did not receive any antiplatelets (N-APT group), 71 patients in whom APT was received but discontinued one week before the operation (D-APT group), and 54 patients undergoing preoperative continuation of aspirin monotherapy (C-APT group). The background characteristics, perioperative factors, and surgical outcome of included patients were compared between the groups.

To assess the predicted TE risk of patients in each group, we adopted revised CHADS₂ scoring system, one of the most widely used scores for the prediction of ischemic stroke or TIA in patients who have atrial fibrillation or flutter (AF)^[22-24]. It is reported that revised CHADS₂ score also predicts ischemic stroke or TIA and death in patients without a history of AF^[25]. The CHADS₂ score is cumulative on the basis of 6 clinical features: congestive heart failure, hypertension, diabetes mellitus, and age \geq 75 years (counted as 1 point each), and a history of stroke or TIA (2 points).

Statistical analysis

Continuous values were expressed as mean (SD) or median (interquartile range), while categorical variables are presented as absolute numbers and percentages. For univariate comparisons, Fisher’s exact probability test was used to evaluate categorical variables; alternatively, continuous variables were analyzed by 1-way ANOVA and Kruskal-Wallis tests for normally and nonnormally distributed data, respectively. All P-values were two sided and P-values less than 0.05 were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Centre, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0)^[26].

RESULTS

In the whole cohort, APT was regularly used in 125 patients (31.4%). The numbers of patients in the N-APT, D-APT, and C-APT groups were 273 (68.6%), 71 (17.8%), and 54 (13.6%), respectively. Table 1 shows patient characteristics in each group. The median ages in the N-APT, D-APT, and C-APT groups were 69 years, 75 years, and 79 years, respectively ($p < 0.001$). Patients with poor performance status (grade 2-4) ($p = 0.005$), diabetes mellitus ($p = 0.030$), history of congestive heart failure ($p < 0.001$), history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) ($p < 0.001$), history of cerebral infarction or TIA ($p < 0.001$), and maintenance of peritoneal dialysis or hemodialysis ($p = 0.020$) were more prevalent in the D-APT and C-APT groups. The mean CHADS₂ scores in the N-APT, D-APT, and C-APT groups were 0.91, 1.82, and 2.07, respectively ($p < 0.001$).

Table 2 shows factors regarding operative procedures in the whole cohort. There was no difference in the type of surgery between the groups ($p = 0.766$), but in the C-APT group, more laparoscopic operations were performed than the N-APT or D-APT groups ($p = 0.012$). Patients in the D-APT and C-APT groups received perioperative heparin bridging more commonly than those in the N-APT group ($p < 0.001$). Concerning intraoperative bleeding events, there were no patients who suffered uncontrollable excessive intraoperative bleeding due to aspirin continuation. The duration of operation ($p = 0.760$), surgical blood loss ($p = 0.862$), and rate of intraoperative red blood cell transfusion ($p = 0.193$) were similar between the groups. Length of postoperative hospital stay was shorter in the C-APT group than in the N-APT and D-APT group (12 d vs 15 d, $p = 0.031$).

Table 3 shows factors regarding postoperative morbidity and mortality in the cohort. Postoperative complications developed in 21.9% of overall patients. The occurrence of severe postoperative complications (CDC class 3 or higher) in the N-APT, D-APT, C-APT groups were 7.3%, 14.1%, 13.0%, respectively ($p = 0.566$). The numbers of overall bleeding and thromboembolic complications were 18 (4.5%) and 6 (1.5%), respectively. The rates of postoperative

Table 1 Background characteristics of patients in the cohort.

Variables	N-APT (n = 273)	D-APT (n = 71)	C-APT (n = 54)	p
Age, y, median (range)	69 (32-89)	75 (54-90)	79 (60-92)	< 0.001
Gender, n (%)				0.002
Female	94 (34.4)	15 (21.1)	7 (13.0)	
Male	179 (65.6)	56 (78.9)	47 (87.0)	
BMI, kg/m ² , median (range)	23.4 (14.8-44.1)	23.4 (16.1-34.3)	23.4 (14.5-38.8)	0.546
Performance status, n (%)				0.005
0, 1	263 (96.3)	65 (91.5)	46 (85.2)	
2, 4	10 (3.7)	6 (8.5)	8 (14.8)	
Concurrent diseases, n (%)				
Hypertension	80 (29.3)	21 (29.6)	22 (40.7)	0.243
Diabetes mellitus	58 (21.2)	21 (29.6)	20 (37.0)	0.03
Hx of congestive heart failure	10 (3.7)	7 (9.9)	13 (24.1)	< 0.001
Hx of PCI or CABG	2 (0.7)	36 (50.7)	40 (74.1)	< 0.001
Hx of cerebral infarction/TIA	7 (2.6)	22 (31.0)	9 (16.7)	< 0.001
Current hemo-/peritoneal dialysis	6 (2.2)	5 (7.0)	5 (9.3)	0.02
Oral anticoagulation therapy, n (%)	21 (7.7)	12 (16.9)	7 (13.0)	0.053
CHADS ₂ score (mean ± SD)	0.91 ± 0.94	1.82 ± 1.21	2.07 ± 1.16	< 0.001
Score 0, n (%)	114 (41.8)	10 (14.1)	5 (9.3)	
Score 1, n (%)	87 (31.9)	20 (28.2)	10 (18.5)	
Score 2, n (%)	58 (21.2)	22 (31.0)	23 (42.6)	
Score 3 or higher, n (%)	14 (5.1)	19 (26.7)	16 (29.6)	

Bald value indicates statistically significant.*Abbreviations: APT: antiplatelet therapy; BMI: body mass index; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; TIA: transient ischemic attack; periop.: perioperative.

bleeding complication were relatively high in the D-APT and C-APT groups, although the difference was not significant (2.9% vs 8.5% vs 7.4%, $p = 0.075$). The operative mortality rate was 0.5% (2/398), and no significant difference was observed between the groups ($p = 0.669$).

Table 4 demonstrates the case details of patients experiencing postoperative TE in the cohort. There were 2 patients suffering from cerebral infarction in the N-APT group, both of them underwent partial liver resection, a rather less invasive operation. On the other hand, 3 TE patients (2 cerebral infarction and 1 mesenteric infarction) in the D-APT group and only 1 TE patient (myocardial infarction) were observed, all of which received more invasive operations (anatomical liver resection). Among 6 TE patients, 3 patients resulted in in-hospital death and other 3 patients were discharged with moderate to severe sequelae.

Figure 1 shows the relationship between the distribution of the CHADS₂ score and the occurrence of TE in each group. The mean score of N-APT group was significantly low compared to those of D-APT and C-APT groups, but the two latter groups had similar scores (Figure 1A, 0.91 ± 0.94 vs 1.82 ± 0.94 vs 2.07 ± 0.94 , $p = 0.001$). Nevertheless, the occurrence of TE was significantly higher in the D-APT group than in the other groups (Figure 1B, 4.2% vs 0.9%, $p = 0.038$).

DISCUSSION

Our study demonstrated that reviewing more than 398 consecutive patients undergoing LR, The occurrence of postoperative overall complication, bleeding complication, and TE were 21.9%, 4.5% and 1.5%, respectively. Patients without APT had significantly lower

Table 2 Factors regarding operative procedures in the cohort.

Variables	N-APT (n=273)	D-APT (n=71)	C-APT (n=54)	p
Type of liver resection, n (%)				0.766
Partial resection	162 (59.3)	42 (59.1)	27 (50.0)	0.864
Sub- or Mono-sectionectomy	58 (21.2)	15 (21.1)	14 (25.9)	
Di- or Tri-sectionectomy	53 (19.4)	14 (19.7)	13 (24.1)	
Mode of surgery, n (%)				0.012
Open surgery	210 (76.9)	51 (71.8)	31 (57.4)	
Laparoscopic surgery	63 (23.1)	20 (28.2)	23 (42.6)	
Periop. heparin bridging, n (%)	16 (5.9)	11 (15.5)	8 (14.8)	0.009
Duration of operation, min, median (range)	250 (74-705)	245 (101-637)	247 (84-678)	0.76
Intraoperative severe bleeding tendency, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Surgical blood loss, mL, median (range)	250 (5-11070)	200 (5-26800)	240 (5-3420)	0.862
Surgical blood loss ≥ 500 mL, n (%)	91 (33.3)	20 (28.2)	18 (33.3)	0.701
Intraoperative RBC transfusion, n (%)	53 (19.4)	14 (19.7)	17 (31.5)	0.193
Length of postop. stay, d, median (range)	15 (4-247)	15 (7-83)	12 (5-103)	0.031

Bald value indicates statistically significant.*Abbreviations: APT: antiplatelet therapy; periop.: perioperative; RBC: red blood cell.

CHADS₂ score compared to APT-prescribed patients, but patients with continued APT and those with discontinued APT revealed to have the similar score distribution. The rate of TE was significantly higher in patients with APT discontinuation than in the others. Although having high CHADS₂ scores, patients with continued APT showed a relatively low TE rate, mainly due to the preventive effect of preoperative aspirin continuation against TE.

Recent updated guidelines concerning antithrombotic management during non-cardiac surgery showed that the prevention of TE is more important than bleeding complications, as it might cause death or severe sequelae^[11-15]. Concerning implantation of coronary stent, recent AHCC/AHA, ACCP, and ESC guideline said that we should continue antiplatelet medications, at least aspirin monotherapy, in the perioperative period for patients with high TE risk^[15,27,28]. In consideration of liver resection, however, there is no evidence or guidelines concerning major digestive surgery for malignancy.

In our hospital, the rate of APT-burdened patients undergoing LR is almost 30-40%, and the number is expected to be increasing. For this reason, we have established and continue to use our protocol of perioperative antithrombotic management, including preoperative single aspirin continuation for patients with TE risks. Originally, our protocol included preoperative discontinuation of APT for patients with relatively low TE risks such as distant past history of ischemic stroke or drug-non-eluting coronary stent implantation^[16,17]. These patients were classified into the D-APT group in the current study, but according to revised CHADS₂ scores, most of these patients were categorized as high or intermediate risk. In addition, our study showed that the rate of TE was significantly higher in patients with APT discontinuation than in the others. Therefore, it is recommended that if APT-received patients undergo LR, preoperative single aspirin continuation should be considered regardless of the degrees of thromboembolic risks.

In APT-burdened patients undergoing LR, both excessive surgical stress and inappropriate antithrombotic management are thought to affect bad surgical outcome. If the patient has high TE risks and preoperative ATT cannot be stopped, the intraoperative and postoperative bleeding risks will increase. To minimize bleeding

Table 3 Factors concerning postoperative morbidity and mortality in the cohort.

Variables	N-APT (n=273)	D-APT (n=71)	C-APT (n=54)	p
Postoperative complication, n (%)				0.566
CDC class 0	220 (80.6)	53 (74.6)	38 (70.4)	
CDC class 1	9 (3.3)	3 (4.2)	3 (5.6)	
CDC class 2	24 (8.8)	5 (7.0)	6 (11.1)	
CDC class 3 or higher	20 (7.3)	10 (14.1)	7 (13.0)	
Postop. bleeding complication, n (%)	8 (2.9)	6 (8.5)	4 (7.4)	0.075
Postop. thrombotic complication, n (%)	2 (0.7)	3 (4.2)	1 (1.9)	0.038
Operative mortality, n (%)	0 (0.0)	1 (1.4)	1 (1.9)	0.668

Bald value indicates statistically significant.*Abbreviations: APT: antiplatelet therapy; CDC: Clavien-Dindo classification; postop.: postoperative.

Table 4 Case details of patients with thromboembolic complications in the cohort.

No.	Age	Gender	Group	CHADS ₂ score	Operative Type	Morbidity	Outcome
1	70	Male	N-APT	2	Partial liver resection	Cerebral infarction	Alive
2	65	Male	N-APT	4	Partial liver resection	Cerebral infarction	Alive
3	66	Male	D-APT	1	Hepatic tri-sectionectomy	Mesenteric infarction	Death
4	60	Male	D-APT	2	Hepatic sub-sectionectomy	Cerebral infarction	Alive
5	79	Male	D-APT	4	Hepatic bi-sectionectomy	Cerebral infarction	Death
6	79	Male	C-APT	2	Hepatic bi-sectionectomy	Myocardial infarction	Death

*Abbreviations: APT: antiplatelet therapy.

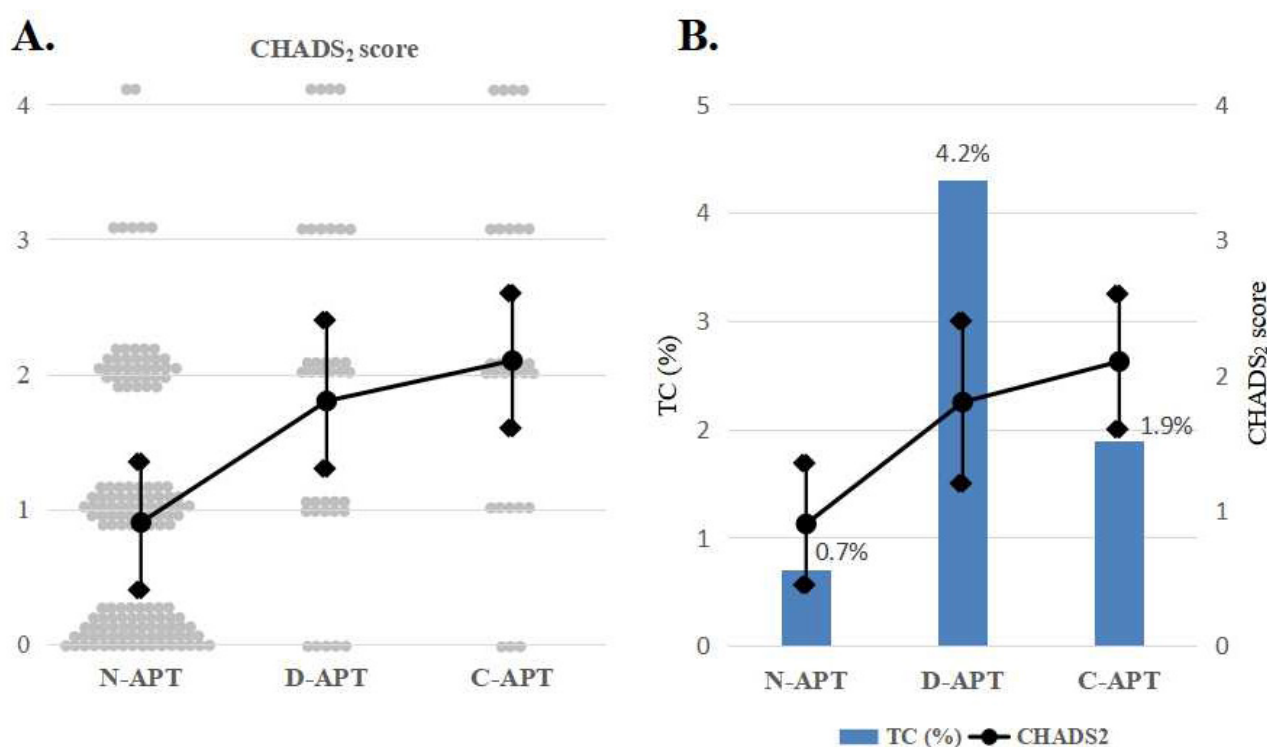


Figure 1 The relationship between the distribution of the CHADS₂ score and the occurrence of TE in each group. (A) The mean score of N-APT group was significantly low compared to those of D-APT and C-APT groups, but the two latter groups had similar scores. (B) The occurrence of TE was significantly higher in the D-APT group than in the other groups (4.2% vs 0.9%, $p = 0.038$).

events especially in this critical patient population, we adopted and currently utilize simple but strong hemostatic devices and technique during LR. As shown in our previous report, both open and laparoscopic LR using two-surgeon technique is safe and feasible, and can be applied to even APT-continued patients^[19,29].

The rates of perioperative TE vary depending on differences in target patient population, study design, and changing of clinical practices. The reported incidence of stroke following noncardiac, nonneurosurgical surgery ranges between 2.9-3.5% in patients at risk of perioperative TE^[30-33]. In consideration of TE after LR, the prevalence of TE seems to be higher. Schroeder et al. reported that analyzing 587 patients undergoing LR from the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) database, overall TE after LR were at 3.6%^[34]. Another research of 5,227 LRs from ACS-NSQIP database showed that the rate of critical cardiac complications including myocardial infarction

and cardiac arrest after LR was at 4.8% in patients with underlying cardiac disease^[35]. The present study demonstrated that the incidence of perioperative TE was maintained at 1.5% overall and at 1.9% in patients with continued APT, a relatively low rate compared to the previous report. Hence, it is suggested that both open and laparoscopic LR can be performed safely under the Kokura Protocol (including preoperative single aspirin continuation), with successful inhibition of TE even in thromboembolic risk patients.

This study has several limitations. First, the current study is single-center retrospective observational design, and it is possible that unmeasured confounders were not included, resulting in residual treatment selection bias. Second, our institution is high-volume tertiary referral hospital for surgical patients receiving antithrombotic therapy; consequently, our findings may not be generalizable to relatively low-volume centers. This restriction will be alleviated by multi-institutional prospective studies.

CONCLUSION

Analysis of consecutive 398 patients undergoing liver resection demonstrated that the rate of TE was significantly higher in patients with APT discontinuation than in the others. Although having high CHADS₂ scores, APT-continued patients had a relatively low TE rate, mainly due to the preventive effect of preoperative aspirin continuation against TE. In APT-prescribed patients, it is suggested that management with continued preoperative single aspirin therapy should be considered regardless of the degree of TE risks.

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