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Postoperative Bleeding After Esophagectomy for Esophageal Cancer in Patients Receiving Antiplatelet and Anticoagulation Treatment

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Abstract. *Background: The aim of the present study was to evaluate the clinical impact of the perioperative use of antiplatelet/anticoagulation therapy for postoperative bleeding after esophagectomy for esophageal cancer. Patients and Methods: Patients were selected from the medical records of consecutive patients who were diagnosed with primary esophageal adenocarcinoma or squamous cell carcinoma and who underwent complete resection at Yokohama City University from January 2005 to September 2018. The patients were divided into the antiplatelet/anticoagulation treatment group and the non-treatment group. We compared the safety and feasibility of esophagectomy between two groups. Results: One hundred and twenty-two patients underwent esophagectomy for esophageal cancer and were analyzed in the present study. Among them, 18 (14.8%) received anti-thrombotic therapy (anticoagulation group). The incidence of postoperative bleeding in patients overall was 8.2% (10/122). The incidence of postoperative bleeding in the anticoagulation group was 22.2% (4/18), while that in the non-anticoagulation group was 5.8% (6/104). Preoperative anticoagulation therapy was identified as a significant independent risk factor for postoperative bleeding (hazard ratio=4.673, 95% confidence interval=1.170-18.519; p=0.029). Conclusion: The perioperative use of anti-thrombotic therapy was a significant risk factor for postoperative bleeding after esophagectomy for esophageal cancer. Thus, when patients receive perioperative antiplatelet/anticoagulation treatment, careful attention is required after esophagectomy due to their increased risk of postoperative bleeding.*

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Key Words: Esophageal cancer, bleeding, antiplatelet treatment, anticoagulation treatment.

Esophageal cancer is the seventh-most common cancer and the sixth leading cause of cancer-related mortality (1). Surgical resection, with or without adjuvant treatment, is the standard treatment for resectable esophageal cancer (2, 3). However, the rate of postoperative surgical complications after esophagectomy is reported to range from 30% to 70% (4-7). Among these, postoperative bleeding represents a critical surgical complication. The incidence of postoperative bleeding in patients undergoing gastrointestinal cancer treatment has been reported to range from 0.5% to 10% (8-10).

The number of elderly patients has been rapidly growing throughout the world. Generally, elderly patients have cardiovascular-morbidities such as atrial fibrillation, chronic heart failure, and myocardial infarction. The American Heart Association and American College of Surgeons reported that 10% of adult surgical patients receive chronic antiplatelet and/or anticoagulation therapy (11, 12). Previous studies have demonstrated that tumor size, chronic kidney disease, and the administration of histamine-2 receptor antagonists instead of proton pump inhibitors are significant risk factors for postoperative bleeding after esophagectomy for esophageal cancer (13-15). On the other hand, there have been limited studies to investigate the relationship between the use of antiplatelet or anticoagulation therapy and postoperative bleeding after esophagectomy.

The aim of the present study was to evaluate the safety and feasibility of the perioperative use of antiplatelet/anticoagulation therapy in patients undergoing esophagectomy for esophageal cancer. In addition, we also evaluated the clinical impact of the perioperative use of antiplatelet/anticoagulation therapy on postoperative bleeding after esophagectomy.

Patients and Methods

Patients. The patients were selected from the medical records of consecutive patients who underwent esophagectomy for esophageal cancer at Yokohama City University from January 2005 to September 2018. The patients met the following inclusion criteria: Histologically proven primary esophageal squamous cell carcinoma, clinical stage IB to III (excluding T4) disease as evaluated using the seventh edition of the tumor-node-metastasis classification established by the Union for International Cancer Control (UICC), and complete (R0) resection of esophageal cancer with radical lymph node dissection. Patients who had undergone R2 or R1 resection were excluded from the study.

Surgical procedure. Our standard procedures consisted of open subtotal esophagectomy *via* right thoracotomy. Subtotal esophagectomy was defined as subtotal esophagectomy with resection of both the lesser curve and the subcardial area of the stomach. A greater curvature tube was used for reconstruction. In addition, cervical anastomosis was performed in all cases.

Perioperative care. The patients were managed by the same perioperative program. Antibiotics were administered 30 min before surgical incision, every 3 hours during surgery, and were continued until postoperative day (POD) 2. After surgery, the patients remained on ventilation overnight. On POD1, enteral nutrition and ambulation were started. On POD5, oral intake was initiated with water and gelatinous foods. On POD10, the patients began to eat solid food.

Management of perioperative antiplatelet and anticoagulation therapy. For patients who were treated with antithrombotic agents, prescribing physicians were consulted on how to manage antithrombotic therapy during the perioperative period. Aspirin was discontinued 7-10 days before surgery. Cilostazol was discontinued 3 days before surgery. Thienopyridine was discontinued 14 days before surgery. Warfarin was discontinued 5 days before surgery and heparin alternative therapy. Heparin therapy was controlled to keep the activated partial thromboplastin time at 1.5- to 2.5-fold that of the control. Heparin therapy was stopped 6 hours before surgery.

Definition of postoperative bleeding. In the present study, postoperative bleeding complications were defined as abdominal or luminal bleeding. Abdominal bleeding was diagnosed based on radiological findings and a drop in hemoglobin by >2 g/dl during a 24-hour period. Luminal bleeding was diagnosed by endoscopic findings and a drop in hemoglobin of >2 g/dl during a 24-h period.

Definition of postoperative surgical complications. Grade 2-5 postoperative complications [according to the Clavien–Dindo classification system (16)] that occurred during hospitalization or within 30 days after surgery were retrospectively determined from the patient records. Grade 1 complications were not evaluated in order to exclude the possibility of a description bias in the patient records.

Evaluation and statistical analysis. A logistic regression analysis was performed to identify risk factors for postoperative bleeding. The unpaired chi-squared test or Student's *t*-test was used to compare the antiplatelet/anticoagulation therapy group and non-therapy group. *p*-Values of less than 0.05 were considered to indicate statistical significance. The SPSS software program (v11.0J Win; SPSS, Chicago, IL, USA) was used to perform all statistical analyses.

Results

Background of the patients. One hundred and twenty-two patients underwent esophagectomy for esophageal cancer and were analyzed in the present study. Among them, 18 (14.8%) received antiplatelet/anticoagulation therapy (anticoagulation group). The medicines included aspirin in five; cilostazol in four; thienopyridine in two; aspirin, warfarin and thienopyridine in one; warfarin in four; and aspirin with warfarin in two. Seven patients required heparin alternative therapy. Table I shows the background characteristics of the patients in the therapy group and the non-therapy group. In the comparison of the two groups, the body mass index was significantly higher in the therapy group (21.6 *vs*. 20.7 kg/m^2, p=0.011), and the incidence rates of hypertension and *diabetes mellitus* were also significantly higher in this group (72.2% *vs*. 37.5%, p=0.021; and 38.9% *vs*. 17.3%, p=0.036, respectively).

Surgical and pathological findings. Table II shows the operative details and pathological findings in the two groups. There were no significant differences in the operative details or pathological findings.

Postoperative outcomes and surgical complications. Table III shows the postoperative outcomes. The rates of postoperative surgical complications and 30-day mortality were similar in the therapy group and non-therapy groups. In addition, the length of post-operative hospital stay was similar at 39.5 days in the therapy group and 30 days in the non-therapy group (p=0.955). Table IV shows the details of the postoperative surgical complications. Anastomotic leakage and pneumonia were the most frequently diagnosed complications in the therapy group, followed by surgical site infection. Similarly, anastomotic leakage was the most frequently diagnosed complication in the non-therapy group, followed by pneumonia and delirium. The overall incidence of postoperative bleeding was 8.2% (10/122) in patients, including abdominal bleeding in four, luminal bleeding in three, and cerebrovascular disorder bleeding in three.

Risk factor analysis for postoperative bleeding. Perioperative factors that were associated with postoperative bleeding were identified by a logistic regression analysis. Table V shows the results of the analysis. Among the factors examined, preoperative antiplatelet/anticoagulation therapy was identified as a significant independent risk factor for increased risk of postoperative bleeding. The incidence of

Table I. *Baseline characteristics of the study patients*.

Characteristic		Therapy group (n=18)	Non-therapy group (n=104)	*p*-Value
Age, years	Median (range)	72 (55-79)	68 (40-82)	0.063
Gender, n (%)	Male	17 (94.4%)	89 (85.6%)	0.579
	Female	1 (5.6%)	15 (14.4%)	
Body mass index, kg/m^2	Median (range)	21.6 (18.1-29.0)	20.7 (14.5-27.3)	**0.011**
ASA-PS, n (%)	1	1 (5.6%)	10 (9.6%)	
	2	16 (88.8%)	94 (90.4%)	
	3	1 (5.6%)	0 (0%)	
Smoking habit, n (%)	Yes	15 (83.3%)	94 (90.4%)	0.371
	No	3 (16.7%)	10 (9.6%)	
Alcohol habit, n (%)	Yes	16 (88.8%)	98 (94.2%)	0.737
	No	2 (11.2%)	6 (5.8%)	
Co-morbidity, n (%)	Hypertension	13 (72.2%)	39 (37.5%)	**0.021**
	COPD	2 (11.2%)	24 (23.1%)	0.252
	Diabetes mellitus	7 (38.9%)	18 (17.3%)	0.036
Pre-operative laboratory data, median (range)	Albumin, g/dl	4.1 (2.3-4.7)	4.1 (1.5-5)	0.858
	Hemoglobin, g/dl	12.7 (9.8-15.4)	12.5 (6.8-16.1)	0.538
	White blood cells, $\times 10^3/\mu l$	6.4 (3.1-11.0)	6.05 (2.8-14.0)	0.376
	C-Reactive protein, mg/dl	0.53 (0.02-4.69)	0.13 (0.01-8.95)	0.480

ASA-PS: American Society of Anesthesiology physical status; COPD: chronic obstructive pulmonary disease. Bold values show significance.

Table II. *Surgical and pathological findings*.

Characteristic		Therapy group (n=18)	Non-therapy group (n=104)	*p*-Value
Type of Surgery	Transthoracic	6 (33.3%)	29 (27.9%)	0.637
	Thoracosopic	12 (66.7%)	75 (72.1%)	
Neoadjuvant chemotherapy	Yes	8 (44.4%)	59 (56.7%)	0.333
	No	10 (55.6%)	45 (43.3%)	
Lymph node dissection	Two-field	10 (55.6%)	58 (55.8%)	0.987
	Three-field	8 (44.4%)	46 (44.2%)	
Operation time, min	Median (range)	582 (259-781)	597 (216-911)	0.391
Blood loss, ml	Median (range)	482 (95-1403)	542 (70-3000)	0.237
Intra operative transfusion	Yes	5 (27.8%)	32 (30.8%)	0.673
	No	13 (72.2%)	72 (69.2%)	
Pathological depth of invasion	T1	6 (33.3%)	37 (35.6%)	0.784
	T2 or more	12 (66.7%)	67 (64.4%)	
Pathological lymph node status	Positive	10 (55.6%)	50 (48.1%)	0.558
	Negative	8 (44.4%)	54 (51.9%)	
Lymphovascular invasion	Positive	5 (27.8%)	33 (31.7%)	0.738
	Negative	13 (72.2%)	71 (68.3%)	

postoperative bleeding was 22.2% (4/18) in the therapy group and only 5.8% (6/104) in the non-therapy group (p=0.019).

Discussion

The aim of the present study was to evaluate the safety and feasibility of the perioperative use of antiplatelet/anticoagulation treatment in esophagectomy for esophageal cancer. The major findings were that the perioperative use of such treatment was a significant risk factor for postoperative bleeding after surgery. Therefore, patients who receive perioperative antiplatelet/anticoagulation treatment require careful attention due to this increased risk of postoperative bleeding after esophagectomy.

In the present study, the incidence of postoperative bleeding in the therapy group was significantly higher than that in the non-therapy group (22.2% *vs*. 5.8%, p=0.019). Similar results were observed after other gastrointestinal cancer surgeries. Fujikawa *et al*. evaluated the clinical impact of antiplatelet

Table III. *Postoperative outcomes*.

Characteristic		Therapy group (n=18)	Non-therapy group (n=104)	*p*-Value
Surgical complications, n (%)	Yes	15 (83.3%)	72 (67.3%)	0.126
	No	3 (16.7%)	32 (32.7%)	
30-Day-mortality, n (%)	Yes	0 (0)	1 (1%)	0.676
	No	18 (100.0%)	103 (99%)	
Post-operative hospital stay, days	Median (range)	39.5 (15-216)	30 (1-412)	0.955

Table IV. *Details of surgical complications*.

Characteristic	Therapy group (n=18), n (%)	Non-therapy group (n=104), n (%)	*p*-Value
Anastomotic leakage	7 (38.9%)	35 (33.7%)	0.666
Anastomotic stenosis	1 (5.6%)	6 (5.8%)	0.971
Pneumonia	9 (50.0%)	26 (25.0%)	**0.030**
Postoperative bleeding	4 (22.2%)	6 (5.8%)	**0.019**
Abdominal abscess	1 (5.6%)	5 (4.8%)	0.892
Deep venous thrombosis	1 (5.6%)	3 (2.9%)	0.557
Cardiovascular disease	2 (11.1%)	7 (6.7%)	0.512
Delirium	3 (16.7%)	6 (5.8%)	0.103
Surgical site infection	2 (11.1%)	9 (8.7%)	0.737
Ileus	1 (5.6%)	3 (2.9%)	0.557

Bold values show significance.

Table V. *Results of univariate analysis of risk factors for postoperative bleeding. Multivariate analysis showed that anticoagulation therapy remained a significant factor [hazard ratio (HR)=4.673, 95% confidence intervaI (CI)=1.170-18.519; p=0.029].*

		Univariate analysis		
Characteristic	Number	HR	95% CI	*p*-Value
Age				
<75 years	98	1.000		
≥75 years	24	1.857	0.443-7.785	0.397
Neoadjuvant chemotherapy				
No	55	1.000		
Yes	67	1.240	0.340-4.524	0.745
Operative type				
Transthoracic	87	1.000		
Thoracosopic	35	1.082	0.261-4.405	0.924
Operative duration				
<590 min	59	1.000		
≥590 min	63	1.677	0.463-6.451	0.415
Blood loss				
<540 ml	61	1.000		
≥540 ml	61	1.004	0.274-3.646	>0.99
Lymph node dissection				
Two-field	68	1.000		
Three-field	54	1.999	0.534-7.476	0.303
Alcohol habit				
No	10	1.000		
Yes	112	1.133	0.130-9.882	0.910
Anticoagulation therapy				
No	104	1.000		
Yes	18	4.673	1.170-18.519	**0.029**

Bold value shows significance.

therapy and postoperative bleeding in 2,012 patients who underwent gastrointestinal surgery between 2005 and 2010. Five hundred and ninety patients (25.8%) received antiplatelet therapy. The incidence of postoperative bleeding was 1.8% (37/2012) considering the whole cohort. When the incidence of postoperative bleeding was compared between the antiplatelet therapy and non-therapy groups, a significant difference ($p<0.001$) was identified, with rates of 3.9% (20/519) and 1.1% (17/1,493), respectively (17). In addition, Mita *et al*. evaluated the clinical impact of perioperative anticoagulation/antiplatelet therapy and postoperative bleeding in 340 patients who underwent gastrectomy for gastric cancer between 2006 and 2010. Sixty-two patients (18.2%) received such therapy. The incidence of postoperative bleeding was 2.1% in the whole cohort. When the incidence of postoperative bleeding was compared between the two groups, it was 8.1% in the anticoagulation/antiplatelet therapy group and 0.7% in the non-therapy group ($p=0.003$) (18). In our multivariate risk factor analysis, the relative risk of perioperative such therapy for postoperative bleeding was 4.673 (95% confidence interval=1.170-18.519, $p=0.029$). A similar relative risk was observed in previous studies. Fujikawa *et al*. showed that use of multiple agents for antiplatelet therapy was a risk factor for postoperative bleeding (odds ratio=4.333, 95% confidence interval=1.339-14.028; $p=0.014$) in a multivariate analysis (17). In addition, Miki *et al*. showed that perioperative antithrombotic treatment was the only independent risk factor for postoperative bleeding complications after radical gastrectomy (odds ratio=8.53, 95% confidence interval=1.47-49.39; $p=0.017$) (18). Considering these findings, perioperative anticoagulation/antiplatelet therapy might affect the risk of postoperative bleeding.

On the other hand, the incidence rates and details of postoperative surgical complications other than postoperative bleeding were similar in the two groups. In the present study, when postoperative bleeding and mortality were excluded, the two groups showed a similar incidence of overall postoperative surgical complications. Fujikawa *et al*. reported that the incidence of overall postoperative surgical complications excluding postoperative bleeding was lower in their antiplatelet therapy group than in the non-therapy group, while the mortality rate of the two groups was similar (1.1% *vs*. 1.5%, p=0.325). In contrast, Mita *et al*. reported that the incidence of overall postoperative surgical complications was 27.4% in a thromboprophylaxis group and 20.1% in the non-thromboprophylaxis group (p=0.207), while the mortality rate was significantly higher (3.2% *vs*. 0%, respectively; p=0.033). Considering these findings, the safety and feasibility of the perioperative use of anticoagulation/antiplatelet therapy remains unclear and controversial. Thus, further studies are needed to clarify this issue.

The present study was associated with some limitations. Firstly, the definition of postoperative bleeding was different from that in previous studies. Although it is difficult to compare the incidence of postoperative bleeding, the incidence of postoperative bleeding might have been overestimated in the present study and underestimated in previous studies due to such a difference. Our definition was similar to that of Mita *et al*. On the other hand, Fujiwara *et al*. defined postoperative complications of Clavien–Dindo grade 2 or higher as being clinically relevant: Clavien–Dindo grade 2 bleeding complications were defined as minor, bleeding of Clavien–Dindo grade 3 or more was defined as major. Secondly, the present study was a retrospective one and the study population was relatively small. In addition, we only analyzed patients who underwent esophagectomy. Thus, our findings might have been by chance. Considering these limitations, the findings of our study should be validated in another cohort.

In conclusion, when patients receive perioperative such treatment, careful attention is required due to the increased risk of postoperative bleeding after esophagectomy.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

Toru Aoyama and Yosuke Atsumi made substantial contributions to the conception and design. Toru Aoyama, Kentaro Hara, Hiroshi Tamagawa, Ayako Tamagawa, Keisuke Komori, Yukio Maezawa, Kazuki Kano, Keisuke Kazama, Itaru Hasimoto, Masaaki Murakawa, Masakatsu Numata, Takashi Oshima, Norio Yukawa, Munetaka Masuda, and Yasushi Rino made substantial contributions to the acquisition of data, or the analysis and interpretation of data. Toru Aoyama, Keisuke Kazama, Yosuke Astumi, Hiroshi Tamagawa, Ayako Tamagawa, Kazuki Kano and Yasushi Rino were involved in drafting the article or revising it critically for important intellectual content. Toru Aoyama, Yukio Maezawa, Keisuke Kazama, Kentaro Hara, gave final approval of the version to be published. Each Author participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All Authors read and approved the final article.

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