

Effect of Antiplatelet Therapy on Surgical Blood Loss and Post-Pancreatectomy Hemorrhage in Patients Undergoing Pancreaticoduodenectomy

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ABSTRACT

AIM: The aim of the study was to assess the feasibility and safety of pancreaticoduodenectomy (PD) in patients with preoperative antiplatelet therapy (APT) for arterial thromboembolic risks.

METHODS: Consecutive 100 patients receiving PD at our institution between 2005 and 2016 were retrospectively reviewed. APT was regularly used in 31 patients (31%) in this series. Our perioperative management ("Kokura Protocol") included maintenance of preoperative aspirin monotherapy and early postoperative reinstitution in patients at high thromboembolic risks. Outcome variables of patients with APT (APT group) were compared

with those of patients without APT.

RESULTS: This series included 31 pancreatic cancer, 27 bile duct cancer, 19 ampullary cancer, 13 intraductal papillary mucinous neoplasms, and 10 others. In APT group, 18 (18%) required preoperative continuation of APT. APT group showed significantly high frequency of history of cerebral infarction and percutaneous coronary intervention. Totally 18 significant pancreatic fistulas (grade B,C, 18%) were observed but no perioperative death was experienced. There was only 1 thromboembolic event (1.0%, cerebral infarction) in a whole cohort, whereas increased surgical blood loss ($\geq 1,000$ mL) and post-pancreatectomy hemorrhage (PPH) occurred in 11 (11%) and 6 (6.0%, totally grade B), respectively. Multivariate analysis showed that high body mass index (≥ 30 kg/m²) is the only significant risk factor for both increased blood loss and PPH (risk ratio = 13.64 and 27.27, $p < 0.05$), whereas either APT or preoperative aspirin continuation did not affect perioperative bleeding complications.

CONCLUSION: Even in APT-burdened patients with arterial thromboembolic risks, PD is safely performed under the Kokura Protocol without any increase of blood loss and PPH, although this patient population is still challenging and should be rigorously managed to prevent both bleeding and thromboembolic complications.

Key words: Antiplatelet therapy; Bleeding complication; Harmonic FOCUS®, Pancreaticoduodenectomy, Pinch-burn-cut technique; Thromboembolic complication

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INTRODUCTION

Lately, patients who have histories of cardiovascular or

cerebrovascular diseases have been seen more often with aging of patients, and those patients frequently receive antiplatelet therapy (APT) for the purpose of primary and secondary prevention of arterial thromboembolic diseases. While indications for APT use have expanded, antithrombotic management during gastrointestinal and/or hepatobiliary-pancreatic surgery is still difficult and often bothersome because of increased risks of perioperative bleeding or thromboembolic events^[1-4]. In our institution, a protocol of risk stratification and perioperative antithrombotic management has been established for APT-burdened patients (“Kokura Protocol”), which includes preoperative continuation of aspirin monotherapy in patients with high thromboembolic risks^{5, 6}. So far, the safety of both open and laparoscopic abdominal surgeries under the Kokura Protocol have been reported with relatively low rates of bleeding and thromboembolic complications^[5-7].

Pancreaticoduodenectomy (PD) is a highly invasive procedure and may expose patients to high risks of severe postoperative complications. Although mortality after PD has markedly decreased to less than 5% thanks to advance in operative techniques and perioperative management^{8, 9}, postoperative complication rates still remain high at 18-50%^[8-11]. The common types of postoperative complications are postoperative pancreatic fistula (POPF), deep surgical site infection (SSI), and post-pancreatectomy hemorrhage (PPH). PPH is related to a high mortality rate of up to 60%^[8-16], and its incidence is at 3-16% after overall pancreatic resection^[8-11], and at 8-29% after PD^[13-16]. When PD is performed especially in APT-burdened patients with high thromboembolic risks, rigorous perioperative antithrombotic management and meticulous intraoperative hemostatic procedures are required to prevent both bleeding and thromboembolic complications. To date, the effect of APT on perioperative complications, especially on surgical blood loss and PPH, in patients undergoing PD still remains unclear.

The aim of this study is to review consecutive 100 patients undergoing PD and to assess the safety and feasibility of PD in thromboembolic risk patients receiving APT.

PATIENTS AND METHODS

Between March 2005 and April 2016, totally 506 patients received major hepatobiliary and pancreatic surgery at our institution, among which pancreatic resection was performed in 155 patients. After excluding patients receiving distal or other pancreatectomy, 100 consecutive patients undergoing PD were included in the current study (Figure 1). Background, perioperative and outcome variables of the patients were collected through a standardized review of the electronic surgery database as well as hospital and clinic charts. The status of patients’ symptoms and functions regarding ambulatory status was described according to the ECOG Scale of Performance Status^[17].

Surgical procedures in this cohort included classical PD (PD with two-thirds distal gastrectomy), pylorus-preserving PD, and subtotal stomach-preserving PD (SSpPD). Our technical aspects during PD, especially in antiplatelet-burdened patients, was previously reported with satisfactory short-term outcomes^[18]. Briefly, we use modified Pinch-Burn-Cut (PBC) technique (the technique from living-donor liver transplantation^[19,20]) in combination with ultrasonically activated shears with a curved thin tip (Harmonic FOCUS®, Ethicon Endo-Surgery, Cincinnati, OH)^[21,22] during PD to minimize surgical blood loss and this modality was also useful even under continuation of preoperative aspirin monotherapy. All procedures were performed by or under the guidance of one of the attending surgeons at our

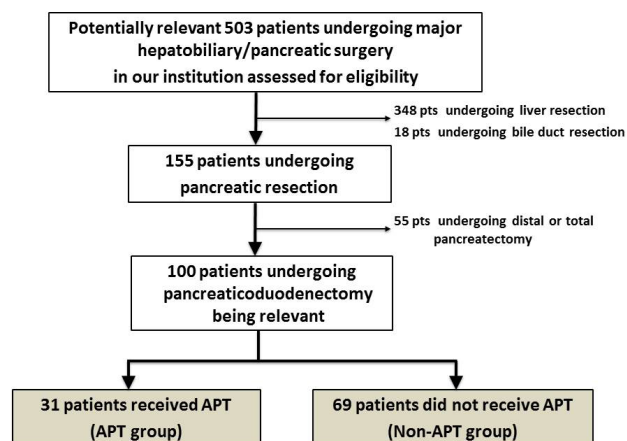


Figure 1 Consort diagram in the current study. Abbreviations: pts, patients; APT, antiplatelet therapy.

institution.

We established and conducted our perioperative antithrombotic management system for abdominal and general surgery, which consisted of thromboembolic risk stratification and perioperative antithrombotic management protocol (“Kokura Protocol”), and have shown that both open and laparoscopic abdominal surgeries in patients with antiplatelet therapy can be performed safely under the Kokura Protocol^[5-7]. The protocol generally consisted of interrupting APT one week before surgery and early postoperative reinstatement in low thromboembolic risk patients, although in case of high thromboembolic risks such as patients with drug-eluting coronary stent (DES) implantation or those with cerebrovascular reconstruction within 3 months, aspirin monotherapy was continued preoperatively, followed by early postoperative reinstatement.

Postoperative complications were assessed and categorized by Clavien-Dindo classification (CDC)^[23] and CDC class II or higher was considered significant. POPF was defined according to the definition of the International Study Group of Postoperative Pancreatic Fistula (ISGPF)^[24]. PPH was defined according to the definition of the International Study Group of Pancreatic Surgery (ISGPS)^[25], and the condition was classified on the basis of three parameters; time of onset, location, and severity. Three different grades of PPH were classified using these parameters. Postoperative thromboembolic complication was defined as previously described^[5,6], including myocardial infarction, cerebral infarction, mesenteric infarction, and pulmonary thromboembolism. Operative mortality included death within 30 days after surgery.

The primary outcome included excessive intraoperative blood loss (1,000 mL or more), PPH, and postoperative thromboembolic complications. Background characteristics, perioperative factors, and outcome variables were compared between patients receiving APT (APT group) and those without APT (non-APT group). Univariate and multivariate analyses were performed to assess the risk factors for excessive intraoperative blood loss and PPH.

The categorized data in each group were compared by chi-square or Fisher’s exact probability test. Continuous variables in the characteristics were expressed as a median with range and compared by Student’s T test or Kruskal-Wallis test. Non-parametric variables were also compared using Kruskal-Wallis test. Multivariable logistic regression analyses were performed to determine risk factors affecting excessive intraoperative blood loss or PPH. Statistical significance was set at $p < 0.05$. Data were analyzed using the SPSS package software.

Our institutional review board approved the current study.

RESULTS

Among patients in the current study, 31% (31/100) of patients undergoing PD received APT. Table 1 shows background characteristics of patients in each group. The patients in the cohort were totally Asian. The median ages in the APT and non-APT groups were 73 and 73 years, respectively. History of percutaneous coronary intervention (PCI, $p < 0.001$) and coronary artery bypass graft ($p = 0.028$), and history of cerebral infarction ($p = 0.003$) were more common in the APT group. There was also a significant difference between the groups in the rate of anticoagulation therapy ($p = 0.044$) and perioperative heparin bridging ($p = 0.010$). In the APT group, 18 patients (18.0%) were classified into high risk for arterial thromboembolism, and were managed with preoperative continuation of aspirin monotherapy.

Table 2 shows operative procedures and postoperative morbidity of patients in each group. The current series included pancreatic cancer in 31 (31.0%), bile duct cancer in 27 (27.0%), ampullary cancer in 19 (19.0%), and intraductal papillary mucinous neoplasms in 13 (13.0%). There was no difference in the type of diseases between the groups ($p = 0.091$). The most prevalent types of the operative procedure, pancreatic reconstruction, and texture of the remnant pancreas were SSPD (95.0%), pancreatico-jejunostomy (93.0%), and soft pancreas (71.0%), respectively; no significant difference was observed in these factors between the groups. The duration of operation, estimated surgical blood loss, rates of intraoperative transfusion were also identical between the groups. Increased surgical

Table 1 Background characteristics of patients in the cohort.

Variables	Total (n = 100)	APT (n = 31)	non-APT (n = 69)	p
Age, y, median (range)	73 (37-86)	73 (60-84)	73 (37-86)	0.357
Gender, n (%)				0.65
Female	33 (33.0)	9 (29.0)	24 (34.8)	
Male	67 (67.0)	22 (71.0)	45 (65.2)	
BMI				0.32
< 30 kg/m ²	95 (95.0)	31 (100.0)	64 (92.8)	
≥ 30 kg/m ²	5 (5.0)	0 (0.0)	5 (7.2)	
Performance status, n (%)				0.7
0,1	92 (92.0)	28 (90.3)	64 (92.8)	
2,3	8 (8.0)	3 (9.7)	5 (7.2)	
Concurrent diseases, n (%)				
Diabetes mellitus	27 (27.0)	10 (32.3)	17 (24.6)	0.47
Hx of congestive heart failure	6 (6.0)	4 (12.9)	2 (2.9)	0.072
Coronary artery disease				
Hx of PCI	15 (15.0)	15 (48.4)	0 (0.0)	< 0.001
Hx of CABG	3 (3.0)	3 (9.7)	0 (0.0)	0.028
Hx of cerebral infarction	11 (11.0)	8 (25.8)	3 (4.3)	0.003
Current hemo-/peritoneal dialysis	4 (4.0)	1 (3.2)	3 (4.3)	1
Anticoagulation therapy, n (%)	12 (12.0)	7 (22.6)	5 (7.2)	0.044
Periop. Heparin bridging, n (%)	14 (14.0)	9 (29.0)	5 (7.2)	0.01
Preop. Aspirin continuation, n (%)	18 (18.0)	18 (58.1)	-	-

*Abbreviations: APT; antiplatelet therapy, BMI; body mass index, PCI; percutaneous coronary intervention, CABG; coronary artery bypass graft, periop.; perioperative, preop.; preoperative.

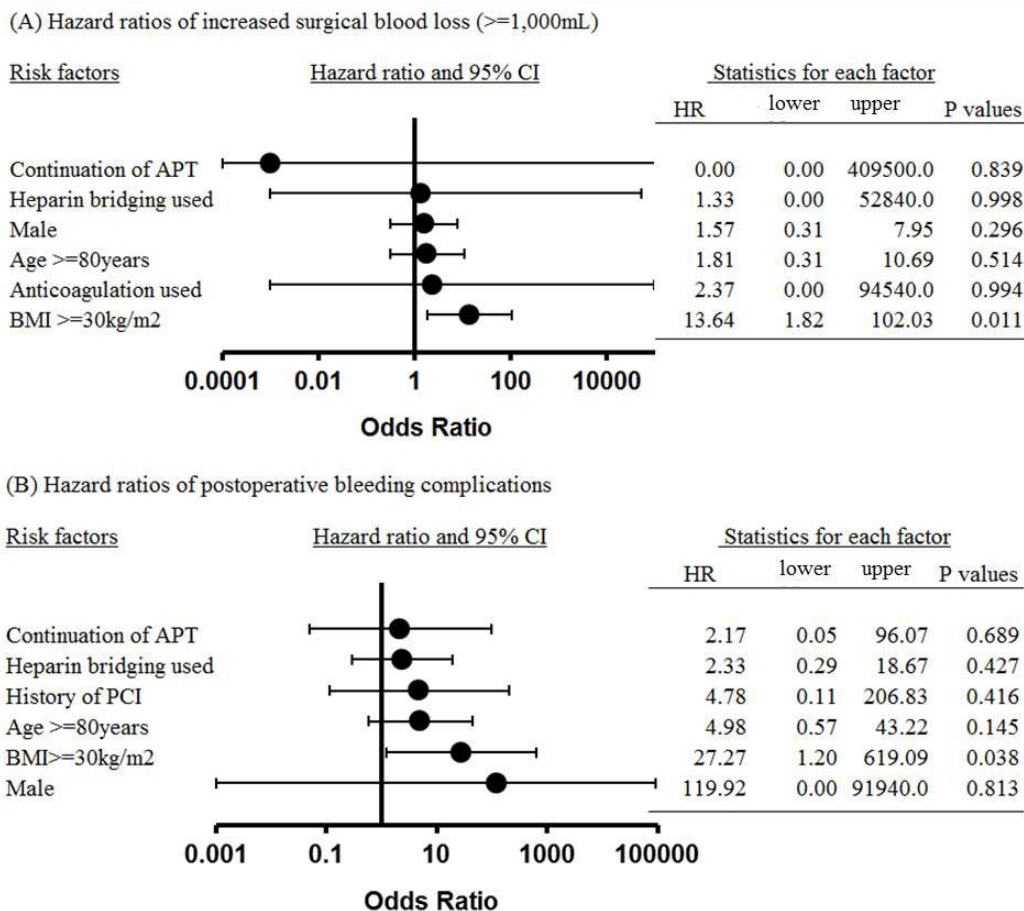


Figure 2 Forest plots showing risk ratios of increased surgical blood loss (A) and postpancreatectomy hemorrhage (B), n=100. Abbreviations: CI, confidence interval; HR, hazard ratio; APT, antiplatelet therapy; BMI, body mass index; PCI, percutaneous coronary intervention.

Table 2 Factors concerning operative procedures and postoperative morbidity

Variables	Total (n = 100)	APT (n = 31)	non-APT (n = 69)	p value
Type of diseases, n (%)				0.091
Pancreatic cancer	31 (31.0)	14 (45.2)	17 (24.6)	
Bile duct cancer	27 (27.0)	5 (16.1)	22 (31.9)	
Ampullary cancer	19 (19.0)	8 (25.8)	11 (15.9)	
Intraductal papillary mucinous neoplasms	13 (13.0)	2 (6.5)	11 (15.9)	
Others	10 (10.0)	2 (6.5)	8 (11.6)	
Type of operation, n (%)				0.837
Subtotal stomach preserving PD	95 (95.0)	29 (93.6)	66 (95.7)	
Conventional PD	2 (2.0)	1 (3.2)	1 (1.4)	
Pylorus-preserving PD	3 (3.0)	1 (3.2)	2 (2.9)	
Mode of pancreatic reconstruction, n (%)				0.431
Pancreatico-jejunostomy	93 (93.0)	30 (96.8)	63 (91.3)	
Pancreatico-gastrostomy	7 (7.0)	1 (3.2)	6 (8.7)	
Texture of the remnant pancreas, n (%)				0.094
Soft pancreas	71 (71.0)	18 (58.1)	53 (76.8)	
Hard pancreas	29 (29.0)	13 (41.9)	16 (23.2)	
Diameter of MPD, mm, median (range)	4 (1-12)	4 (1-12)	4 (1-10)	0.072
Duration of ope., min, median (range)	438 (310-710)	474 (320-587)	430 (310-710)	0.586
Surgical blood loss, mL, median (range)	500 (10-2470)	530 (50-2250)	500 (10-2470)	0.704
Intraoperative RBC transfusion, n (%)	18 (18.0)	8 (25.8)	10 (14.5)	0.259
Postoperative complication, n (%)				
None	59 (59.0)	19 (61.3)	40 (57.9)	0.828
POPF (Grade B,C)	18 (18.0)	6 (19.3)	12 (17.4)	0.786
deep SSI	11 (11.0)	4 (12.9)	7 (10.1)	0.735
Anastomotic/bile leak	5 (5.0)	1 (3.2)	4 (5.8)	1
DGE	4 (4.0)	0 (0.0)	4 (5.8)	0.308
Pulmonary infection	4 (4.0)	3 (9.6)	1 (1.4)	0.087
Cardiac insufficiency	2 (2.0)	1 (3.2)	1 (1.4)	0.526
Small bowel obstruction	1 (1.0)	0 (0.0)	1 (1.4)	1
Bleeding complication (PPH)	6 (6.0)	4 (12.9)	2 (2.9)	0.072
Thromboembolic complication	1 (1.0)	1 (3.2)	0 (0.0)	0.31
Operative mortality, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Length of postop. stay, d, median (range)	29 (13-212)	29 (15-212)	32 (13-132)	0.377

*Abbreviations: APT: antiplatelet therapy; PD: pancreaticoduodenectomy; MPD: main pancreatic duct; RBC: red blood cell; ope.: operation; POPF: postoperative pancreatic fistula; SSI: surgical site infection; DGE: delayed gastric emptying; PPH: post-pancreatectomy hemorrhage; postop.: postoperative.

blood loss ($\geq 1,000$ mL) occurred in 11 (11.0%) patients, but no case suffering uncontrollable excessive intraoperative bleeding due to the continuation of APT and requiring platelet transfusion was experienced in the APT group.

Postoperative complications developed in 41.0% of overall patients. The most common complication was POPF (18.0%, Grade B/C according to ISGPF definition); the occurrence of POPF was similar between the groups. There was only 1 thromboembolic event (1.0%, cerebral infarction) in a whole cohort. PPH occurred in 6 patients (6.0%); all 6 PPH was classified into Grade B including 2 extra-luminal and 4 intra-luminal bleeding. No case of Grade C PPH requiring urgent hemostasis by relaparotomy or interventional arterial coiling was experienced in the current cohort.

Univariate and multivariate analyses for increased surgical blood loss and PPH were performed and shown in Table 3 and Figure 2, respectively. High body mass index (BMI, ≥ 30 kg/m²) was the only significant risk factor for increased surgical blood loss on both univariate and multivariate analyses [risk ratio (RR) = 13.64, $p = 0.011$], although use of APT or preoperative continuation of aspirin was not significantly associated. Concerning PPH, history of PCI was significantly associated on univariate analysis, although only high

BMI was independently associated with PPH on the multivariate analysis (RR = 27.27, $p = 0.038$). Neither APT use nor preoperative aspirin continuation was a significant risk factor for PPH.

DISCUSSION

Our study demonstrated that the current cohort comprised 100 patients undergoing PD, among which 31% were receiving APT. According to our perioperative management protocol, aspirin monotherapy was maintained perioperatively in case of high thromboembolic risks. The rate of thromboembolic event is only 1.0% in the whole cohort, whereas the occurrence of increased blood loss and PPH were 11% and 6%, respectively. Multivariate analysis showed that high BMI is the only significant risk factor for both increased blood loss and PPH, but either use of APT or preoperative aspirin continuation did not affect bleeding complications. Thus, PD is performed safely without increase of surgical blood loss, PPH, or thromboembolic complications even in APT-burdened patients.

Since APT for prevention of cardiovascular/cerebrovascular events is widely used^[26-28], patients receiving APT frequently receive surgical procedures. About 5-15% of patients who received coronary stent

implantation have undergone non-cardiac surgery within 2 years^[29]. Premature discontinuation of antiplatelet agents is the known risk factor for late coronary stent thrombosis, which is rare but life-threatening sequelae with the mortality rate at 9-45%^[28-30]. We have to balance bleeding risk against thromboembolic risk in patients undergoing APT. Current guidelines of post-PCI surgical intervention specify that in the perioperative period, the continuation of APT, but not using heparin bridging, should be considered, particularly in high thromboembolic risk patients^[31-34]. In addition, recent trends in

Table 3 Univariate analysis of increased surgical blood loss ($\geq 1,000$ mL) and postpancreatectomy hemorrhage in the cohort, n=100.

Variables	Increased surgical blood loss		Postpancreatectomy Haemorrhage	
	present/total (%)	p	present/total (%)	p
Total	11/100 (11.0)		6/100 (6.0)	
Age		0.182		0.197
>=80 years	8/86 (9.3)		2/14 (14.3)	
<80 years	3/14 (21.4)		4/86 (4.7)	
Gender		1		0.174
Female	3/33 (9.1)		0/33 (0.0)	
Male	8/67 (11.9)		6/67 (9.0)	
BMI, n (%)		0.009		0.271
<30 kg/m ²	8/95 (8.4)		5/95 (5.3)	
≥ 30 kg/m ²	3/5 (60.0)		1/5 (20.0)	
Performance status		0.213		1
0,1	9/92 (9.8)		6/92 (6.5)	
2-4	2/8 (25.0)		0/8 (0.0)	
Diabetes mellitus		1		0.66
Yes	3/27 (11.1)		2/27 (7.4)	
No	8/73 (11.0)		4/73 (5.5)	
Hx of CI/TIA		1		0.513
Yes	1/11 (9.1)		1/11 (9.1)	
No	10/89 (11.2)		5/89 (5.6)	
Hx of PCI, n (%)		0.209		0.042
Yes	0/15 (0.0)		3/15 (20.0)	
No	11/85 (12.9)		3/85 (3.5)	
APT used		0.165		0.072
Yes	1/31 (3.2)		4/31 (12.9)	
No	10/69 (14.5)		2/69 (2.9)	
Preop. aspirin continuation		0.206		0.07
Yes	0/18 (0.0)		3/18 (16.7)	
No	11/82 (13.4)		3/82 (3.7)	
Anticoagulation used		0.125		0.545
Yes	3/12 (25.0)		1/12 (8.3)	
No	8/88 (9.1)		5/88 (5.7)	
Periop. heparin bridging		0.182		0.197
Yes	3/14 (21.4)		2/14 (14.3)	
No	8/86 (9.3)		4/86 (4.7)	
Texture of the remnant pancreas		0.726		0.669
Soft pancreas	7/71 (9.9)		5/71 (7.0)	
Hard pancreas	4/29 (13.8)		1/29 (3.4)	
Presence of major pancreatic fistula		0.206		0.588
Yes	0/18 (0.0)		0/18 (0.0)	
No	11/82 (13.4)		6/82 (7.3)	

*Abbreviations: BMI: body mass index; APT: antiplatelet therapy; CI: cerebral infarction; TIA: transient ischemic attack; PCI: percutaneous coronary intervention; preop: preoperative; periop: perioperative.

several guidelines clearly show that prevention of thromboembolism is more important since it might cause severe postoperative life-threatening complications^[35-38]. If the thromboembolic risk is low, interruption of antiplatelets might be possible. However, if the risk of thromboembolism is high, continuation of at least single APT is adequate. Considering those circumstances, we have established our own perioperative antithrombotic protocol ("Kokura Protocol"), and shown that both laparoscopic and open abdominal surgery can be safely performed even in APT-prescribed patients under the Kokura Protocol^[5-7]. The current study also demonstrated that the Kokura Protocol is valid and feasible in the setting of performing PD, resulting in satisfactorily low incidence of thromboembolic events and PPH even under the high prevalence of APT-burdened patients.

Concerning perioperative arterial thromboembolic complications including cerebrovascular stroke or major adverse cardiovascular event (MACE), the rates of perioperative thromboembolisms vary depending on differences in patient population, study design, and changing clinical practices. In cardiac, neurologic, and carotid surgery, the incidence of perioperative stroke is known to be high (2.2-5.2%)^[39,40]; the reported incidence of stroke following noncardiac, nonneurosurgical surgery ranges between 0.1-0.4% overall, and 2.9-3.5% in patients at risk of perioperative stroke^[41-44]. In consideration of thromboembolic events after PD, the prevalence of thromboembolism seems to be higher. Haigh et al. reported that analyzing 2,610 patients undergoing PD from the American College of Surgeons-National Surgical Quality Improvement Program database, a rate of MACE after PD in the whole cohort was at 1.9%, and that in the elderly (aged > 70 years) was at 3.0%^[45]. The current study demonstrated that the incidence of perioperative thromboembolic complication was maintained at 1.0%, a relatively low rate compared to the previous report. Thus, it is suggested that PD is performed safely under the Kokura Protocol, with successful inhibition of thromboembolic events even in patients having thromboembolic risks.

Reduction of intraoperative blood loss and PPH is another important goal when PD is performed, and various technical development has been introduced^[21,22,46]. In our institution, the rate of APT-burdened patients requiring major hepatobiliary and pancreatic surgery is almost 30-40%, and the number is expected to be increasing. For this reason, a simple but strong hemostatic devices and technique should be adopted and utilized especially in this critical patient population. In this aspect, the combination of modified PBC technique and Harmonic FOCUS® is one of the preferred technical options during PD to minimize surgical blood loss¹⁸.

It was reported that several operations such as hip arthroplasty, neurosurgical surgery, or gastrectomy might be associated with increased surgical blood loss and postoperative hemorrhage when performed in patients receiving antithrombotic agents^[3,47,48]. Concerning the pancreatic surgery, however, only one report from Japan reported the effect of antiplatelets and anticoagulation on PPH after pancreatic resection^[12], and they concluded that rigid thromboprophylaxis including antiplatelet continuation and heparin bridging was significantly related to PPH. The incidence of PPH in their study was relatively high with the rate of 11.4% (18/158), among which 7 (4.4%) patients were grade C and PPH-associated mortality rate was 16.7%. In the current study, the incidence of PPH in the whole cohort was 6.0%, and there was no patient with grade C PPH and the mortality was zero; it is concluded that use of APT and occurrence of PPH was independent in the current series. Active intervention for rigid hemostasis using several techniques and devices could reduce intraoperative surgical blood loss, as well

as the incidence of PPH^[18,21,46]. Not only the rigorous perioperative antithrombotic management, but also various modification and innovation in technique, like the procedures proposed by us or others, can lead us to perform PD, a highly invasive procedure, more safely even in antiplatelet-burdened patients with high thromboembolic risks.

The present study possesses some limitations. It is a retrospective cohort study from a single institution, which weakens the statistical efficacy and conclusion. This restriction will be lessened in a later follow-up study or in a prospective multicenter study. Additionally, as we continue to manage APT patients undergoing PD using the same surgical policy and perioperative management protocol, we will accumulate more patients to help us understand the safety of our management in this challenging patient population.

CONCLUSION

Analyzing consecutive 100 patients undergoing pancreaticoduodenectomy, we showed that this procedure is safely performed even in antiplatelet-burdened patients with arterial thromboembolic risks without any increase of surgical blood loss or PPH, although this challenging group should be managed carefully to prevent severe postoperative complications.

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