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ORIGINAL ARTICLE

Preoperative continuation of aspirin administration in patients undergoing major abdominal malignancy surgery

Kazumi Ono[1] · **Hidekuni Hidaka**[2] · **Masuya Sato**[2] · **Hideki Nakatsuka**[1]

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Abstract

Purpose In contrast to that in a nonoperative setting, it has been shown that perioperative administration of aspirin did not decrease the rate of death or myocardial infarction but increased major bleeding risk. Since these conflicting results might be due to concurrent use of anticoagulants and a lower thrombotic risk of patients, this cohort study was carried out for patients at a high thrombotic risk without concurrent use of anticoagulants.

Methods Medical records for patients who underwent major abdominal malignancy surgery and who were on a preoperative antiplatelet regimen were reviewed. The patients were divided into two groups according to perioperative antiplatelet management: administration of all preoperative antiplatelet agent-suspended (no aspirin) group and only aspirin administration-continued (aspirin) group. The incidence of symptomatic thromboembolic events, frequency of exogenous blood transfusion within 30 days after surgery and the amount of intraoperative bleeding were compared between the two groups.

Results After propensity score matching, 105 patients of each group were matched. The incidence of perioperative thromboembolic events in the no-aspirin group was significantly higher than that in the aspirin group [7/105 (6.7%) vs 0/105 (0%), 95% CI 1.44–∞, $P=0.016$]. In contrast, neither the frequency of exogenous transfusion [21.0% vs 11.4%, 95% CI 0.88–4.38 $P=0.110$] nor the amount of intraoperative bleeding [median (interquartile range), ml: 230 (70–500) vs 208 (50–500), $P=0.325$] was different between the two groups.

Conclusion Although the sample size is relatively small, our findings suggest that continuation of aspirin administration is likely to reduce the thrombotic risk but unlikely to increase the bleeding risk of patients who undergo major abdominal surgery for malignancy.

Keywords Perioperative · Aspirin · Thromboembolism

Introduction

Previous reports have provided substantial evidence that aspirin reduces the incidence of thromboembolic events in a nonoperative setting [1–3]. Aspirin is, therefore, widely used for secondary prevention of ischemic cardiovascular disorders in clinical practice. In the perioperative period, however, considering the risk of excessive bleeding, the administration of aspirin is sometimes stopped well in advance of a surgical procedure despite the possible increased thrombotic risk. The results of a previous meta-analysis [4] and results of small-scale randomized controlled trials (RCTs) [5, 6] suggested that preoperative continuation of aspirin administration in patients undergoing noncardiac surgery was unlikely to increase the bleeding risk to a clinically significant degree, while a more recent larger scale RCT, the POISE-II trial, showed that aspirin administration increased the risk of major bleeding [7]. The latter RCT also showed that perioperative aspirin administration was not associated with a decrease in the incidence of death or myocardial infarction. Clinicians are, therefore, in a dilemma about whether to continue or discontinue aspirin administration in the perioperative period.

The different findings in the POISE-II trial and previous studies in a non-operative setting were partly due to an aspirin-induced increase in perioperative bleeding, and the resulting mismatch between oxygen supply and demand

✉ Kazumi Ono
kono@med.kawasaki-m.ac.jp

[1] Department of Anesthesiology and Intensive Care Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan

[2] Fukuyama City Hospital, Fukuyama, Japan

balance. Additionally, the patients who were enrolled in the trial were likely to have had less serious comorbidities and to have had a higher frequency of concurrent use of anticoagulants, which might have affected the results [8].

It is well known that thromboembolism is a common complication in patients with malignancy [9, 10]. Major abdominal malignancy surgery is, therefore, prone to be associated with perioperative thromboembolic events as well as major bleeding due to invasive procedures. This higher thrombotic and bleeding risk should be exaggerated further if patients are on a preoperative aspirin regimen for secondary prevention of ischemic cardiovascular disorders. The thrombotic risk may increase when administration of aspirin is suspended, while the bleeding risk may increase when administration is continued. This study was undertaken in such patients who were at higher thrombotic and bleeding risk without concurrent use of anticoagulants, thereby comparing the data obtained from the RCT with real-world data for a Japanese population. We hypothesized that continuation of aspirin administration does not increase perioperative bleeding risk but decreases thrombotic risk in patients undergoing major abdominal malignancy surgery.

Methods

Our institutional ethics committee approved the study, and the committee agreed to waive informed consent because of its retrospective nature without specific intervention. The observational retrospective study was performed for patients who underwent gastric, colorectal, hepato/biliary/pancreatic or urological malignancy surgery at our institution during a 10-year period from April 2005 to March 2015. To determine the overall and surgical procedure-specific perioperative thrombotic risks of these patients, the incidences of symptomatic thromboembolic events [cerebral infarction (CI) and/or transient ischemic attack (TIA), acute coronary syndrome (ACS), systemic thromboembolism (STE) and pulmonary thromboembolism (PTE)] within 30 days after surgery were investigated. Diagnosis of these thromboembolic events was confirmed by magnetic resonance imaging, a coronary angiogram and a contrast-enhanced computed tomography scan. Patients who were receiving therapy with antiplatelet agents preoperatively for secondary prevention of ischemic cardiovascular diseases were identified and divided into two groups according to their perioperative management of antiplatelet agents. One of the groups consisted of patients for whom preoperative administration of all antiplatelet agents was suspended (no-aspirin group) well in advance of the surgical procedure (usually more than 7 days), and the other group consisted of patients for whom only aspirin administration was continued until the day of surgery after the suspension of administration of all other antiplatelet agents (aspirin group) during the perioperative period. Patients who were on a regimen of both anticoagulants and antiplatelet agents were excluded from the study since they were reported elsewhere [11]. DVT prophylaxis with anticoagulants was not initiated postoperatively except for in patients who underwent urological malignancy surgery (6000 units/day unfractionated heparin infusion for a few days). Aspirin administration was reinitiated in the aspirin group as soon as oral intake was resumed after surgery, while administration of antiplatelet agents was reinitiated in the no-aspirin group after the surgeon agreed to do so at least 4–5 days after surgery. The incidences of thromboembolic events within 30 days after surgery were compared in the no-aspirin group and the aspirin group. To determine the bleeding risk of continuation of aspirin administration until the day of surgery, both the frequency of exogenous blood transfusion within 30 days after surgery and the amount of intraoperative bleeding were compared in the no-aspirin group and the aspirin group.

Since patients were not randomized for aspirin administration between the no-aspirin group and the aspirin group, we used propensity score matching with a multivariate logistic regression model to adjust for the likelihood of aspirin administration [12]. The covariates in this model included age, sex, ASA physical status, type of surgical procedure, comorbidities such as diabetes mellitus, chronic kidney disease with or without hemodialysis, congestive heart failure, cerebral infarction, carotid artery disease, peripheral artery disease, and a history of prior percutaneous coronary intervention (PCI) and deep vein thrombosis. These covariates were chosen from variables measured at baseline before treatment for their potential association with the treatment and/or the outcome based on clinical knowledge. One patient in the no-aspirin group was matched to one patient in the aspirin group using nearest-neighbor matching without replacement. Propensity scores were matched using a caliper width of 0.03 logit of the SD, and the standardized difference was used to measure covariate balance. Statistical analyses were performed using R program/software (version 3.4.1, 2017) [13]. Proportional data before propensity score matching were compared with the chi-square test. Continuous outcomes of the propensity score-matched samples were assessed by the Wilcoxon signed rank test. Proportional outcomes of the matched samples were assessed by the McNemar test and differences were considered significant if $P < 0.05$.

Results

As shown in Table 1, a total of 3645 patients underwent surgery and 27 (0.7%) of them had thromboembolic events within 30 days after surgery during the 10-year period.

Table 1 Incidences of perioperative thromboembolic events

Type of surgical procedure	Perioperative thromboembolic events (no.)				
	CI/TIA	ACS	STE	PTE	Total
Gastric surgery ($n=991$)	1	1	1	0	3
Hepato/biliary/pancreatic surgery ($n=678$)	1	1	1	1	4
Colon and rectal surgery ($n=1194$)	5	1	1	1	8
Urological surgery ($n=782$)	4	1	1	6	12
Total ($n=3645$) [%]	11 [0.3%]	4 [0.1%]	4 [0.1%]	8 [0.2%]	27 [0.7%]

CI/TIA cerebral infarction/transient ischemic attack, *ACS* acute coronary syndrome, *STE* systemic thromboembolism, *PTE* pulmonary thromboembolism

There were 379 patients who were on an antiplatelet regimen preoperatively, including 164 in the no-aspirin group and 215 in the aspirin group. The incidence of thromboembolic events in the 379 patients on a preoperative antiplatelet regimen was significantly higher than that in patients not on an antiplatelet regimen [7/379 (1.8%) vs 20/3266 (0.6%), odds ratio (OR) 3.05, 95% confidence interval (CI) 1.31–7.15, $P=0.006$].

Baseline patient characteristics and standardized differences before and after propensity score matching are shown in Tables 2 and 3, respectively. After propensity score matching, 105 patients of each group were matched and the covariate balance was considerably improved. The incidence of perioperative thromboembolic events in the no-aspirin group was significantly higher than that in the aspirin group [7/105 (6.7%) vs 0/105 (0%), 95% CI 1.44–∞, $P=0.016$]. Seven thromboembolic events in the no-aspirin group consisted of 4 CI/TIAs, 2 ACSs and 1 PE. In contrast, neither the frequency of exogenous transfusion [21.0% vs 11.4%, 95% CI 0.88–4.38 $P=0.110$] nor the amount of intraoperative bleeding [median (interquartile range), ml: 230 (70–500) vs 208 (50–500), $P=0.325$] was significantly different between the two group (Table 4).

Discussion

The first main finding of our study was that the incidence of symptomatic thromboembolic events within 30 days after major abdominal surgery for malignancy was 0.7%. CI/TIA

Table 2 Patient characteristics before propensity score matching

Patient characteristics	Aspirin group ($n=215$)	No-aspirin group ($n=164$)	Standardized difference (%)
Age, mean (SD)	74.3 (8.2)	74.0 (11.9)	2.2
Female sex, no. (%)	48 (22.3)	36 (21.9)	0.9
Comorbidities—no. (%) diabetes mellitus	103 (47.9)	58 (35.4)	25.6
Chronic kidney disease	13 (6.0)	12 (7.3)	5.1
Hemodialysis	5 (2.3)	2 (1.2)	8.4
Chronic heart failure	11 (5.1)	6 (3.7)	7.1
Prior coronary intervention	122 (56.7)	26 (15.9)	94.0
Cerebral infarction	64 (29.8)	95 (57.9)	59.2
Carotid artery disease	13 (6.0)	17 (10.4)	15.6
Peripheral artery disease	13 (6.0)	16 (9.8)	13.8
Deep vein thromboembolism	0 (0)	1 (0.6)	11.1
Type of surgery—no. (%) gastric surgery	61 (28.4)	56 (34.1)	1.6
Hepato/biliary/pancreatic surgery	39 (18.1)	21 (12.8)	
Colon and rectal surgery	70 (32.6)	49 (29.9)	
Urological surgery	45 (20.9)	36 (23.2)	
ASA—no. (%) PS.1	0 (0)	2 (1.2)	31.1
PS.2	83 (38.6)	84 (51.2)	
PS.3	130 (60.5)	78 (47.6)	
PS.4	2 (0.9)	0 (0)	

Table 3 Patient characteristics after propensity score matching

Patient characteristics	Aspirin group (n = 105)	No-aspirin group (n = 105)	Standardized difference (%)
Age, mean (SD)	74.3 (7.9)	74.5 (10.6)	9.8
Female sex, no. (%)	24 (22.9)	24 (22.9)	0
Comorbidities—no. (%) diabetes mellitus	47 (44.8)	45 (42.9)	3.8
Chronic kidney disease	5 (4.8)	8 (7.6)	11.9
Hemodialysis	2 (1.9)	2 (1.9)	0
Chronic heart failure	6 (5.7)	5 (4.8)	4.3
Prior coronary intervention	27 (25.7)	26 (24.8)	2.2
Cerebral infarction	48 (45.7)	52 (49.59)	7.6
Carotid artery disease	10 (9.5)	8 (7.6)	6.8
Peripheral artery disease	9 (8.6)	8(7.6)	3.5
Deep vein thromboembolism	0 (0)	0 (0)	0
Type of surgery—no. (%) gastric surgery	31 (29.5)	18(17.1)	5.6
Hepato/biliary/pancreatic surgery	19 (18.1)	19 (18.1)	
Colon and rectal surgery	29 (27.6)	40 (38.1)	
Urological surgery	26 (24.8)	28 (26.7)	
ASA—no. (%) PS.1	0 (0)	0 (0)	0
PS.2	52 (49.5)	56 (53.3)	
PS.3	53 (50.5)	49 (46.7)	
PS.4	0 (0)	0 (0)	

Table 4 Outcome data

	Aspirin group (n = 105)	No-aspirin group (n = 105)	P value
Symptomatic thromboembolic events No./total no. (%)	0/105 (0)	7/105 (6.7)	0.016
Exogenous blood transfusion No./total no. (%)	12/105 (11.4)	22/105 (21.0)	0.110
Amount of intraoperative bleeding [median (interquartile range), ml]	208 (50–500)	230 (70–500)	0.325

(0.3%) was the most frequent perioperative thromboembolic event and PTE was the next most frequent (0.2%). These data are partly consistent with the results of a previous study by Kikura et al. on the incidences of postoperative symptomatic myocardial infarction and stroke (0.33% and 0.34%, respectively) [14], and a study by Kunisawa et al. on the incidence of postoperative symptomatic PTE [15]. Second, the incidence of perioperative thromboembolic events in patients on a preoperative antiplatelet regimen was 3 times higher than that in patients who had not been taking antiplatelet agents. In addition, the incidence of thromboembolic events increased significantly when administration of all antiplatelet agents was suspended preoperatively compared with that when only aspirin administration was continued until the day of surgery. Third, the amounts of surgical bleeding and the exogenous transfusion rates were similar in the two groups, suggesting minimal bleeding risks if aspirin administration is continued.

The POISE-II trial demonstrated that the incidence of major bleeding was higher for the aspirin group than for the placebo group. Since bleeding risk has been reported to increase when aspirin and anticoagulants were administered simultaneously [16, 17], the difference in the frequencies of concurrent use of anticoagulants, more than two-thirds of the patients in the POISE-II trial vs less than one-fourth of the patients in our study, might explain the different results for aspirin-induced bleeding in the two studies. Additionally, in the POISE-II trial, 10,010 patients were stratified according to whether they had not been taking aspirin before surgery (initiation stratum) or whether they were already on an aspirin regimen (continuation stratum). In patients of the initiation stratum, administration of either aspirin (aspirin group) or a placebo (placebo group) was started on the day of surgery and was continued until 30 days after surgery. In patients of the continuation stratum, however, administration of aspirin was suspended at least 3 days before surgery and resumed either on the day of surgery (aspirin group) or 7 days after surgery (placebo group). This may be because the duration of aspirin suspension was intended to be shortened to make it possible to carry out the large-scale RCT. It is conceivable, therefore, that the antiplatelet action of aspirin persisted through the day of surgery and early postoperative period in both the aspirin and placebo groups of the continuation stratum. Consistent with this assumption, strata analysis of that trial showed that significant difference existed in the rates of major bleeding and stroke in the initiation stratum but not in the continuation stratum. Furthermore, because of differences in the inclusion criteria, the enrolled patients in our study were at higher thrombotic risk than those in the POISE-II trial. Only 10% of the patients enrolled in the trial had high-risk comorbidities such as prior stroke or percutaneous coronary intervention (PCI), much lower than the percentage in our study (70%), thus leading to negative results regarding the prevention of perioperative stroke or myocardial infarction by aspirin. This was corroborated by the results of their subgroup analysis showing that aspirin administration was associated with a reduction in the incidence of myocardial infarction in patients with previous PCI [18]. The conflicting results of the POISE-II trial and our study might reflect the above differences in bleeding and thrombotic risks of the enrolled patients as well as differences in the experimental design. Differences in surgeon and type of surgical procedures might have affected the results as well.

A limitation of this study is that the experimental design is a retrospective observational design in which the decision to continue or suspend aspirin administration might have been affected by the severity of patient-specific preoperative risks. It is unlikely, however, that this introduced much bias since the thrombotic and bleeding risks were supposedly higher for patients in whom aspirin administration was continued than for patients in whom administration of all antiplatelet agents was suspended. Additionally, we used propensity score matching to adjust for the likelihood of aspirin administration, and the covariate balance improved considerably after matching. Last and most importantly, because of the small sample size, different results might be attributable to a type-2 error, and further study is necessary.

In conclusion, our findings suggested that preoperative continuation of aspirin administration is likely to be effective for reducing the thrombotic risk but is unlikely to increase the bleeding risk in patients undergoing major abdominal surgery for malignancy without concomitant use of anticoagulants.

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