Unfractionated Heparin during the Interruption of Antiplatelet Therapy for Non-cardiac Surgery after Drug-eluting Stent Implantation

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Abstract

Objective Heparin is not recommended to be administered during the interruption of antiplatelet therapy for non-cardiac surgery. However, there are insufficient data to determine the value. The purpose of the present study was to evaluate the clinical results of the administration of unfractionated heparin during the interruption of antiplatelet therapy in non-cardiac surgery patients who had previously undergone drug-eluting stent (DES) implantation.

Methods We retrospectively identified 210 elective non-cardiac surgical procedures that were performed with the administration of unfractionated heparin during interruption of all antiplatelet therapies in patients who had previously undergone DES implantation. Heparin was administered during the perioperative period in accordance with the local practice guideline at our institution. We examined the clinical outcomes within 30 days of surgery.

Results The mean number of implanted DESs was 2.1 ± 1.3 . No major adverse cardiac events (including cardiac death, definite stent thrombosis, and non-fatal myocardial infarction) occurred in any of the 210 cases within 30 days of surgery. Four of the 210 cases (1.9%) required reoperation for bleeding within 30 days of surgery.

Conclusion Our data showed the potential for the perioperative management with unfractionated heparin administration in Japanese patients who had previously undergone DES implantation who required non-cardiac surgery with the interruption of all antiplatelet therapies.

Key words: unfractionated heparin, drug-eluting stent, antiplatelet therapy, non-cardiac surgery

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Introduction

The risk of adverse cardiac events is significantly increased in the week following non-cardiac surgery in comparison to any other week after drug-eluting stent (DES) implantation (1). The interruption of antiplatelet therapy (APT) for surgery is considered to be one of the main reasons for the increased risk (2-5). The optimal perioperative manage-

ment of APT in patients undergoing non-cardiac surgery after DES implantation has not been clearly elucidated. Recent guidelines do not recommend the administration of heparin, which had been widely used in clinical practice as a “bridging therapy” for APT. However, the data on this issue are scarce and are not sufficient to determine the value (2, 6-9).

The purpose of this study was to evaluate the clinical results of heparin administration during the interruption of all APTs for the performance non-cardiac surgery in Japanese

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Figure. Heparin administration according to the local institutional practice guideline. Heparin administration was recommended for all DES patients who underwent non-cardiac surgery with the interruption of all APT agents regardless of the period after DES implantation. Continuous heparin administration was started at a rate of 200 U/kg/day soon after the cessation of antiplatelet drugs. The dose was adjusted to maintain a patient-to-control ratio of activated partial thromboplastin time from 1.5 to 2.0, and the administration of heparin was stopped 3 hours before surgery. After surgery, heparin infusion was restarted as soon as possible (2-6 hours after the confirmation of hemostasis or 10-12 hours after the confirmation of hemostasis if postoperative bleeding was expected). The administration of heparin was continued until 3-4 days after APT was restarted.

patients who had previously undergone DES implantation.

Materials and Methods

We retrospectively identified 210 elective non-cardiac surgical procedures after DES implantation that required the interruption of all APT and were performed with the administration of heparin in the perioperative period at Nagoya University Hospital between January 2008 and October 2013. We excluded the patients who underwent surgery to treat active bleeding and emergency cases. Each attending surgical team administered heparin in accordance with the local institutional guideline regarding the provision of antithrombotic therapy. The local institutional guideline was as follows: the administration of heparin was recommended for all DES patients who underwent non-cardiac surgery with the interruption of all APT agents regardless of the length of time after DES implantation. Continuous heparin administration was started at a rate of 200 U/kg/day soon after the interruption of antiplatelet drugs. The dose was adjusted to maintain a patient-to-control ratio of activated partial thromboplastin time from 1.5 to 2.0, and the administration was stopped 3 hours before surgery. After surgery, heparin infusion was restarted as soon as possible (2-6 hours after the confirmation of hemostasis, or 10-12 hours after the confirmation of hemostasis if postoperative bleeding was expected) and was continued until 3-4 days after APT was restarted (Figure). The practice guidelines did not refer to the administration of glycoprotein IIb/IIIa inhibitors because

they had not been approved in Japan.

This study was performed according to the guidelines of the Declaration of Helsinki and was approved by the local Ethics Committee, which waived the requirement for written informed consent.

The first-generation DESs included sirolimus- and paclitaxel-eluting stents. The second-generation DESs included zotarolimus-, everolimus-, and biolimus-eluting stents. The types of surgical procedures that were performed were defined in accordance with the American College of Cardiology/American Heart Association guideline (8). Surgical hemorrhagic risk was categorized into 3 groups [low risk (transfusion normally not required); intermediate risk (transfusion frequently required); high risk (possible bleeding in a closed space)] (10).

The occurrence of major adverse cardiac events (MACE), stroke, and bleeding events within 30 days of the surgical procedures was investigated. MACE was defined as cardiac death, definite stent thrombosis, or non-fatal myocardial infarction. Stroke was defined as the newly-developed persistent loss of neurological function and an acute lesion identified with magnetic resonance imaging. For bleeding events, the requirement of postoperative transfusion and reoperations for bleeding were recorded. Bleeding events were also evaluated on the basis of thrombolysis in myocardial infarction (TIMI) bleeding classification [major bleeding: intracranial hemorrhage (>5 g/dL decrease in hemoglobin concentration, or a >15% absolute decrease in the hematocrit count); minor bleeding: observed blood loss (>3 g/dL de-

Table 1. Baseline Characteristics at Surgical Procedure.

	n=210
<i>Characteristics at surgical procedure</i>	
Age, y	71±8
Male, n(%)	177 (84.3%)
Hypertension, n(%)	159 (75.7%)
Dyslipidemia, n(%)	181 (86.2%)
Diabetes, n(%)	73 (34.8%)
Current smoker, n(%)	17 (8.1%)
eGFR<60 mL/min/1.73m ² , n(%)	93 (44.3%)
Hemodialysis, n(%)	6 (2.9%)
Prior myocardial infarction, n(%)	74 (35.2%)
Prior CABG, n(%)	10 (4.8%)
No of vessel implanted DES (1/2/3/unknown), n	131/65/9/5
Treated coronary artery	
Right coronary artery	78
Left anterior descending artery	120
Left circumflex artery	71
Left main trunk	21
Unknown	6
No of DES implanted before, n	2.1±1.3
Type of DES, n	
1st-generation DES	147
2nd-generation DES	35
Both	12
Unknown	16
Ejection fraction, %	63±10
<i>Medications before surgical procedure</i>	
Aspirin, n(%)	189 (90.0%)
Thienopyridine, n(%)	148 (70.5%)
Aspirin + Thienopyridine, n(%)	129 (61.4%)
Cilostazol, n(%)	23 (11.0%)
Warfarin, n(%)	20 (9.5%)
Direct inhibitor of factor Xa, n(%)	1 (0.5%)
Statin, n(%)	163 (77.6%)
β-blocker, n(%)	94 (44.8%)
ACEI/ARB, n(%)	144 (68.6%)
Ca-antagonist, n(%)	105 (50.0%)
Nicorandil, n(%)	37 (17.6%)
Nitrate, n(%)	30 (14.3%)
eGFR: estimated glomerular filtration rate, CABG: coronary artery bypass grafting, DES: drug eluting stent, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor II blocker	

Table 3. Clinical Events within 30 Days of Surgery.

	n = 210
MACE, n (%)	0 (0%)
Cardiac death	0
Myocardial infarction	0
Definite stent thrombosis	0
Stroke, n (%)	0 (0%)
Bleeding event, n (%)	
Reoperation for bleeding	4 (1.9%)
Postoperative transfusion	15 (7.1%)
TIMI major/minor	5/11
MACE: major adverse cardiac event, TIMI: thrombolysis in myocardial infarction	

crease in hemoglobin concentration or >10% decrease in hematocrit) or no observed blood loss (>4 g/dL decrease in hemoglobin concentration or a >12% decrease in hematocrit)] (11).

The data are presented as the mean ± SD. The categorical

Table 2. Characteristics of Surgical Procedure.

	n=210
Cardiac risk stratification, n	
Vascular	21
Intermediate	89
Low	100
Type of surgical procedure	
Vascular surgery	21
Intraperitoneal surgery	47
Intrathoracic surgery	14
Carotid endarterectomy	1
Head and neck surgery	3
Orthopedic surgery	5
Prostate surgery	3
Endovascular aneurysm repair	16
Endoscopic procedures	51
Superficial procedure	40
Eye surgery	8
Breast surgery	1
Malignancy	95 (45.2%)
Hemorrhagic risk, n	
High	11
Intermediate	88
Low	111
Term after DES implantation	
0-1y, n	45
1-2y, n	50
2y-, n	115
Duration of discontinuation of all APT, day	
Before surgical procedure	7.6±3.1
After surgical procedure	4.5±5.9
APT: antiplatelet therapy	

variables are expressed as numbers and percentages.

Results

The patient characteristics at the time of the surgical procedure and the medications that were administered before the interruption of APT are shown in Table 1. The mean age was 71±8 years, and the majority (84.3%) were men. The mean number of implanted DESs was 2.1±1.3.

The characteristics of the surgical procedures are shown in Table 2. The mean interval from the last DES implantation to the surgical procedure was 31.9±23.0 months (45 procedures within 1 year; 50 procedures from 1 to 2 years; and 115 procedures in a period of more than 2 years). The administration of all oral APT agents was stopped in the perioperative period, and the mean duration of the interruption was from 7.6±3.1 days before the procedure to 4.5±5.9 days after the procedure.

Table 3 shows the clinical events that occurred within 30 days of surgery. No case developed MACE (0/210; 0%) or suffered a stroke within the period. Four cases required reoperation for bleeding within 30 days (4/210; 1.9%). Postoperative bleeding occurred 8 days and 10 days after surgery in 2 patients who underwent an endoscopic submucosal dissection for early-stage gastric cancer and 6 days after surgery in 1 patient who underwent an endoscopic mucosal resection for a rectal carcinoid. A postoperative hematoma was revealed by computed tomography just after surgery in 1 pa-

tient who underwent a tumorectomy for a meningioma. The reoperations of all of the patients were successful and they all survived to discharge.

No patients required the cessation of heparin administration due to suspected serious heparin-induced thrombocytopenia.

Discussion

In this report, there were no cases of MACE after 210 non-cardiac surgical procedures with unfractionated heparin during the interruption of all APTs among the DES patients. The frequency of significant bleeding events was not thought to exceed that which is commonly accepted.

Recent reports have shown that the risk of adverse cardiac events was significantly increased after non-cardiac surgery in patients who had previously undergone DES implantation (1). The perioperative cardiac risk among the DES patients is considered to be mainly related to the interruption of APT and a surgery-induced prothrombotic state (2-5, 12). Therefore, the continuation of APT has been considered to be beneficial when the surgical bleeding risk is not prohibitive (12), and guidelines recommend the continuation of APT in the perioperative period when possible (7-9, 13). However, a cardiologist often encounters situations in which a surgeon is hesitant to continue APT and requests the temporary cessation of APT for surgery to reduce the risk of perioperative bleeding. Although the risk of perioperative bleeding that is associated with the continuation of APT has to be balanced against the perioperative cardiac risk that is associated with the interruption of APT, the effectiveness of continuing APT in reducing perioperative cardiac events in patients who have previously undergone coronary stenting remains unclear (14, 15). We have to admit that there is still not enough data to strongly reject the request. There is a wide variety of potential approaches, and eventually, perioperative management on an individual case-by-case basis will be required (2, 16, 17).

In the clinical setting, heparin has been widely used in perioperative management as a bridging therapy during the interruption of APT. However, data regarding the administration of heparin in this period are scarce, and the value of perioperative heparin therapy remains to be elucidated (2, 6-8, 16). Some prior reports concluded that heparin bridging therapy might be ineffective because some degree of platelet inhibition seemed to be required to prevent stent thrombosis (6). Furthermore, other reports have indicated an association between perioperative cardiac events and the administration of unfractionated heparin (18-20). Vicenzi et al. evaluated 103 non-cardiac surgeries within 1 year after coronary stenting and reported a high incidence of perioperative adverse cardiac events, particularly in patients who received unfractionated heparin (18). Although they also suggested caution in interpreting the positive association between the administration of unfractionated heparin and the occurrence of postoperative cardiac events, Dent et

al. referred to the possibility of "heparin rebound" - a period of hypercoagulability after the abrupt cessation of unfractionated heparin before surgery (19). Anwarddin et al. assessed the cardiac risk of surgery in 606 patients after DES implantation, and noted that heparin was administered intravenously in about 20% of the patients before surgery (20). They showed that the intravenous administration of heparin in the preoperative period might increase the risk of adverse cardiac events. They also described the heparin rebound phenomenon and platelet activation caused by the administration of unfractionated heparin as possible explanations (20-22). Contrary to those results, no MACE occurred within 30 days of non-cardiac surgery in 210 DES cases received unfractionated heparin in our study. The level of perioperative cardiac risk peaks immediately after surgery (12, 23). The main cause of this might be a prothrombotic state associated with surgical stress. Heparin does not have an antiplatelet effect, but could control the hypercoagulable state after surgery, which might prevent postoperative cardiac events. Our local institutional practice guideline recommended that heparin infusion be resumed as soon as possible after surgery, which might have resulted in the low frequency of perioperative cardiac events in contrast to other reports (18, 20). Our results might not be sufficient to demonstrate the effect of unfractionated heparin, but at the very least can support that heparin, as administered within our experiments, was not harmful.

In this study, reoperation for bleeding was only required in 4 cases (1.9%) and postoperative transfusion was performed in 15 cases (7.9%). As in a previous heparin study (18), the frequency of significant bleeding was not thought to exceed that which is commonly accepted (6).

There are several limitations associated with the present study. First, this was a single center study of a relatively small population. Second, we could not compare the study group to patients who did not receive heparin or in whom the administration of APT was continued. Therefore we cannot deny the existence of other factors that related to the study results. Third, the interval from last DES implantation to the surgical procedure was relatively long in the majority of cases, which might be associated with a low incidence of MACE. Fourth, the decisions to consult cardiologists and require the interruption of APT for the procedure were basically left to the discretion of the attending surgical team. Therefore it might not be appropriate to perform some procedures with the interruption of APT. Fifth, we could not deny the existence of silent stent occlusion. Notwithstanding these limitations, to date, only a few investigations have assessed the perioperative administration of heparin and this clinical study will be meaningful in the accumulation of data regarding this issue. It is not recommended to administer heparin during the interruption of all APTs for non-cardiac surgery; however, there are insufficient data to determine the value. Furthermore, there is wide variability in the circumstances surrounding the administration of APT among different countries. Large multicenter prospective clinical in-

vestigations and further discussion about this issue are required.

In conclusion, our data showed the potential for perioperative management with unfractionated heparin administration in Japanese patients who had previously undergone DES implantation who required non-cardiac surgery with the interruption of all APTs.

The authors state that they have no Conflict of Interest (COI).

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