Preoperative Cessation of Both Dual Anti-Platelet Agents Is Safe after 1 Year in Patients Receiving Percutaneous Coronary Intervention

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ABSTRACT

Objective: The aim of this study was to investigate the atherothrombotic and bleeding risk of discontinuing both components of dual antiplatelet therapy (DAPT) before surgery in patients with an intracoronary stent after 1 year.

Methods: We retrospectively enrolled 212 patients who received an evaluation of perioperative cardiac risk and underwent surgery from March 2017 to March 2019. We divided them into 2 groups: the discontinuation of both antiplatelet agents group (DCAP, no use of any antiplatelet agent) and the continuation of at least 1 antiplatelet agent group (CAP). The primary composite endpoint was the occurrence of major adverse cardiovascular events (MACE), including death, angina, postoperative coronary angiography, stroke, and readmission within 30 days postoperatively. The second endpoint was bleeding requiring the transfusion of ≥2 packs of red blood cells (RBCs).

Result: A total of 136 patients were enrolled in the study, with 68 in the DCAP group and 68 in the CAP group. The occurrence of MACE did not significantly differ between the groups (25% vs. 17.6%, p=0.295). The incidence of bleeding that required a transfusion was higher in the CAP group (16.2% vs. 30.9%, p=0.044). The postoperative change in hemoglobin levels (−1.9 g/dL vs. −1.8 g/dL, p=0.742), and the number of transfused packs of RBCs (3.5 vs. 5.3, p=0.347) were not significantly different between the groups.

Conclusion: Preoperative discontinuation of DAPT did not increase the risk of MACE. However, continuation of at least 1 antiplatelet agent increased the incidence of bleeding requiring RBC transfusion. Further research with a large cohort is warranted.

Keywords: Surgery; Platelet aggregation inhibitors; Withholding treatment; Patient outcome assessment

INTRODUCTION

Increasingly many people are prescribed dual antiplatelet agents after revascularization therapy. Dual antiplatelet therapy (DAPT) after coronary stent implantation is associated with reduced rates of stent thrombosis, myocardial infarction, ischemic stroke, and mortality. Meanwhile, many of these patients undergo non-cardiac and cardiac surgery while prescribed antiplatelet agents; hence, the issue of interrupting DAPT is of utmost clinical importance.
However, the temporary discontinuation of these agents is commonly coordinated by the surgical department without a cardiology consultation. Cessation of DAPT can be catastrophic because it can lead to major adverse cardiovascular events (MACE), including myocardial infarction and death. However, the dilemma is—as can be expected—that continuation of DAPT during surgery may result in severe bleeding complications and even death.

The 2016 American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that elective non-cardiac surgery should be delayed for 30 days after bare metal stent (BMS) implantation and optimally for 6 months after drug-eluting stent (DES) implantation (class I recommendation) and after that period, one of the antiplatelet agents—most commonly an adenosine diphosphate receptor antagonist—could be interrupted according to the patients’ ischemic and bleeding risk profile. However, even this guideline recommends continuing a single antiplatelet agent during surgery. Despite this guideline, it is challenging for physicians to decide whether to stop one or both antiplatelet agents. This decision involves weighing the risk of delaying the surgical procedure, the risk of MACE, and the risk of excessive bleeding.

In recent years, the duration of DAPT has become shorter because of improvements in stents, which now have a lower risk of stent thrombosis. In some cases, the discontinuation of all antiplatelet agents (single or dual) appears to be safe except for some operations on critical organs such as the brain, spine, and posterior chamber of the eye, especially when new-generation stents with thinner struts are used. Especially for low-risk surgery in patients with a low risk of ischemia, it may be possible to discontinue even single antiplatelet therapy (SAPT) 1 year or longer after stent implantation. However, little supporting evidence has been reported regarding this possibility, even in the new-generation stent era.

We investigated the hypothesis that cessation of either DAPT or SAPT for surgery may not be associated with an increased risk of MACE and bleeding in patients who had received revascularization therapy more than 1 year prior to the operation.

**MATERIALS AND METHODS**

1. **Study design**

We recruited 4,668 patients retrospectively who underwent perioperative risk consultations at the cardiology department of Hallym University Sacred Heart Hospital from March 2017 to March 2019. We included those who planned to undergo cardiac or non-cardiac surgery, of whom 212 had received revascularization treatment before the operation. Data were collected on patients’ age, sex, comorbidities, reason for revascularization, smoking history, time period after percutaneous coronary intervention (PCI), type of operation, and operation time. We excluded patients who did not undergo surgery after the consultation, who did not have enough available information about antiplatelet agent use, and who were not on antiplatelet therapy after stent insertion (Fig. 1). Patients who underwent more than one operation were counted as separate cases.

Patients who were prescribed at least 1 antiplatelet agent (aspirin, clopidogrel, prasugrel, ticagrelor) after stent insertion were included. Patients who stopped all prescribed antiplatelet agents before surgery were included in the discontinuation group (DCAP, no use of any antiplatelet agents before surgery). Patients who took at least 1 antiplatelet (aspirin or clopi...
a P2Y12 receptor inhibitor) during the perioperative period were placed in the continuation group (CAP). No matching was done when distributing patients between the groups.

The primary endpoint was the occurrence of MACE during 30 days after surgery, which was defined as a composite of all-cause mortality, angina, coronary angiography after surgery, acute cerebral infarction, and readmission or an emergency department visit within 30 days after surgery. We defined angina as chest pain or discomfort that was severe enough to consult a cardiologist, but did not require intervention. Regardless of whether this symptom was determined to indicate “real” ischemic chest pain, we counted events as angina if a consultation was done. If a symptom or a finding upon further evaluation (echocardiography, electrocardiography, or serum cardiac enzyme level) required coronary angiography, patients were counted as having undergone postoperative coronary angiography. The patients in the angina and postoperative coronary angiography categories did not overlap.

The secondary endpoint was bleeding that required transfusion of at least 2 packs of red blood cells (RBCs). The number of packs of RBCs transfused during surgery and within 7 days after the operation was counted and analyzed for those who had received more than 2 packs of RBCs. The difference in hemoglobin (Hb) levels before and after surgery was assessed. We included all patients who had data about Hb levels, and compared the level just before surgery with the lowest level within 5 days after surgery.

2. Statistical analysis
Descriptive statistics (average, minimum and maximum, and standard deviation) were calculated for continuous variables. Comparisons for continuous variables were performed by means of the unpaired Student t-test. Absolute frequencies and percentages were obtained for qualitative variables. Qualitative variables were compared using the Pearson χ² test. p-values <0.05 were considered to indicate statistical significance. We used the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist for the study. Statistical analysis was carried out using SPSS version 23 (IBM Corp., Armonk, NY, USA). This study was not approved by the Institutional Review Board of Hallym University Sacred Heart Hospital.
RESULTS

The study flow is presented in Fig. 1. Among 4,668 patients who received a perioperative risk consultation before surgery, 212 patients had previously undergone revascularization therapy; of these patients, 35 did not undergo surgery. Eight patients were not on antiplatelet therapy after stent insertion, and 33 patients were excluded because they did not have enough data for the study (Fig. 1). As a result, 136 patients were included: 68 in the DCAP group and 68 in the CAP group. The reasons for stent insertion were stable angina in 17 patients, unstable angina and non-ST segment elevation myocardial infarction in 42 patients, and ST segment elevation myocardial infarction in 47 patients. The other 30 patients did not have records about their prior cardiac diseases (Table 1). The duration after stent insertion was shorter in the CAP group than in the DCAP group (4.96 years vs 6.99 years, \( p = 0.009 \)). Other factors did not show significant differences between the 2 groups.

The occurrence rate of MACE at 30 days after surgery did not significantly differ between the DCAP and CAP groups (25% vs. 17.6%, \( p = 0.295 \)) (Table 2). The incidence of angina was higher in the DCAP group than in the CAP group. The number of patients who required coronary angiography, were readmitted, and died within 30 days were similar in both groups.

| Table 1. Baseline characteristics | DCAP (n=68) | CAP (n=68) | \( p \)-value |
|-----------------------------------|------------|------------|---------------|
| Mean age (yr)                     | 70.24      | 70.71      | 0.809         |
| <65                               | 18 (26.5)  | 21 (30.9)  | 0.569         |
| \geq 65                           | 50 (73.5)  | 47 (69.1)  |               |
| Sex                               |            |            | 0.857         |
| Male                              | 45 (66.2)  | 44 (64.7)  |               |
| Female                            | 23 (33.8)  | 24 (35.3)  |               |
| Comorbidities                     |            |            |               |
| Hypertension                      | 52 (76.5)  | 55 (80.9)  | 0.530         |
| Diabetes mellitus                 | 35 (51.5)  | 32 (47.1)  | 0.607         |
| Dyslipidemia                      | 11 (16.2)  | 20 (29.4)  | 0.066         |
| Cerebral infarction               | 5 (7.4)    | 8 (11.8)   | 0.382         |
| Height (cm)                       | 162.04     | 161.54     | 0.779         |
| Weight (kg)                       | 63.9       | 63.2       | 0.747         |
| BMI (kg/m\(^2\))                  | 24.2       | 24.1       | 0.860         |
| Smoking                           |            |            | 0.536         |
| Current smoker                    | 12 (17.6)  | 9 (13.2)   |               |
| Ex-smoker                         | 4 (5.9)    | 7 (10.3)   |               |
| Never-smoker                      | 52 (76.5)  | 52 (76.5)  |               |
| Reasons for PCI                   |            |            | 0.717         |
| Stable angina                     | 10 (14.7)  | 7 (10.3)   |               |
| Unstable angina, NSTEMI           | 20 (29.4)  | 22 (32.4)  |               |
| STEMI                             | 25 (36.8)  | 22 (32.4)  |               |
| Others                            | 13 (19.1)  | 17 (25.0)  |               |
| Duration after PCI (yr)           | 6.99       | 4.96       | 0.009         |
| Operation                         |            |            | 0.090         |
| High risk                         | 10 (14.7)  | 4 (5.9)    |               |
| Low risk                          | 58 (85.3)  | 64 (94.1)  |               |
| Operation time (min)              | 168.72     | 179.13     | 0.638         |
| No. of antiplatelet agents        |            |            | 0.053         |
| SAPT                              | 55 (80.9)  | 44 (64.7)  |               |
| DAPT                              | 13 (19.1)  | 24 (35.3)  |               |

Data are presented as number (%).
DCAP, discontinuation of antiplatelet agents group; CAP, continuation of antiplatelet agents group; BMI, body mass index; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; SAPT, single antiplatelet agent treatment; DAPT, dual antiplatelet agent treatment.
In the CAP group, 2 patients visited the emergency department for non-cardiac reasons: 1 for upper respiratory symptoms and 1 for vomiting. In the 2 cases of mortality, 1 was because of septic shock and 1 was a death of unknown cause. In the CAP group, 1 patient was readmitted to the hospital for an acute cerebral infarction.

The incidence of bleeding that required transfusion was higher in the CAP group (16.2% vs. 30.9%, \( p = 0.043 \)) (Table 3). More packs of RBCs were transfused in the CAP group, but without statistical significance (3.5 packs vs. 5.3 packs, \( p = 0.347 \)). Hb levels significantly decreased in the CAP group, with the largest decrease being from 14.3 to 7.2 g/dL. However, the average perioperative change in Hb levels was similar in both groups, and was not statistically remarkable (-1.9 g/dL vs. -1.8 g/dL, \( p = 0.742 \)). Nine patients did not have data available on their postoperative Hb levels, including 3 from the DCAP group and 6 from the CAP group.

According to perioperative cardiac risk, we divided patients into high-risk and low-risk groups. The high-risk group included patients who underwent surgery on some critical organs, such as the brain, spine, and posterior chamber of the eye. The operation types are described in detail in Table 4.

Most patients in the CAP group received SAPT with either aspirin or clopidogrel. In the CAP group, 44 patients (64.7%) were on SAPT, while 24 patients (35.3%) were on DAPT and 2 were on aspirin plus either prasugrel or ticagrelor. In the DCAP group, 55 patients (80.9%) were on SAPT, 13 patients (19.1%) were on DAPT, and 2 patients were on aspirin and ticagrelor. We also compared the incidence of MACE and bleeding complications between the SAPT and DAPT groups, and found similar trends (21.2% vs. 21.6%, \( p = 0.959 \); 21.2% vs. 29.7%, \( p = 0.297 \), respectively; Table 5).
In our study, 15 patients underwent surgery within 1 year after revascularization therapy: 5 within 1 month, 5 within 3 months, 4 within 6 months, and 1 within 9 months. More details about patients’ baseline characteristics are provided in Supplementary Table 1. Two patients experienced MACE in the CAP group: 1 was re-admitted to the hospital for an additional operation, and 1 was re-admitted for an acute cerebral infarction. However, the groups did not show a statistically significant difference (0% vs. 15.4%, \( p = 0.743 \)). The incidence of bleeding complications that required transfusion of at least 2 packs of RBCs also did not show a statistically significant difference between the groups (50% vs. 30.8%, \( p = 0.591 \)) (Supplementary Table 2).

**DISCUSSION**

In our study, perioperative discontinuation of all prescribed DAPT or SAPT did not increase the risk of MACE. Instead, continuation of at least 1 antiplatelet agent could increase the risk of excessive bleeding, defined as bleeding that required transfusion of at least 2 packs of RBCs. The postoperative change in Hb levels and the amount of RBCs transfused during and after surgery did not differ significantly between the 2 groups.

In 2000, a report was published describing catastrophic outcomes in patients who underwent non-cardiac surgery less than 6 weeks after coronary stent placement. In that study, 40 patients met the inclusion criteria, and there were 7 myocardial infarctions, 11 major bleeding episodes, and 8 deaths. Since that study, the 2014 ACC/AHA guideline recommended a delay of 30 days after BMS implantation and 12 months after DES implantation for elective non-cardiac surgery.

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### Table 4. Type of surgery

| Surgery name                                   | No. |
|------------------------------------------------|-----|
| Brain operation\(^a\)                         | 8   |
| Spine operation                               | 6   |
| Aortic valve operation                        | 1   |
| Intrathoracic operation\(^b\)                 | 5   |
| Intraperitoneal operation\(^c\)               | 42  |
| Head and neck surgery\(^d\)                   | 1   |
| Orthopedic surgery                            | 44  |
| Urological or gynecological surgery\(^e\)     | 25  |
| Others                                        | 4   |

\(^a\)Brain operations included craniotomy, cranioplasty, and pituitary adenoma operations that required general anesthesia. \(^b\)Intrathoracic operations included lobectomy and wedge resection surgery. \(^c\)Intraperitoneal operations included hepatobiliary surgery, gastrointestinal surgery, appendectomy, and cholecystectomy. We included both laparoscopic surgery and open surgery. \(^d\)Head and neck surgery included a single total thyroidectomy. \(^e\)Urological or gynecological surgery included ureter stone surgery, prostate surgery, bladder cancer surgery, nephrectomy, and hysterectomy.

### Table 5. Incidence of MACE and bleeding

| Events                | SAPT      | DAPT      | \( p \)-value |
|-----------------------|-----------|-----------|---------------|
| MACE\(^*\)            | 21 (21.2) | 8 (21.6)  | 0.959         |
| Bleeding\(^†\)        | 21 (21.2) | 11 (29.7) | 0.297         |

Data are presented as number (%).

SAPT, single antiplatelet agent treatment; DAPT, dual antiplatelet agent treatment; MACE, major adverse cardiovascular events; RBC, red blood cell.

\(^*\)MACE included total mortality, angina, coronary evaluation after operation, stroke, readmissions and emergency department visits within 30 days after surgery. \(^†\)Bleeding was defined as the transfusion of at least 2 packs of RBCs during and within 7 days after the operation.
However, with the use of newer-generation DES that have a lower risk of stent thrombosis, the duration of DAPT use after the intervention became shorter. In a national retrospective cohort study, 28,029 patients who had undergone coronary stent insertion within 24 months before non-cardiac surgery were assessed regarding the rate of 30-day MACE, and it was found that 1,980 patients (4.7%; 95% confidence interval [CI], 4.5%–4.9%) had adverse events. The rate of adverse events showed an association with the time period between stenting and surgery (<6 weeks, 11.6%; ≥6 weeks to <6 months, 6.4%; ≥6 to <12 months, 4.2%; ≥12 to <24 months, 3.5%; p<0.001). If surgery was performed more than 6 months after the stent procedure, the risk of adverse events did not significantly increase. A meta-analysis of 4 trials showed that short-term (3 months or 6 months) DAPT after DES placement had a similar rate of MACE to that associated with long-term (1 year) use of DAPT. Additionally, short-term DAPT was associated with a lower incidence of bleeding.

We did not have data about the type of stent inserted, but we can assume that the newer-generation DES stent use is currently predominant in Korea; this is reflected by the overall low incidence rate of MACE in our study, with no significant difference between the 2 groups (24% vs. 17.6%, p=0.295). However, angina was more common in the DCAP group.

A randomized controlled trial of administration of aspirin in patients planning to undergo surgery who were at risk for vascular complications (not patients with a history of coronary stent placement) demonstrated no significant effect on the rates of mortality or nonfatal myocardial infarction (hazard ratio [HR], 0.99; 95% CI, 0.86–1.15; p=0.92). In this trial, major bleeding was more common in the aspirin group than in the placebo group (HR, 1.23; 95% CI, 1.01–1.49; p=0.04). On the contrary, another study discussed the benefits of perioperative aspirin use in non-stented patients. They enrolled 220 patients and reported that treatment with aspirin yielded a 7.2% absolute risk reduction in 30-day MACE (95% CI, 1.3%–13%), with no significant differences in bleeding complications. However, unlike our study, the above 2 studies included patients who did not receive coronary stenting; instead, they only tested the efficacy of preoperative aspirin treatment. Nonetheless, our findings are consistent with their results, in that continuation of at least 1 antiplatelet agent could lead to massive bleeding with no gain in cardiovascular protection from the antiplatelet agent, even in patients with a coronary stent.

The amount of transfused RBCs during the surgery was higher in the CAP group than in the DCAP group, but without significance (3.5 vs 5.3 packs, p=0.347). Accordingly, the change in Hb levels was almost the same in both groups (−1.9 g/dL vs. −1.8 g/dL, p=0.742). The 2007 ACC/AHA guideline recommended delaying non-cardiac surgery for 12 months after revascularization, and subsequently that 1 antiplatelet agent could be stopped before surgery, but these recommendations were based on observations of those treated with first-generation DES. Our study included patients who had been stented more than 5 years ago, in whom cessation of DAPT seemed safe. Even in patients who underwent PCI 1 year previously, the DCAP and CAP groups showed no statistically significant differences in the incidence of MACE and excessive bleeding. Furthermore, the established safety of new-generation DES regarding cardiac death and stent thrombosis provides a rationale for our study design and results showing the safety of discontinuation of all antiplatelet agents. Moreover, nearly all medical centers now use second- or third-generation stents with improved stent strut and polymer profiles; thus, our results furnish additional convincing evidence regarding the discontinuation of antiplatelet agents.
There are some limitations of our study. First, since a small number of patients was recruited, there might have been selection bias. A study with a larger population may have a different result. Second, data were collected retrospectively from documented records, and many patients received revascularization treatment at other centers. Hence, data on stent type, the number of stents implanted, and some laboratory test results (including echocardiography) were missing, which may have led to information bias. Third, when massive bleeding occurs intraoperatively, preemptive transfusion may be performed at the surgeon’s discretion, which might affect the number of transfused packs of RBCs and Hb levels before and after surgery.

In conclusion, discontinuation of all antiplatelet agents (in patients receiving DAPT or SAPT) before surgery was not associated with a higher risk of MACE, but was associated with a lower requirement for RBC transfusion. Future, larger-scale randomized clinical trials are warranted.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Baseline characteristics of patients within 1 year of PCI

Click here to view

Supplementary Table 2
Incidence of MACE and bleeding within 1 year of revascularization

Click here to view

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