

A preliminary study: aspirin discontinuation before elective operations; when is the optimal timing?

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Purpose: To evaluate the optimum timing of aspirin cessation before noncardiac surgeries. We have conducted a pilot study to minimize the aspirin cessation time before various surgeries.

Methods: Eighty patients who were taking regular aspirin for secondary prevention undergoing elective surgical operations were enrolled in the study. We separated the patients into two groups. The control group had 35 patients who stopped aspirin intake 10 days before surgery. The study group had 45 patients who stopped their aspirin intake and underwent surgery one day after arachidonic acid aggregation tests were within normal limits. Bleeding, blood loss, and transfusion requirements were assessed perioperatively.

Results: The mean time between aspirin cessation and aspirin nonresponsiveness were found to be 4.2 days with a median value of 4 days. In addition, the mean time between aspirin cessation and operation day were found to be 5.5 days with a median value of 5 days. No perioperative bleeding, thromboembolic or cardiovascular complications were encountered.

Conclusion: Reducing time of aspirin cessation from 7–10 days to 4–5 days is a possibility for patients using aspirin for secondary prevention without increased perioperative complications.

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Key Words

Aspirin, Arachidonic acid, Blood platelets,
Perioperative period, General surgery

INTRODUCTION

Acetylsalicylic acid (aspirin) is a noncompetitive irreversible antagonist of the enzyme cyclooxygenase 1 (cox1) that inhibits the synthesis of prostaglandins and thromboxane A2 from arachidonic acid (AA). Even though its benefits of prevention of cardiovascular and cerebrovascular events are indisputable, the increased risk of surgical hemorrhage and limitation of regional anesthetic techniques due to its use perioperatively are still a debate. The traditional recommendation has been to stop aspirin intake 7–10 days prior to surgical interventions. The optimum cessation date is highly debatable and varies a lot between clinics. Delaying of some surgeries has disadvantages for both the patient and the surgeon. In this report we try to evaluate the optimum timing of aspirin cessation before surgeries using AA platelet aggregation test (arachidonic acid platelet aggregation test [ASPI] test).

Received March 18, 2013

Revised June 4, 2013

Accepted June 9, 2013

J Korean Surg Soc 2013;85:185-190
<http://dx.doi.org/10.4174/jkss.2013.85.4.185>

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METHODS

Eighty patients between the ages of 40 to 73 years needing surgical interventions were enrolled in the study. After the study protocol was approved by the regional ethics committee, written informed consent was sought and taken from each participant. Thirty-five patients were considered as the control group who, before admission, had taken regular aspirin (100 mg/day) for at least 6 months or more for the prevention of established coronary artery atherosclerotic disease, and their aspirin prevention therapy was discontinued by the admitting clinician 10 days before surgery. The 45-patient study group, before admission, had taken regular aspirin (100 mg/day) for at least 6 months or more for the prevention of established coronary artery atherosclerotic disease. Their aspirin prevention therapy was also discontinued by the admitting clinician. Patients using any other antithrombotic drugs (antiplatelet agents, anticoagulants, fibrinolytic agents) as well as patients with known coagulopathy were excluded from the study. Patients were followed up to the day of surgery and left the study upon completion of surgery and hospitalization.

Blood was initially drawn from the last aspirin intake day and on the third and the fifth day from the antecubital vein by puncture without stasis using a 21 G butterfly needle. After the first 2-mL blood was discarded, we collected the blood into 4.5-mL tubes containing 25 µg/mL hirudin (Dynabyte, Munich, Germany) as an anticoagulant, according to the recommendations of the manufacturer.

Platelet function analysis was performed using the Multiplate analyzer; a whole blood impedance aggregometer and Platelet aggregation was initiated using AA (ASPI test, 0.5 mM) reagents supplied by the manufacturer (Dynabyte, Munich, Germany). The tests and results were evaluated as described before by Jambor et al. [1] and Toth et al. [2], as follows: Increased impedance due to attachment of platelets to the electrodes was continuously measured for each sensor unit over a period of 6 minutes. Data were transformed to arbitrary aggregation units (AU) and plotted as two separate aggregation curves versus time. Aggregation measured by multiple electrode aggregometry (MEA) was quantified as the area under the aggregation curve (AUC, [AU*min]). Alternatively, the software of the analyzer allows for the expression of AUC values in (U), where 10 (AU*min) correspond to 1 (U). The duplicate sensors served as an internal control to reduce the occurrence of systematic errors. Pearson correlation coefficients of the individual data points of the curves as assessed by the two electrode pairs and the differences between the AUC values detected by each sensor unit and the mean AUC were calculated. When the values were outside the acceptable range (correlation coefficient, <0.98; difference

from the mean curve, >20%), the results were flagged and the measurement was repeated. To study the effect of the resting, both assays were also performed immediately after blood drawing. The cutoff value of 300 AUC was used in each testing.

The study group patients were taken to surgery one day after ASPI testing showed platelet aggregation within normal limits (>300 AUC) indicating aspirin nonresponsiveness. Control group patients underwent surgery one day after the first ASPI test was performed (which was the 9th day for 15 patients and 10th day for 20 patients after discontinuation of aspirin intake) except for 2 patients who had acute abdomen with appendicitis. All patients were followed up for bleeding complications, intraoperative blood loss, and transfusion requirements during and after the surgeries; while the length of postoperative hospital stay was also noted.

In addition, high sensitive troponin T (Tnt) was measured in all patients to evaluate myocardial damage due to aspirin cessation. The measurements were done 1 hour before surgery; Tnt was also measured at 12, 24 and 48 hours after operation and was analyzed by using Elecsys 2010 (Roche diagnostics, Mannheim, Germany). Myocardial damage was defined as Tnt level ≥ 0.04 µg/L on at least one occasion in the perioperative period.

Statistical Analysis was performed using IBM SPSS ver. 20.0 (IBM Co., Armonk, NY, USA). Continuous variables were reported as mean, median, standard deviation and compared using the Wilcoxon and the Mann Whitney U test. The level of statistical significance was specified as $P \leq 0.05$.

RESULTS

The diagnosis and surgical operations are listed in Table 1. There were no statistically significant differences between the gender of control and study group ($P = 0.134$). Control group mean age were found to be younger than the study group ($P < 0.001$). At initial visits prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR) and thrombocyte count were within normal limits in both groups whereas PT, INR, and aPTT were found to be lower in the control group. Also, thrombocytes counts were found to be higher in control group but both in normal limits (Table 2).

In the study group, 45 patients' blood samples were evaluated on the third day and ASPI testing showed that in 31 patients aspirin nonresponsiveness was achieved. These patients were taken for required surgeries the following day. The remaining 14 patients' blood was retrieved on the 5th day and all of them showed aspirin nonresponsiveness on the 5th day. In the study group, the mean time between aspirin

Table 1. The diagnosis and surgical operations list

Diagnosis	Operation	Study group (n = 45)	Control group (n = 35)
Cholelithiasis	Laparoscopic cholelithiasis	12 (26.6)	9 (25.8)
Inguinal hernia	Inguinal hernia repair with graft	9 (20.0)	3 (8.6)
Gastric carcinoma	Partial gastrectomy	3 (6.7)	3 (8.6)
Multinodular guatr	Total thyroidectomy	3 (6.7)	3 (8.6)
Colon carcinoma	Hemicolectomy	3 (6.7)	1 (2.9)
Diabetic foot	Foot amputation	3 (6.7)	-
Lipoma	Lipom excision	3 (6.7)	1 (2.9)
Breast carcinoma	Modified radical mastectomy	2 (4.4)	1 (2.9)
Incisional hernia	Incisional hernia repair with graft	2 (4.4)	1 (2.9)
Ileus	Diagnostic laparotomy for ileus	1 (2.2)	-
Liver cyst-hidatic	Liver cyst-hidatic drenage and omentopexi	1 (2.2)	-
Rectal prolapsus	Rectal prolapsus repair (abdominal)	1 (2.2)	1 (2.9)
Rectum carcinoma	Low anterior colon resection	1 (2.2)	2 (5.8)
Hemoroid	Hemoroidectomy	1 (2.2)	1 (2.9)
Appendicitis	Appandectomy	-	2 (5.8)
Dermoid cyst	Dermoid cyst excision	-	2 (5.8)
Epigastric hernia	Epigastric hernia repair	-	1 (2.9)
Lymphadenopatı	Lymph node biopsy	-	1 (2.9)
Breast cyst	Breast biopsy	-	1 (2.9)
Esophagus carcinoma	Esophajectomy + partial gastrectomy + splenectomy	-	1 (2.9)
Pancreatic carcinoma	Whipple operation	-	1 (2.9)

Table 2. Age, gender, 1st ASPI test results and blood tests for study and control groups

Variable	Study group (n = 45)	Control group (n = 35)	P-value
Gender (M/F)	28/17	15/20	0.134
Age (yr)	65.9 ± 10.1	53.5 ± 16.7	<0.001
1st ASPI test results	264.2 ± 162.7	835.1 ± 128.3	<0.001
PT	15.7 ± 1.5	15.1 ± 1.1	0.025
aPTT	32.2 ± 4.8	29.6 ± 2.6	0.002
INR	1.09 ± 0.09	1.04 ± 0.08	0.008
Thrombocyte count	255,756 ± 74,289	291,486 ± 63,809	0.004

Values are presented as mean ± standard deviation.

ASPI, arachidonic acid platelet aggregation test; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio.

cessation and aspirin nonresponsiveness were found to be 4.2 days with a median value of 4 days. In addition, the mean time between aspirin cessation and operation day were found to be 5.5 days with a median value of 5 days (Table 3).

Both groups were similar in terms of median intraoperative

Table 3. ASPI test results for study group

	Mean ± SD	Median (range)
Time interval between aspirin cessation and operation day	5.5 ± 2.0	5 (2-9)
Time interval between aspirin cessation and aspirin nonresponsiveness	4.2 ± 1.7	4 (2-7)
1st ASPI test value (n = 45)	264.2 ± 162.7	221 (38-578)
2nd ASPI test value (n = 45)	736.8 ± 245.9	745 (107-1,265)
3rd ASPI test value (n = 14)	761.1 ± 188.3	748 (446-1,291)

SD, standard deviation; ASPI, arachidonic acid platelet aggregation test.

blood loss, which was approximately 50 mL. Only 3 patients (8%) from control group (pancreatic carcinoma; whipple operation, esophagus carcinoma; esophajectomy + partial gastrectomy + splenectomy and gastric carcinoma; partial gastrectomy) and only 2 patients (4%) from study group (rectum carcinoma; low anterior resection and colon carcinoma; hemicolectomy) were administered blood transfusion in the perioperative period. There were no perioperative bleeding complications and other related variables in both groups. The

duration of similar surgeries was compared and no significant differences of operation time or length of postoperative hospital stay were seen.

Also, no thromboembolic events or cardiovascular complications regarding discontinuation of aspirin were encountered during the surgeries and during the time of hospitalization.

None of the patients in both groups had pre or postoperative elevated TnT levels except for one patient in control group undergoing whipple operation for pancreatic carcinoma. That patient was also dealing with severe arrhythmia that was taken under control 12 hours after surgery.

DISCUSSION

Aspirin plays a critical role in the secondary (preventing recurrence of disease) and primary (preventing first occurrence of disease) prevention of acute myocardial infarction and stroke by the effect of inhibiting platelet aggregation and preventing thrombosis [3,4]. The benefits of aspirin in secondary prevention of cardiovascular disease are well recognized. According to guidelines from the American Heart Association/American College of Cardiology and the American College of Chest Physicians, aspirin therapy should be started and continued indefinitely unless absolutely contraindicated in almost all patients with established coronary artery or other atherosclerotic disease [5,6].

Despite its benefits in preventing cardiac and cerebrovascular complications, aspirin treatment is often discontinued before surgery due to the risk of perioperative bleeding [7]. In addition, the question of when to stop aspirin for the optimum benefit for the patient is still sought. Aspirin's platelet aggregation reduction effect was shown to be 8–10 days depending on the lifetime of platelet cells [8]. It is also known that the ability of platelets aggregation is partially restored within 4–5 days after stopping the intake of aspirin. Due to this data, it is a common practice to stop aspirin intake at least for 7 days to 10 days and this provides a wide security window for bleeding potential in surgeries within most clinics.

The debate on whether to continue aspirin perioperatively is still about. In a randomized controlled trial, it is shown that discontinuation of aspirin in high cardiovascular risk patients, perioperatively, did not alter bleeding complications [9]. They continued aspirin therapy in 109 patients and gave placebo to 111 patients perioperatively. Although no significant differences were reported between groups in bleeding endpoints, two patients from aspirin group (2%) had encountered bleeding which required reoperation in the perioperative period. Primarily, this study was not designed to assess the differences in bleeding complications between

groups; their first objective was to assess major adverse cardiac events due aspirin cessation. In another meta-analysis of 474 studies, it is reported that the use of aspirin increased intraoperative bleeding by a factor of 1.5 [7]. There is also accumulating evidence of the fact that preoperative aspirin increased the volume of postoperative bleeding and rates of reoperation were significantly higher in the preoperative aspirin groups [10].

In contradiction, in a recent review assessing publications where PubMed and MEDLINE literature searches using keywords aspirin, withdrawal, and perioperative were sought; it is stated that the current literature strongly supports the continued use of aspirin in patients for secondary prevention when undergoing most surgeries. The evidence indicates that patients have a significantly increased risk of a major ischemic event when aspirin is discontinued. The perceived risks of bleeding do not justify the practice of counseling patients to hold their aspirin before surgery, except in cases where surgical bleeding may lead to major perioperative complication. They strongly advise to abandon the practice of empirically discontinuing aspirin perioperatively [11]. There is no literature that we know of evaluating optimum timing for aspirin discontinuation that benefit from both postoperative bleeding, cardiac and thromboembolic events. Although we were unable to show any advantages of reducing myocardial damage by reducing the time of aspirin cessation, further studies might show its benefits.

In our study, we have shown that aspirin discontinuation timing can be reduced to an average of 4 to 5 days without any increased risk of bleeding complications during surgeries. We believe this finding has some advantages of saving time in planning surgeries. In our study group, we reduce aspirin stopping time from 7 days to 5 days before surgeries relying on platelet aggregometry tests and had no disadvantages of bleeding complications during or after surgeries. Comparing the data with control group of nonaspirin users, the results of bleeding and complication rates were not statistically different, especially between similar surgeries.

In conclusion, reducing the time of aspirin cessation might have advantages of for both bleeding complications and major adverse cardiac events. Although our data needs confirmation with larger study groups, it supports the idea that reducing time of aspirin cessation might be possible without increased complication rates. In addition, no myocardial damage assessed by Tnt were shown in our patient group. But before suggesting the reduction of time of aspirin discontinuation before surgeries, our findings should be expanded to evaluate major adverse cardiac events between patients who had stopped aspirin intake 4 to 5 days and 7 to 10 days.

In our study, we used the most common laboratory

method of assessing platelet function which is reported to be MEA [2]. MEA (Multiplate, Dynabyte, Munich, Germany) technique evaluates platelet function in whole blood, based on classical whole blood impedance aggregometry [2]. MEA has recently been used to study the effects of aspirin [12,13], nonopioid analgesics [14], clopidogrel [15,16], anticoagulants [17], antifibrinolytics [18], colloids [19], on platelet aggregation. Platelet aggregation as determined by MEA is calculated from the AUC and quantified by arbitrary aggregation units over time (AU*min). A cutoff value of 300 AU*min for a therapeutic antiplatelet effect of aspirin was determined, as AA-induced platelet aggregation was below 300 AU*min in 96% of the patients receiving long-term aspirin treatment [12].

At initial testing, values from aspirin-treated patients were significantly lower than those from control group blood donors. In our study, we relied on this test to show aspirin responsiveness for surgical time. We encountered no preoperative complications and believe ASPI testing is a reliable test as it was confirmed for its accuracy and precision to assess aspirin responsiveness.

Our preliminary study has some limitations as the sample size is very small with the surgeries being broad in spectrum. A variety of surgical procedures was included in this study from minor surgery (lymph node biopsy) to major surgery (esophagectomy). Period of discontinuation or necessity of discontinuation should be discussed separately depending on surgical procedures, degrees of surgical stress or surgical sites, because the risks of bleeding and thrombosis are much different. We will reconsider the selection and grouping of patients in the continuation of the study.

Future clinical trials should be conducted with large study groups and with similar types of surgical interventions. Nevertheless, the results of this study could help to improve the perioperative management of aspirin treated patients and hopefully will lead to larger confirmative studies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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