Cross-Sectional Study

Aspirin Cessation Before Interventional Procedures: Not Blindly Following Guidelines but Making Test-based Decisions

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Background: Deciding whether to continue or discontinue aspirin prior to interventional procedures is a major concern for pain physicians. Many guidelines have been published on the discontinuation of aspirin before invasive procedures; however, the recommendations are inconsistent and do not consider individual platelet function. Furthermore, many studies have shown a high prevalence of aspirin resistance in patients taking this medication.

Objectives: To determine the necessity of discontinuing aspirin prior to interventional pain procedures in relation to individual platelet function.

Study Design: Multicenter, cross-sectional study.

Setting: University-affiliated hospitals.

Methods: We examined platelet function among patients scheduled for an interventional pain procedure by measuring their closure time using collagen/epinephrine cartridges in a commercial platelet-function analyzer. The patients were categorized into either an aspirin-taking or nonaspirin-taking group (Group A or Group N, respectively). The proportion of patients who showed normal/abnormal platelet function was calculated and compared between the groups.

Results: A total of 1,111 patients were included in this study. In Group A, 56.4% (102/181) showed normal platelet function, whereas 43.6% (79/181) showed abnormal platelet function. In Group N, 85.8% (798/930) and 14.2% (132/930) showed normal and abnormal platelet function, respectively.

Limitation: The proportion of laboratory, not clinical aspirin resistance was evaluated. Factors affecting platelet function were not investigated exhaustively.

Conclusion: The high prevalence of normal platelet function in patients taking aspirin suggests no necessity of discontinuation before procedures in such patients. Abnormal platelet function can occur even in patients who are not taking aspirin. Therefore, platelet function should be measured and considered on a case-by-case basis prior to interventional procedures, and discontinuation of aspirin should be decided based on these factors.

Keywords: Aspirin, collagen, epinephrine, guideline, nerve block, pain, platelet aggregation,; platelet-function tests

IRB Approval: This study and all its protocols were approved by the Institutional Review Board of the Hallym University Gangnam Hospital (IRB No. HKS 2022-03-033), Ajou University Hospital (IRB No. AJIRB-MED-MDB-22-106) and the Seoul National University Bundang Hospital (IRB No. B-2203-746-106). Informed consents were waived for this study. All procedures were followed in strict conformity with the seventh revision of the Helsinki Declaration of 2013.

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The administration of aspirin has increased due to the significant benefits it offers for primary and secondary prevention of cardiovascular or cerebrovascular diseases; however, patients receiving aspirin therapy who undergo interventional procedures are exposed to a greater risk of bleeding than patients not receiving aspirin therapy (1). Continuation of aspirin during the periprocedural period can increase the risk of bleeding and potentially catastrophic complications such as spinal epidural hematoma or cauda equina syndrome (2,3). The postprocedural bleeding risk is a long-standing challenge that pain physicians face (4).

There are various guidelines relating to the use of aspirin prior to interventional procedures; yet, the point at which aspirin administration should be discontinued prior to invasive procedures remains under debate. Despite the risk of aspirin-induced platelet dysfunction, the recommendation by the European Society of Anaesthesiology, published in 2010, surprisingly did not recommend discontinuation of aspirin before a neuraxial block because aspirin does not increase the risk of spinal epidural hematoma (5). In contrast, the New England Journal of Medicine guideline recommends aspirin to be discontinued 7–10 days prior to invasive procedures (6), while the French Society for Anesthesia and Intensive Care recommends discontinuing aspirin 3 days prior to an intervention (7).

To address the discrepancies in the current guidelines, a coalition of 6 scientific societies met in 2018 to agree on recommendations for antiplatelet and anticoagulant drugs for interventional procedures (8). The conclusion was that aspirin should be discontinued 4–6 days before invasive procedures were to be carried out. Then again, the 2019 guidelines of the American Society of Interventional Pain Physicians recommends discontinuing aspirin 3–5 days before an interventional pain treatment (9). Notably, these guidelines do not guarantee prevention of bleeding complications and many cases of spinal hematoma have been reported after interventional spinal procedures despite strict adherence to guidelines (10).

A major limitation of current guidelines is that the recommended points of discontinuation do not consider individual patients' platelet function; reportedly, 5%–60% of patients taking aspirin are resistant to the inhibition of platelet function by aspirin, a phenomenon known as aspirin resistance (AR) (11). When patients have AR, they do not need to discontinue aspirin based on the guidelines (12). Furthermore, platelet rebound phenomenon has been reported; this thromboembolic complication significantly increased following abrupt aspirin withdrawal during the periprocedural period (13). It is characterized by increased synthesis of thromboxane A2 and decreased fibrinolysis (14,15). Thus, for the guidelines to be meaningful, there must be a prerequisite that the proportion of platelet dysfunction in patients taking aspirin is high.

The present cross-sectional study addresses the question of whether the guidelines relating to aspirin discontinuation prior to interventional procedures should be followed without considering platelet function on a case-by-case basis. To answer this, we enrolled patients who were scheduled for interventional pain procedures and evaluated the proportions of normal and abnormal platelet function based on aspirin intake.

Methods

Patient Recruitment and Enrollment

This multicenter cross-sectional study recruited patients who attended pain centers at 3 university-affiliated hospitals in South Korea for interventional procedures due to chronic pain from January 2018 through February 2022.

Exclusion criteria were as follows and based on previous studies (16,17): 1) unavailable data of platelet and hematocrit count; 2) thrombocytopenia or thrombocytosis (platelet count of < 100,000/ μL or > 450,000/ μL, respectively) 3) anemia or polycythemia (hematocrit of < 30% or > 52%, respectively); 4) taking antiplatelet or anticoagulant drugs other than aspirin; 5) taking antidepressants (tricyclic antidepressants/selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors); and 6) hematologic disorders. We collected data on medical history including use of antiplatelets, anticoagulants, and antidepressants along with laboratory data including hematocrit and platelet count at the time of platelet-function testing. Enrolled patients were classified into either the aspirin-taking or nonaspirin-taking group (Group A or Group N, respectively).

This study and all its protocols were approved by the Institutional Review Board of the Hallym University Gangnam Hospital (IRB No. HKS 2022-03-033), Ajou University Hospital (IRB No. AJIRB-MED-MDB-22-106) and the Seoul National University Bundang Hospital (IRB No. B-2203-746-106). All procedures were followed in strict conformity with the seventh revision of the Helsinki Declaration of 2013 (18).

Platelet-function Analysis

Platelet-function analysis was performed using the Platelet Function Analyzer-100® device (PFA-100®, Siemens). This device consists of a reservoir for the blood sample, a narrow tube, and a biologically active membrane with a central aperture coated with collagen and either epinephrine or adenosine diphosphate as stimulators (C/Epi or C/ADP, respectively).

The blood sample in the reservoir is aspirated through the narrow tube to simulate the resistance of a small vessel, after which it passes through the aperture and comes into contact with the membrane under high shear stress. Platelets adhere and aggregate to form a plug which gradually clogs up the aperture. The time required to occlude the aperture fully is termed "closure time" (CT). For the present study, CT was measured according to the manufacturer's instructions for both C/Epi and C/ADP cartridges. Between the 2 cartridges, CT measurement using the C/Epi cartridge was selected as a screening test for this study because this has been reported to have a higher sensitivity and predictive values compared to the C/ADP cartridge, and is a reliable screening test for platelet dysfunction caused by aspirin as well as disorders of primary hemostasis (19,20). The abnormal platelet function was defined as CT > 185 seconds for the C/Epi cartridge based on the previous study (17).

Statistical Analyses

The required sample size was calculated under the following parameters using G*power software version 3.1.9.6 (Heinrich-Heine-Universität): 1) anticipated proportion of platelet-function abnormality in Groups A and n = 0.40 and 0.25, respectively, estimated from our pilot results; 2) allocation ratio of Groups N/A = 6; 3) α = 0.05 and power (1 – β) = 0.95 for 2-tailed test; and 4) dropout rate = 15%. This calculation yielded a sample size of 992, with 826 and 166 participants in Group N and Group A, respectively.

Statistical analyses were performed using NCSS 2021 Statistical Software (NCSS, LLC). The distribution of CT was plotted on violin plots, and the proportion of patients with normal/abnormal platelet function was calculated and depicted. The Kolmogorov–Smirnov test was used to check the distribution of data. The difference in mean CT between the 2 groups was compared using Student's t-test. Data are presented as mean ± standard deviation. *P* values of less than 0.05 were considered statistically significant.

Results

Of the 1,302 patients scheduled for interventional pain procedures, 1,111 were eligible for this study based on the inclusion and exclusion criteria and were finally enrolled. The Consolidated Standards of Reporting of Trials (CONSORT) diagram is shown in Fig. 1; patient characteristics are presented in Table 1. Among the enrolled patients, 181 were allocated into Group A and 930 into Group N. The distribution of CT in each group is illustrated in Fig. 2. The average CT value of Group A was significantly higher than Group N (187.8 versus 135.4 seconds; $P < 0.001$). The proportion of normal and abnormal platelet function in both groups showed significant differences ($P < 0.001$). In Group A, 56.4% (102/181) showed normal platelet function, and only 43.6% (79/181) showed abnormal function. In group N, 85.8% (798/930) showed normal platelet function, and 14.2% (132/930) showed abnormal test results (Fig. 3).

Discussion

The proportion of patients with normal platelet function was 56.4% in Group A, which was on the high side compared to other studies; incomplete inhibition of platelet function by aspirin has been reported with a prevalence of 5%-60% (11). Further, it is noteworthy that 14.2% of patients in Group N exhibited abnormal platelet function.

Despite administering aspirin for primary or secondary prevention of cardiovascular or cerebrovascular diseases, some individuals still experience recurrent thromboembolic events (21). There have been numerous possible mechanisms suggested for this resistance to the effects of aspirin. The inadequate administration of aspirin or concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs)—which prevent the aspirin binding to cyclooxygenase (COX)-1 (22,23)—are considered to be major causes. Nonaspirin NSAIDs can interfere with platelet aggregation (24) and those with a higher affinity to COX-1 and a longer half-life than aspirin can competitively bind at the active site of the COX-1 enzyme, thus causing AR (25).

The present study enrolled patients with chronic pain; such patients often have a history of chronic administration of NSAIDs or may even be concurrently taking them for pain control, which could have influenced the results. Patients with chronic pain often take multiple medications for underlying diseases, such as angiotensin converting enzyme inhibitors or proton pump inhibitors, which may also affect the action of aspirin (22). Furthermore, patients with chronic pain

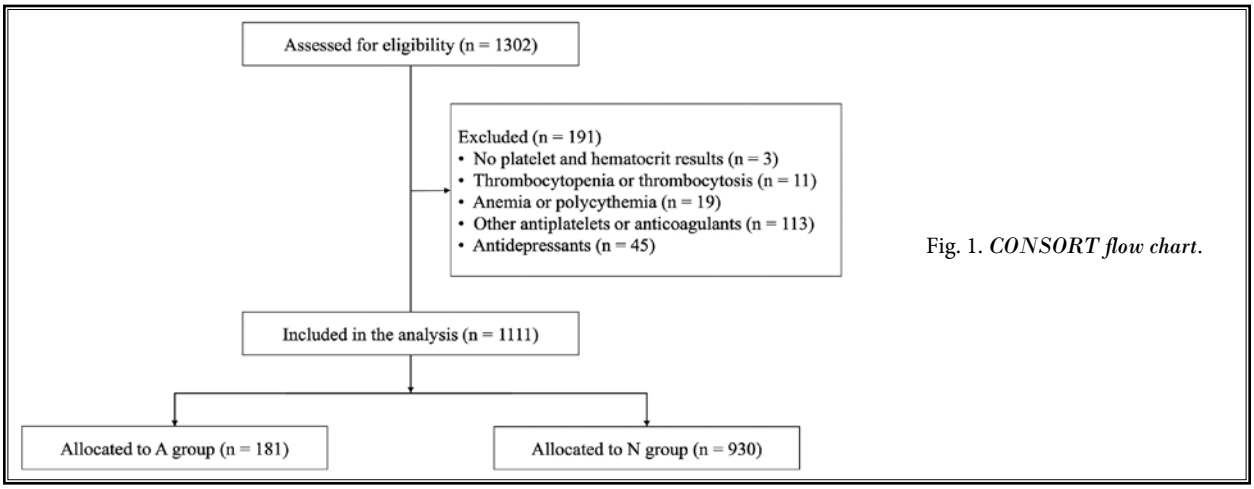

Fig. 1. *CONSORT flow chart.*

Table 1. *Baseline characteristics of the study population.*

Variables	Values
Gender (M/F)	494/617 (n = 1,111)
Age (year)	64.5 ± 14.5
Aspirin (Yes/No)	181 (16.3%)/930 (83.7%)
Location of pathology	
Head	49 (4.4%)
Cervical spine	234 (21.1%)
Thoracic spine	72 (6.5%)
Lumbar spine	696 (62.6%)
Others	60 (5.4%)
Diagnosis	
Herniation of intervertebral disc	529 (47.6%)
Spinal stenosis	143 (12.9%)
Spondylolisthesis	76 (6.8%)
Failed back surgery syndrome	128 (11.5%)
Post herpetic neuralgia	49 (4.4%)
Others	186 (16.7%)

Data are presented as mean ± standard deviation or number (%).

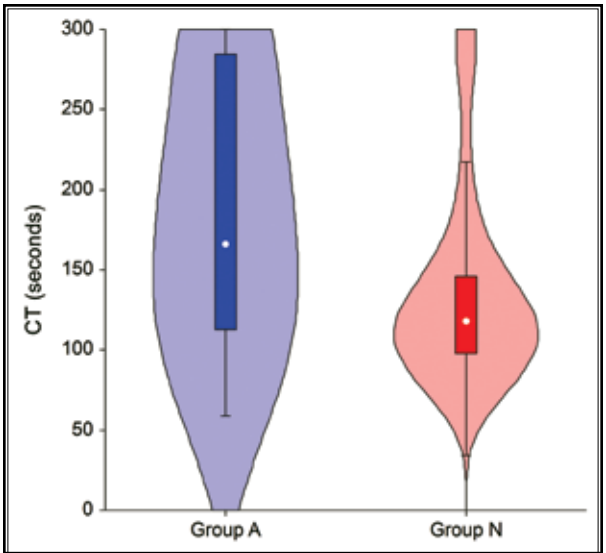

Fig. 2. *Violin plots illustrating the distribution of closure time (CT) among patients taking aspirin (Group A) or not (Group N). The boxes and whiskers in the violin plots represent interquartile range (IQR) and 1.5 × IQR, respectively. The CT was significantly prolonged in Group A compared with Group N (187.8 versus 135.4 seconds; P < 0.001).*

are more likely to be older in age or have hypertension, diabetes mellitus, or hypercholesterolemia, which are all risk factors for AR (11). Catecholamine-induced platelet activation due to chronic pain and stress or thromboxane A2 synthesis induced by cytokines due to the inflammatory process also influences AR and could have affected the prevalence of AR that we observed (8).

Patients with unexpected abnormal platelet function often pose a challenge for pain physicians. Elderly patients often take herbal medicines or dietary supplements that can influence platelet function (26). Green tea is the most widely consumed beverage in the world and is reported to have antithrombotic effects through dose-dependent inhibition of platelet aggregation (27). Ginseng, ginkgo, and garlic can also compromise platelet function. Guidelines suggest that consumption of these be stopped about one week before an interventional procedure (8,9). Caution should be taken with other dietary supplements such as omega-3 polyunsaturated fatty acid, vitamin E, and aronia extract prior to procedures due to their potential influence on platelet activity (28-30).

Appropriate assessment of platelet function is crucial before invasive procedures in the case of AR or

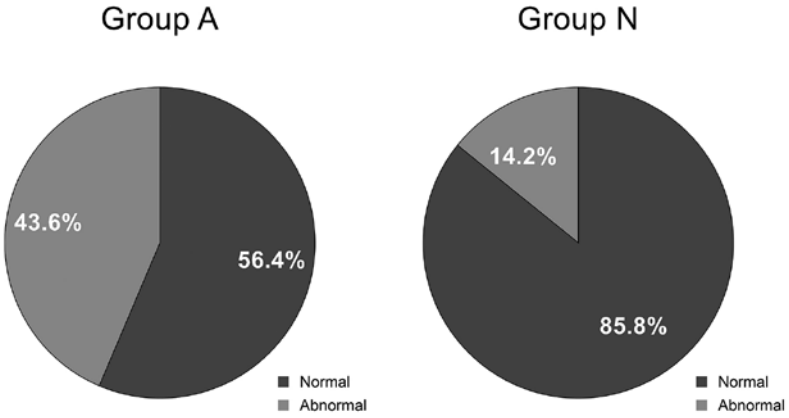

Fig. 3. *Pie charts comparing the proportion of patients with normal and abnormal platelet function. The proportion of normal/abnormal platelet function was significantly different between groups ($P < 0.001$).*

unexpected abnormal platelet function. The present study is the first to assess platelet function among patients undergoing interventional procedures in order to evaluate the optimal timing for discontinuation of aspirin prior to interventional procedures, with current guidelines recommending timeframes ranging from 0 to 10 days (5-9). Unconditional adherence to the guidelines may not be necessary once individual platelet function is considered, and it may not be necessary to discontinue aspirin use in patients with normal platelet function.

There are various methods to assess platelet function including PFA, light transmission aggregometry (LTA), flow cytometry, urinary thromboxane, VerifyNow® (Accumetrics), and thromboelastography. However, the ideal test for outpatients should be rapid, affordable, easy to perform, and able to be used with physiologically relevant agonists with high sensitivity and specificity.

While none of the current methods are ideal, LTA is currently regarded as the gold standard method. However, LTA has critical limitations for outpatients (31) as it measures the increase in light transmission in response to the addition of a platelet-aggregation agonist through an optically dense sample of platelet-rich plasma (PRP) (32). Therefore, this process requires high levels of laboratory skill, constant preanalytical conditions, appropriate PRP preparation, and different concentrations of various exogenous agonists, all of which can result in significant interoperator variation. Furthermore, LTA is expensive and time consuming, restricting its implementation in routine clinical practice (31).

We assessed platelet function using the PFA system, one of the most extensively used tests for measuring platelet function as a point-of-care test (33-36). Although the PFA system is not specific to a particular disorder, it is primarily used to screen platelet function and its use has gradually increased (37) because it is more affordable, rapid, easier to perform, and standardized compared with the LTA system (23). Moreover, the PFA system more closely reproduces the physiological process of platelet adhesion and aggregation since placing whole blood under high shear stress in a thin capillary simulates a transected small blood vessel (17). A previous review (19) that analyzed 736 articles reported the pooled weighted sensitivity and specificity of the C/Epi versus C/ADP cartridges for detecting disorders of primary hemostasis to be 82.5% and 88.7% versus 66.9% and 85.5%, respectively (19). The sensitivity of the PFA system for detecting platelet-associated coagulation abnormalities is higher than that of thromboelastography (38).

Prolongation of CTs of the C/Epi cartridge has been shown to effectively detect AR (20), and ingestion of aspirin reportedly causes a dose-dependent increase in CT of the C/Epi cartridge in healthy volunteers (39,40). The concordance of the detection of aspirin effect by PFA-100 and multiple platelet-function tests including LTA, VerifyNow, and urinary thromboxane has been shown to be higher than 90% (41), which also indicates PFA-100 as a reliable test for detecting aspirin effect.

The present study has some limitations, which should be acknowledged. First, the history of dietary supplements or over-the-counter medication was not fully evaluated. It is almost impossible to investigate all the food, dietary supplements, and over-the-counter medications that affect the platelet functions in the study population; therefore, the most practical method for screening for high risk of bleeding complications

is to investigate platelet function in each individual. The present study demonstrates the possibility of this, and reveals that unexpected platelet dysfunction can be detected using PFA without the in-depth investigation of all the foods and supplements that have been consumed by the patient.

Second, the dosage and duration of aspirin ingestion was not investigated. An aspirin dose of 100 mg/d or less is associated with a higher AR incidence than a dose of 150–300 mg/d (42). Although adequate platelet inhibition is achieved within the first month, long-term aspirin administration, particularly for more than 500 days, diminishes the therapeutic advantage (43). It is unfortunate that we could not investigate the dose and duration of aspirin ingestion of all patients. Nonetheless, this study is meaningful in that it evaluated the platelet function of patients ahead of interventional procedures.

Third, this study investigated laboratory AR, not clinical AR. However, the comparison of laboratory AR analyzed via in vitro platelet-function assays and clinical AR (e.g., actual thromboembolic outcomes) has indicated that laboratory AR determined by PFA suggests a higher risk of ischemic events such as death, stroke, and myocardial infarction (44). Therefore, we can infer that if AR is measured by PFA, the patient will have a lower true risk of bleeding complications after invasive procedures compared to a patient without AR.

Conclusion

In conclusion, a significant prevalence (56.4%) of AR was shown in patients taking aspirin before interventional pain procedures. In addition, it should be noted that unexpected abnormal platelet function appeared in 14.2% of patients who were not taking any antiplatelet agents. The risk of bleeding can be reduced by identifying unexpected abnormal platelet function resulting from unreported herbal medicine intake or unrecognized antiplatelet agents. Discontinuation of aspirin should be decided based on individual platelet function obtained by laboratory tests in order to avoid unnecessary discontinuation. Therefore, we recommend that platelet function should be tested as a point-of-care test prior to interventional procedures, before any decision is made on cessation of aspirin. Current guidelines should be modified to reflect this and include consideration of platelet-function analysis.

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