Aspirin Resistance May Not Be Associated with Clinical Outcome after Acute Ischemic Stroke: Comparison with Three Different Platelet Function Assays

Nam-Tae Yoo1, Hyo-Jin Bae2, Ji-Eun Kim2, Ri-Young Goh2, Jin-Yeong Han2, Moo-Hyeon Kim2 and Jae-Kwan Cha2

1Department of Neurology, Samsung Changwon Hospital, Changwon, 2Dong-A University Hospital, Regional Clinical Trial Center, Busan, Korea

Background: Aspirin resistance (AR) in platelet function assays showed substantial variation depending on the methods used to evaluate it. Methods: In this study, we prospectively compared the results of Multiplate impedance platelet aggregometry (IPA) with those of light transmission aggregometry (LTA) and VerifyNow® system in determination of the prevalence of aspirin resistance (AR) and investigated the correlation between its presence and poor outcome (modified Rankin scale >2) in 105 patients with aspirin after acute ischemic stroke (AIS). Results: After 5 days of using aspirin, 15 patients (14.3%) were classified as aspirin-resistance with the use of IPA, 24 patients (22.9%) by the LTA, and 14 patients (13.3%) by VerifyNow. Good agreement between the results of IPA and VerifyNow, was found (R=0.674, P<0.01). The concordance rate of AR detection was high between VerifyNow and IPA (k=0.72, P<0.01), albeit quite low between LTA and IPA. Regarding on its influence on clinical outcome after AIS, there wasn't any significant relationship between occurrence of poor outcome and the presence of AR in three platelet function assays. Conclusion: This study reveals that the incidence of AR in AIS might be highly test-specific. IPA seems to be similar to VerifyNow as a platelet function test. (Korean J Stroke 2012;14:35-42)

KEY WORDS: Aspirin resistance, Acute ischemic stroke, Platelet function test

Introduction

Aspirin has been widely used to prevent recurrent ischemic events after ischemic stroke.1,2 The effects of aspirin in acute ischemic stroke (AIS) have already been proven in several trials.3,4 However, the action of aspirin is still weak and thus insufficient to prevent recurrence of ischemic events despite its use after ischemic stroke.5

Laboratory aspirin resistance (AR) might be one of the causes of clinical aspirin failure in ischemic stroke.6,7 A recent meta-analysis showed that patients with AR were significantly related with recurrent ischemic events, compared to those without AR.8 Several previous reports have also suggested the AR may be associated with poor outcome in AR after ischemic stroke.9,10

Unfortunately, there are several drawbacks associated with the clinical utility of AR measurement in ischemic stroke being treated with aspirin. Evaluation of AR with platelet function assays is somewhat complex and variable, because these assays are based on different principles, ranging from cartridge-based systems to flow cytometric methods, and because the cutoff values chosen for each treatment vary. Moreover, there is no consensus on the methodology, agonists, or cutoff values to

Received: February 8, 2012 / Revised: April 2, 2012 / Accepted: April 6, 2012
Address for correspondence: Jae-Kwan Cha, MD, PhD
Department of Neurology, Dong-A University Hospital, 26 Daesilingongwon-ro, Seo-gu, Busan 602-715, Korea
Tel: +82-51-240-5266, Fax: +82-51-244-8338, E-mail: nrcjk65@gmail.com

This study was supported by the Dong-A University Research Fund.
establish AR in platelet function tests for routine clinical use. Several methods have been introduced to detect AR in the clinical field. Light transmission aggregometry (LTA), which has been historically considered to be a gold standard, has several limitations because it cannot be adopted for widespread clinical use.11

Recently, several point-of-care (POC) devices such as PFA-100 and VerifyNow® system have been introduced for clinical measurement of platelet function.6 Multiple impedance platelet aggregometry (IPA), another kind of POC device, has also been used to evaluate platelet function.12 This method provides several advantages through the use of whole blood: the cellular environment remains unchanged, thus allowing for rapid evaluation of platelet aggregation by means of ready-to-use test cuvettes having two independent sensor units.

Nevertheless, data on the comparison of IPA with other platelet function assays is lacking.13,14 In this study, we prospectively investigated the differences in residual platelet activity and incidence of AR between 3 different platelet function tests: LTA, VerifyNow, and IPA. We also evaluated the influences of AR on the clinical outcome of patients with AIS being treated with aspirin.

Subjects and Methods

We prospectively enrolled AIS patients (within 72 hr of their ischemic events) who had been hospitalized in Dong-A University Hospital from May 2010 to March 2011. All patients had received aspirin (300 mg) in the emergency room and were subsequently maintained on 100 mg aspirin for 5 days. During admission day, their medical history was recorded, and a complete physical and neurological examination was performed. All patients were subjected to a standard investigation on according to our protocol including routine blood tests, transcranial Doppler ultrasonography, electrocardiogram (ECG) and brain computed tomography (CT) and/or magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). Transthoracic echocardiography had been performed in selected cases. For brain imaging, we examined the brain CT and/or MRI and MRA of all the patients. According to the above findings, we classified the patients into five groups based on their presumed etiologies: large artery atherosclerotic infarction, cardioembolic infarction, lacunar infarction, other or unknown type infarction on the basis of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.15 Neurologic status were assessed using the National Institutes of Health Stroke Scale (NIHSS) in each patient on the first day. This study was approved by the local ethics committee and informed consent was obtained from patients before we used their laboratory and clinical data.

Light transmission aggregometry (LTA)

We evaluated the extent of platelet aggregation 5 days after aspirin therapy (100 mg/day). For this purpose, 30 mL of whole blood was anticoagulated with 3.2% sodium citrate. Platelet rich plasma (PRP) was prepared by centrifugation at 160 g for 10 min at room temperature. The platelet count of the PRP was adjusted to 200,000/mm³ using platelet poor plasma (PPP) obtained by centrifugation at 4,000 g for 5 min. Platelets were stimulated with arachidonic acid (AA, 0.5 mg/mL) or adenosine diphosphate (ADP, 10 μM) and the extent platelet aggregation was measured over 6 min after stimulation with the agonist, using an optical aggregometer (Chrono Log, 560 VS). Results are expressed as the percentage aggregation, estimated as the difference in percentage light transmission between the PPP and the PRP. This method has already been verified in several previous studies.16,17

VerifyNow

Tubes containing whole blood were gently inverted 3-5 times, and aspirin-induced platelet inhibition was measured quantitatively with the VerifyNow® system. We used the aspirin assay cartridges containing AA as the agonist. The instrument provides a digital readout of platelet inhibition in aspirin reaction units (ARU).18

Multiplate impedance platelet aggregometry (IPA)

Whole blood aggregation was performed using the Multiplate analyzer, a novel impedance aggregometer (Multiplate®; Dynabyte Medical, Munich, Germany). IPA measures platelet aggregation via electrical impedance of multiple electrodes and performs aspirin-sensitive patients identification tests when activated with 20 mM AA. Theresults obtained were quantified as the area under the aggregation curve (AUC).13,14

Definition of aspirin resistance

AR was defined as >20% AA or >70% ADP in the case of LTA, >550 ARU in that of VerifyNow, and >30 AUC in that of IPA.
Clinical outcome

We evaluated the 90-day clinical outcome measuring the mRS after onset of the patients’ ischemic symptoms. We defined a poor outcome as an mRS of >2 at 90 days after AIS. We investigated the relationship between AR in each platelet function and the prevalence of poor outcome after 90 days of ischemic stroke.

Statistical analysis

All data are presented as mean±SD. Statistical analysis was performed using the statistical analysis study (SAS) program. Continuous variables were compared using the t-test and the wilcoxon rank sum test, while statistical intergroup analysis was examined using the Chi-squared or the Fisher’s exact test for categorical variables. We used the Pearson correlation coefficient to measure the correlation of AR between the three above statistical tests. We used the kappa value to know the concordance rate between platelet function tests.

Results

In this study, we recruited 138 patients being treated with aspirin for AIS. Among them, 33 patients dropped out of this study; 20 patients failed to complete the three platelet function tests, 10 patients stopped taking aspirin before being submitted to the platelet function tests, and three patients withdrew their consent for this study. Finally, 105 patients were enrolled in this study. Table 1 shows the basic characteristics of the subjects. The mean±SD age was 66.0±12.1 years. The median NIHSS score was 4.6±4.3 at admission time. Among the 105 patients, 29 used clopidogrel in addition to aspirin. With LTA, the mean AA-induced platelet aggregation was 5.2±12.7% and the ADP-induced platelet aggregation was 54.8±18.0%. With VerifyNow, the mean ARU reading was 437.9±72.4. With IPA, the mean AUC was 21.7±18.4.

Frequency of aspirin resistance in three platelet function tests

24 patients (22.9%) exhibited AR in LTA testing, 14 patients (13.3%) in VerifyNow, and 15 patients (14.3%) in IPA. Table 2 shows that clinical and laboratory findings between aspirin-sensitive and aspirin-resistant groups were not significantly different in each platelet function tests except higher prevalence of AR in women than men in IPA.

Correlations of IPA with LTA and VerifyNow

Significant correlations were found between IPA and VerifyNow in patients being treated for AIS within aspirin for 5 days (R=0.674, P<0.01, Figure 1). However, there was no significant correlation between IPA- and AA-induced platelet aggregation in LTA, VerifyNow and ADP-induced platelet aggregation in LTA, or IPA and LTA after all stimulations.

Concordance rates of aspirin resistance for the platelet function tests

AR incidence in AIS was significantly concordant between IPA and VerifyNow (k=0.720, P<0.01). However, there were low concordance rates between IPA and LTA (k=0.160, P=0.08), and VerifyNow and LTA (k=0.177, P=0.06) (Table 3).

Relationship between clinical outcome and the platelet function test

In this study, 30 AIS patients (28.6%) had a poor outcome as estimated by mRS after 90 days of ischemic symptom onset. For all three kinds of platelet function tests, the occurrence of AR was not related with the prevalence of poor outcome after AIS at 90 days (Table 4).

TABLE 1. Clinical and laboratory findings among study population

|                          |     |
|--------------------------|-----|
|                          | Men |
| Age, yr                  | 66.0±12.1 |
| Hypertension             | 59 (56.2) |
| Diabetes mellitus        | 31 (29.5) |
| Smoking                  | 36 (34.3) |
| TOAST classification     |     |
| LAA                      | 41 (37.1) |
| Cardioembolism           | 8 (7.6) |
| Small vessel disease     | 43 (40.9) |
| Other or undetermined    | 13 (12.4) |
| NIHSS                    | 4.6±4.3 |
| Aspirin+Clopidogrel      | 29 (27.6) |
| Statin                   | 100 (95.2) |
| LDL cholesterol, mg      | 104.1±34.7 |
| C-reactive protein, mg/dL| 0.8±2.1 |

Values are presented as or n (%), or mean±SD. TOAST: Trial of Org 10172 in Acute Stroke Treatment, LAA: large artery atherosclerosis, NIHSS: National Institute of Health Stroke Scale, LDL: low-density lipoprotein.
|                          | LTA          | VerifyNow    | IPA          |
|--------------------------|--------------|--------------|--------------|
|                          | AS (n=81)    | AR (n=24)    | P*           | AS (n=91)    | AR (n=14)    | P*           | AS (n=90)    | AR (n=15)    | P*           |
| %                        |              |              |              |              |              |              |              |              |              |
| Men                      | 49 (79.0)    | 13 (21.0)    | 0.64         | 52 (83.9)    | 10 (16.1)    | 0.39         | 50 (83.9)    | 12 (16.1)    | 0.02         |
| Age, yr                  | 64.9±12.7    | 67.6±9.9     | 0.49         | 65.0±12.4    | 69.3±10.2    | 0.21         | 64.9±12.2    | 69.5±11.5    | 0.20         |
| First stroke             | 65 (73.0)    | 24 (27.0)    | 0.02         | 76 (85.4)    | 13 (16.4)    | 0.69         | 76 (87.5)    | 13 (12.5)    | 1.00         |
| TOAST                    | 0.17         |              |              | 0.77         |              |              | 0.79         |              |              |
| LAA                      | 35 (85.4)    | 6 (14.6)     |              | 37 (90.2)    | 4 (9.8)      |              | 35 (85.4)    | 6 (14.6)     |              |
| Cardioembolism           | 5 (62.5)     | 3 (37.5)     |              | 6 (75.0)     | 2 (25.0)     |              | 7 (87.5)     | 1 (12.5)     |              |
| Small vessel diseases    | 32 (74.4)    | 11 (25.6)    |              | 37 (86.1)    | 6 (13.9)     |              | 38 (88.4)    | 5 (11.6)     |              |
| Other or undetermined    | 9 (69.2)     | 4 (30.8)     |              | 11 (84.6)    | 2 (15.4)     |              | 11 (84.6)    | 2 (15.4)     |              |
| Diabetes mellitus        | 25 (80.7)    | 6 (19.3)     | 0.80         | 25 (80.7)    | 6 (19.3)     | 0.34         | 26 (83.9)    | 5 (16.1)     | 0.76         |
| Hypertension             | 46 (78.0)    | 13 (22.0)    | 0.82         | 49 (83.1)    | 10 (16.9)    | 0.26         | 48 (81.4)    | 11 (18.6)    | 0.17         |
| Smoking                  | 25 (69.4)    | 11 (30.6)    | 0.22         | 33 (91.7)    | 3 (8.3)      | 0.37         | 31 (86.1)    | 5 (13.9)     | 1.00         |
| NIHSS                    | 4.5±3.8      | 4.9±5.9      | 0.62         | 4.4±4.1      | 6.1±5.5      | 0.24         | 4.2±3.7      | 7.1±6.7      | 0.11         |
| Concomitant clopidogrel  | 28 (96.6)    | 1 (3.5)      | <0.01        | 27 (93.1)    | 2 (6.9)      | 0.34         | 27 (93.1)    | 2 (6.9)      | 0.23         |
| Statin                   | 78 (78.0)    | 22 (22.0)    | 0.32         | 87 (87.0)    | 13 (13.0)    | 0.52         | 86 (86.0)    | 14 (14.0)    | 0.55         |
| Platelet counts (×10^3 μL) | 216.9±50.9 | 243.3±109.0 | 0.35         | 224.8±70.9   | 211.3±54.8   | 0.65         | 223.9±71.8   | 217.4±49.3   | 1.00         |
| LDL cholesterol, mg      | 105.1±34.0   | 100.8±37.3   | 0.44         | 106.5±35.0   | 88.4±28.4    | 0.06         | 105.5±35.9   | 95.7±25.3    | 0.44         |
| C-reactive protein, mg/dL | 0.9±2.3     | 0.6±1.2      | 0.65         | 0.8±2.2      | 0.9±1.6      | 0.26         | 0.7±1.9      | 1.6±3.3      | 1.00         |

Values are presented as mean±SD unless otherwise indicated.
*Nonparametric test (Wilcoxon rank sum, Fisher’s exact test). AS: aspirin sensitive, AR: aspirin resistance, LAA: large artery atheroclerosis, TOAST: Trial of Org 10172 in Acute Stroke Treatment, NIHSS: National Institute of Health Stroke Scale, LDL: low-density lipoprotein.
FIGURE 1. Correlation of aspirin responses among three platelet function tests. (A) Multiplate impedance platelet aggregometer and VerifyNow (r=0.67, P<0.01). (B) VerifyNow and ADP induced platelet aggregation in light transmission aggregometer (r=0.19, P=0.06). (C) Multiplate impedance platelet aggregometer and ADP induced platelet aggregation in light transmission aggregometer (r=0.12, P=0.02). (D) VerifyNow and AA induced platelet aggregation in light transmission aggregometer (r=0.24, P=0.01). (E) Multiplate impedance platelet aggregometer and AA induced platelet aggregation in light transmission aggregometer (r=0.04, P=0.71). (F) AA and ADP induced platelet aggregation in light transmission aggregometer (r=0.04, P=0.71). IPA: impedance platelet aggregometer, LTA: light transmission aggregometer, ADP: adenosine diphosphate, AA: arachidonic acid.
In the present study, the incidence of AR was 14.3% when measured by IPA. In particular, the platelet responses after aspirin ingestion, evaluated by IPA, showed a similar pattern to those obtained using VerifyNow, another type of POC device. However, IPA displayed quite different patterns of aspirin response, when compared to LTA: different correlation and concordance rates were obtained between the two tests. These results imply that the differences in AR measurements might have been related to the type of platelet function assay used. There are several differences in above two types of platelet function tests, the most important one being the method of blood sample preparation before evaluating platelet function. Generally, platelet function tests are divided into two categories; platelet assays to check the platelet itself, such as LTA, and platelet assays to evaluate whole
blood cells, such as PFA-100, VerifyNow, and IPA. Therefore, we hypothesized that there might be differences in aspirin response between LTA and other POC devices using whole blood samples. It is known that the progression of atherothrombosis into conditions such as myocardial infarction and stroke often depends on other blood cell types, like leukocytes and erythrocytes, apart from platelets. Leukocytes play a role in stimulating platelets and endothelial cells to promote the progression of atherothrombosis. Moreover, the effects of aspirin are not confined to the platelets but extend to a variety of blood cells. In line with the above facts, it might be more reasonable to use whole blood samples rather than PRP, to evaluate platelet function after aspirin treatment. In a previous report, three POC tests have shown a good correlation of platelet function following aspirin treatment in various vascular diseases. In contrast, the concordance rate between LTA and POC devices showed variable results. These facts further support the idea that the incidence of AR might depend on the methodology used to evaluate it. Recently, there has been an increasing tendency to use POC devices for evaluating platelet function in the clinic. These POC devices have several advantages like convenient operation method and a rapid evaluation time. The most important advantage of POC devices, however, is the use of unprocessed whole blood, thus offering a more unchanged, physiologic milieu for detecting platelet function in atherothrombosis. IPA, for example, uses only a small quantity of blood and has an advantage in cost, compared to VerifyNow. It would therefore be an attractive option to have IPA a standard platelet function test in the clinical fields. However, so far, comparison of data between the use of IPA and other types of platelet function tests in stroke has not been performed extensively. To the best of our knowledge, this is the first study comparing the differences in aspirin response, as measured by IPA and VerifyNow in AIS. Practically, the high concordance rate of AR, obtained with VerifyNow, suggests its greater clinical potential.

Several studies have reported that the presence of AR might be related to poor outcome after AIS, both in the short as well as in the longterm. It has been postulated that its presence stimulates inflammatory reactions and the formation of microthrombi, eventually leading to progression of vascular damages in the acute phase of ischemic stroke. In each of the three tests used in this study, there was no significant correlation between the clinical outcome and AR. It is of note, however, its influence on the clinical outcome after ischemic stroke (IS), have been debated. It is well known that atherothrombosis is one of the main causes of coronary artery diseases, but we also know that several diverse mechanisms are involved in the occurrence of IS. Thus, the effects of aspirin in reducing recurrent ischemic events are limited in IS compared to those in coronary artery diseases. Furthermore, platelet hyperactivation does not incorporate the whole pathophysiological mechanism but is just one explanation for the occurrence of stroke. Although, we measured platelet function profiles by three different types of platelet function assays, we might have not been able to cover every aspects of platelet hyperactivation after AIS. Its activation during AIS is too diverse to be measured using the platelet function assays we have been using in the clinical field until now. Therefore, we could not conclude the role of AR over the clinical outcome after AIS by using this study. In the future, to prove the relationship between AR and clinical outcome after stroke, we need to more precise platelet function test to cover the entire changes of its activation during AIS.

The majority of the studies on similar lines were done in a retrospective manner and just one type of platelet assay was measured. Therefore, it is likely that incomplete results were obtained due to selection bias and incomplete measurement of whole platelet functions during aspirin treatment. To compensate for these issues, we evaluated the presence of AR with three different types of platelet function tests simultaneously and investigated the influences of AR in each test prospecively.

Although some of the findings of this study were significant, this study had also several limitations. First, our sample size was too small for the validity of our conclusions to be confirmed. Second, to make precise conclusions, all subjects should have been treated with aspirin only. However, we were not able to restrict the use of clopidogrel in addition to aspirin, because this would have meant a breach in medical ethics towards the AIS patients.

In conclusion, the prevalence of AR in AIS was quietly depend on the type of platelet function assay. Particularly, the IPA, a kind of POC device, showed similar patterns of aspirin response to those obtained using VerifyNow, but had different aspects when compared to the LTA. This difference might have been related to the preparation of blood samples: whole blood or PRP. Importantly, the occurrence of AR did not impact the clinical outcome after AIS.
Aspirin Resistance in Acute Ischemic Stroke

Conflicts of Interest

The authors have no financial conflicts of interest.

REFERENCES

1. van Gijn J, Algra A. Aspirin and stroke prevention. Throm Res 2006;2:517-523.
2. Ferguson JJ. The role of oral antiplatelet agents in atherothrombotic disease. Am J Cardiovasc Drugs 2006;6:149-157.
3. CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: Randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. Lancet 1997;349:1641-1649.
4. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. Lancet 1997;349:1569-1581.
5. Liao JK. Secondary prevention of stroke and transient ischaeamic attack: is more platelet inhibition the answer? Circulation 2007;115:1615-1621.
6. Mason PJ, Jacobs AK, Freedman JE. Aspirin resistance and atherothrombotic diseases. J Am Coll Cardiol 2005;46:986-993.
7. Jeon SB, Song HS, Kim BJ, Kim HJ, Kang DW, Kim JS, et al. Biochemical aspirin resistance and recurrent lesions in patients with acute ischemic stroke. Eur Neurol 2010;64:51-57.
8. Krasopoulos G, Brister SJ, Beattie WS, Buchanan MR. Aspirin “resistance” and risk of cardiovascular morbidity: systematic review and meta-analysis. BMJ 2008;336:195-198.
9. Bugnicourt JM, Roussel B, Garcia PY, Canaple S, Lamy C, Godefroy O. Aspirin non-responder status and early neurological deterioration: a prospective study. Clin Neurol Neurosurg 2011;113:196-201.
10. Englert NA, Horsfield G, Kwan J, Byrne CD. Aspirin resistance is more common in lacunar strokes than embolic strokes and is related to stroke severity. J Cereb Blood Flow Metab 2008;28:1196-1203.
11. Gurbel PA, Becker RC, Mann KG, Steinhubl SR, Mickelson AD. Platelet function monitoring in patients with coronary artery disease. J Am Coll Cardiol 2007;50:1822-1834.
12. Tóth O, Calatzis A, Penz S, Losonczy H, Siess W. Multiple electrode electroaggregation: a new device to measure platelet aggregation in whole blood. Thromb Haemost 2006;96:781-788.
13. Paniczia R, Antonucci E, Maggini N, Romano E, Gori AM, Marucci R, et al. Assessment of platelet function on whole blood by multiple electrode aggregometry in high-risk patients with coronary artery disease receiving antiplatelet therapy. Am J Clin Pathol 2009;131:834-842.
14. Mueller T, Dieplinger B, Podz W, Haltmayer M. Utility of the PFA-100 instrument and the novel multiplate analyzer for the assessment of aspirin and clopidogrel effects on platelet function in patients with cardiovascular disease. Clin Appl Thromb Hemost 2009;15:652-659.
15. Adams HP, Bendixen HP, Krappel LJ, Biller J, Loeve BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.
16. Gum PA, Kotke-Marchant K, Welch PA, White J, Topol EJ. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. J Am Coll Cardiol 2003;41:961-965.
17. Jeon HW, Cha JK. Factors related to progression of middle cerebral artery stenosis determined using transcranial Doppler ultrasonography. J Thromb Thrombolysis 2008;25:265-269.
18. Harrison P. Progress in the assessment of platelet function. Br J Haematol 2000;111:733-744.
19. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115-126.
20. Neumann F-J, Marx N, Gawaz M, Brand K, Ott I, Rokitta C, et al. Induction of cytokine expression in leukocytes by binding of thrombin-stimulated platelets. Circulation 1997;95:2387-2394.
21. McEver RP. A receptor for neutrophils and monocytes on activated platelets and endothelium. J Cell Biochem 1991;45:156-161.
22. Kharbanda RK, Walton B, Allen M, Klein N, Hingorani AD, MacAllister RJ, et al. Prevention of inflammation-induced endothelial dysfunction: a novel vasculo-protective action of aspirin. Circulation 2002;4:2600-2604.
23. Can MM, Tanboğa IH, Türkylmez E, Karabay CY, Akgun T, Koca F, et al. The risk of false results in the assessment of platelet function in the absence of antiplatelet medication: comparison of the PFA-100, multiplate electrical impedance aggregometry and verify nowadays. Thromb Res 2010;125:132-137.
24. Harrison P, Segal H, Silver L, Syed A, Cuthbertson FC, Rothwell PM. Lack of reproducibility of assessment of aspirin responsiveness by optical aggregometry and two platelet function tests. Platelets 2008;19:119-124.
25. Harrison P, Segal H, Blasbery K, Furtado C, Silver L, Rothwell PM. Screening for aspirin responsiveness after transient ischemic attack and stroke: comparison of 2 point-of-care platelet function tests with optical aggregometry. Stroke 2005;36:1001-1005.
26. Pamukcu B, Lip GY, Snezhitskiy V, Shantsila E. The CD40-CD40L system in cardiovascular disease. Ann Med 2011;43:331-340.
27. Boncoraglio GB, Bodini A, Brambilla C, Corsini E, Carrerio MR, Parati EA. Aspirin resistance determined with PFA-100 does not predict new thrombotic events in patients with stable ischemic cerebrovascular disease. Clin Neurol Neurosurg 2009;111:270-273.
28. Ogata J, Yutani C, Otsuru B, Yamanishi H, Naritomi H, Yamaguchi T, et al. Heart and vessel pathology underlying brain infarction in 142 stroke patients. Ann Neurol 2008;63:770-781.