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LETTER TO THE EDITOR

Lack of subjective tendency to bleed as clinical marker for aspirin resistance

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The anti-platelet effect of aspirin (ASA) is widely proven to be effective in the prevention of fatal and non-fatal cardiovascular events in high risk patients. However, despite being on aspirin therapy, 10–20% of patients experience recurrent vascular events over a long period of time, thus the term ASA treatment failure. On the other hand, ASA resistance is commonly used to define the failure of aspirin to inhibit the thromboxane A2 production or the platelet aggregation at the laboratory level. The direct correlation between the laboratory and the clinical aspirin resistance has been shown previously. The demographic and the clinical markers of bleeding (through questionnaire) were collected in 114 patients on routine ASA treatment for cardiovascular events. The rapid platelets functional assay for aspirin was measured. The proportion, Fisher's exact test, Spearman rho correlation, and cyclooxygenase-proportional univariate analysis were used. The statistical significance value was considered for $p < 0.05$. Out of 134 eligible patient, 114 (85%) agreed to participate in this study. ASA resistant was found in 13.8% in male as compared to 4.7% in female with $p = 0.04$. There was no significant correlation between ASA resistance and age, race, absence of mucocutaneous bleeding, smoking, diabetes, hypertension, kidney diseases, and other comorbidities. There is no clinical correlation to ASA resistance. However, ASA resistance is seen more with male gender. Further prospective studies to validate such correlation should be designed to eliminate the compliance confounder factor.

The anti-platelet effect of aspirin is widely proven to be effective in the prevention of fatal and non-fatal cardiovascular events in high risk patients [1]. Aspirin (ASA) reduces the activation of platelets by irreversibly acetylating cyclooxygenase-1 [2–6]. However, despite being on aspirin therapy, 10–20% of patients experience recurrent vascular events over a long period of time [7]. Thus, the term ''aspirin treatment failure'' has been used to describe the occurrence of any atherothromboembolic ischemic events in compliant patients [8, 9]. On the other hand, the term ''aspirin resistance'' detected with laboratory tests is used to define the failure of aspirin to inhibit the thromboxane A2 production or the platelet aggregation and varies from 0.5% to 45% [10–12]. The direct correlation between the laboratory and the clinical aspirin resistance has been shown previously [13, 14], however, a clinical tool that predict ASA resistance is still lacking. The clinical implication of such simple tool will be of great benefit in preventing secondary cardiovascular events, since testing for aspirin resistance is expensive and not widely available.

The goal of this project is to find any clinical marker that can predicts ASA resistance. Therefore, this project is designed to test the correlation between the ASA resistance testing and the absence of any mucocutaneous bleeding. To our knowledge, Clinical markers (through questionnaire) assessing for aspirin resistance has not been described yet.

In an effort to find clinical markers that help in identifying aspirin resistant patients, we designed a pilot prospective cohort study. The study aim was to test aspirin resistance using rapid platelets functional assay for aspirin (RPFA-ASA) (VerifyNow® aspirin by Accumetrics®) and correlate it with subjective mucocutaneous bleeding as reported by a self-documented questionnaire. As questionnaires are becoming an important tool in human research, we took several steps in developing a self-reporting questionnaire. Two groups involving different health care professional workers (physicians, nurses, administrative, and public health professionals) at Staten Island University Hospital and School of public health at State University of New York-Downstate, met on a weekly basis for 3 months to create and develop this questionnaire. At the end of this period, this questionnaire was presented to randomly chosen patients as a testing group. All questions,

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Table I. Demographic characteristics.

	$N = 102$ (ARU < 550)	$N = 12$ (ARU ≥ 550)
Age, mean (years)	70 [43–87]	66.2 [47–83]
*Sex**		
Male	62 (60)	10 (83.3)
Female	40 (40)	2(16.6)
Race		
White	96 (94%)	10 (83.3)
Others	6 (6%)	2 (16.6)
Smoking history		
Positive	65 (64)	6 (50%)
Negative	37 (36)	6 (50%)
Family history of bleeding		
Positive	2 (1.75)	0
Negative	112 (98.25)	

Note: *$p = 0.04$.

Table II. Clinical correlation of ASA resistance and ASA sensitive.

	ARUs cut off*	
	<550 (sensitive)	≥550 (resistant)
Any bleed		
Yes	38 (37.25)	4 (33.3)
No	64 (62.75)	8 (66.6)

Note: *$p = 1.00$.

concerns, and inputs were taken into consideration and a final format was approved as presented (supplement).

Patients presenting to the cardiology outpatient clinic and for elective cardiac catheterization were included in the study if they met the inclusion criteria. All patients above 21 years old on a daily aspirin for at least 30 days were considered illegible for the study. A blood sample was drawn and a questionnaire was given to be answered by the patient with the help of any family member and if necessary the physician in charge.

Blood samples of 5 cc were collected in a EDTA-containing tube for testing within 30 minutes, using the RPFA-ASA machine, which utilizes arachidonic acid as the agonist to measure platelet aggregation [15]. RPFA-ASA expresses aspirin resistance in aspirin reaction units (ARUs). The therapeutic range for platelet function is defined by the manufacturer to be between 350 and 549. ARU values equal or superior to 550 are defined as aspirin resistant. The selection of RPFA-ASA as a measurement was mainly guided by its high sensitivity and specificity when compared to other assays [16]. All the results of patients having ARU equal or superior to 550 were reported to their cardiologist.

The wide range of the ASA resistance prevalence in previous studies was a major factor to increase the number of participants above 100 in such a pilot study. The proportion of patients in each ARU groups was calculated. Fisher's exact test was used to compare the proportion of patients who were ASA resistant (ARU ≥ 550) and responded negatively to the anybleed variable as compared with the ASA responsive patients. A Spearman rho correlation was conducted between the ARU score and the anybleed variable. The statistical significance value was considered for $p < 0.05$. All statistical analyses were conducted using the SAS Statistical Package Edition 9.2 (Carey, NC, USA).

Between September 2007 and April 2008, 134 patients met the inclusion criteria, among them 114 (85%) agreed to participate in this study. Table I summarizes the demographics of the participants with the correlation to ARU results. Ten out of 72 (13.8%) male are ASA resistant as compared to 2 out of 42 (4.7%) females with a p-value of 0.04. None of the other demographic characteristic, including age and race, contributes to the difference in the ARU results. Twelve patients (10.5%) were ASA resistance (ARU ≥ 550), among them 8 patients (66.6%) answered ''NO'' to all the bleeding questions. Among the 102 patients, who were sensitive to ASA (ARU <550), 38 patients (37.25%) answered at least 1 ''YES'' to any of the bleeding questions. When comparing the two groups of ASA resistance and ASA sensitive in term of their answers to the bleeding questionnaire, there was no statistical difference between the two groups (Table II). The univariate analysis failed to show any correlation between ARU and any of the comorbid conditions, including smoking, diabetes, hypertension, and kidney disease.

Over the past decade, aspirin resistance was of interest to many clinicians interested in secondary prevention of cardiovascular events. Previous observation studies have shown some correlation between ASA resistance and increase risk of cardiovascular events [13, 14]. This pilot study aimed to explore any clinical factor that could play a role in identifying ASA resistance.

The physiopathology of ASA resistance is not fully understood yet; though few explanations have been described. The presence of alternative pathways not blocked by aspirin, the possibility of a hereditary contributing factor, and arachidonic acid metabolism occurring in macrophages could all play a major role in platelets activation and thus ASA resistance [17, 18].

The incidence of ASA resistance in our population group (10.5%) correlates well with previous reported data. On the other hand, our results showed that ASA resistance are more seen in males than females (13.8% vs. 4.7%, $p = 0.04$). Surprisingly, none of the known conventional cardiovascular risk factors except for male sex were found to correlate with ASA resistance.

The absence of clinical correlation of ASA resistance as shown in our results validates previous data of inadequacy of mucosal petechiometry as a measure of ASA efficacy and that aspirin-induced platelet dysfunction is not the only contributor to the development of petechiae in healthy subjects [15].

The limitations of our study include the paucity of non-white race participants as well the absence of ASA compliance factor determination. Further prospective larger studies are still needed to validate such correlation and to eliminate the compliance confounder factor.

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