Acetyl salicylic acid resistance in patients with chronic stable angina and the correlation with coronary risk factors

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ABSTRACT

الأهداف: تقييم مقاومة حامض أسيتيل الساليسيليك لدى مرضى الجهاز القلبي الوعائي، بالإضافة إلى تقييم العلاقة بين هذه المقاومة والعوامل التي تزيد من خطر الإصابة بمرض الشريان التاجي.

الطريقة: أُجريت هذه الدراسة المقطعية في قسم العيادات الخارجية، قسم أمراض القلب، كلية الطب، جامعة سيمنان للعلوم الطبية، سيمنان، إيران، واستمرت خلال الفترة من مايو إلى أغسطس 2008م. شملت الدراسة 124 مريض مصاب بأمراض الشريان التاجي المستقرة. لقد كان كافة المرضى مصابين بتاريخ سابق بأمراض الشريان التاجي، وقد عولجوا بأخذ حامض أسيتيل الساليسيليك بمقدار 80 ملغ يومياً على مدى 7 أيام. لقد قمنا بقياس مقاومة المرضى للأسبرين باستخدام المقايسة المناعية الأنزيمية.

النتائج: لقد ثبت من خلال النتائج مقاومة 49.2% من المرضى لحامض أسيتيل الساليسيليك، فيما كانت الاستجابة حدية لدى 15.3% من المرضى، وأظهر 35.5% من المرضى حساسيتهم لهذا الحامض. لقد كان المرضى الذين أظهروا مقاومة لتناول الأسبرين على الأرجح من المدخنين والكبار في السن (63% مقابل 45.4%) (37.7% أصغر من 70 عاماً، و53.7% بين 60-69 عاماً، و63.3% أكبر من أو يساوي 70 عاماً). ولقد كانت المتغيرات التالية غير مرتبطة ارتباطاً واضحاً من الناحية الإحصائية بمقاومة المرضى للأسبرين وهي كالتالي: الجنس، والسكري، وانخفاض ضغط الدم، والكولسترول، وثلاثي الجليسريد، والكولسترول عالي الكثافة، والكولسترول منخفض الكثافة، ومستويات الهيموغلوبين.

خاتمة: أثبتت الدراسة بأن مقاومة المرضى لحامض أسيتيل الساليسيليك قد كانت ظاهرة لدى عدد كبير من المرضى المصابين بالذبحة المزمنة المستقرة. ولقد كان التدخين وتقدم العمر من العوامل المؤثرة على مقاومة الأسبرين.

Objectives: To evaluate acetyl salicylic acid (ASA) resistance in patients with cardiovascular diseases and evaluate correlation with coronary risk factors.

Methods: One hundred and twenty-four patients with stable coronary artery diseases (CAD) were enrolled in this cross sectional study from the outpatient clinic of the Department of Cardiology, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran, between May 2008 and August 2008. All patients had prior history of cardiovascular disease and were under treatment of 80 mg daily ASA for at least 7 days. Aspirin resistance was measured by urinary 11-dehydro-thromboxane beta-concentrations with an enzyme immunoassay kit.

Results: Approximately 49.2% patients were resistant to ASA, 15.3% borderline response, and 35.5% were sensitive to ASA. Acetyl salicylic acid-resistant patients were more likely to be smokers and older ages (63% versus 45.4%) (37.7% less than 60 years, 53.7% between 60-69 years, and 63.3% aged ≥70 years). Other variables such as gender, diabetes mellitus, hypertension, cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and hemoglobin levels were not significantly associated with aspirin resistance.

Conclusions: Acetyl salicylic acid resistance was present in a high number of patients with chronic stable angina. Moreover, advanced age and smoking had a direct influence on the aspirin resistance.

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Platelets have an important role in atherosclerotic cardiovascular disease and its complications. Acetyl salicylic acid (ASA) is an oral anti-platelet drug that has been shown to reduce adverse clinical events across the wide spectrum of patients with atherothrombotic disease. Acetyl salicylic acid is the cornerstone of oral antiplatelet therapy for preventing ischemic events of atherothrombotic disease. It inhibits platelet cyclooxygenase-1 by irreversible acetylation of a serine residue at position 530, which prevents the conversion of arachidonic acid to TxA2. The antithrombotic effect of aspirin is resulting from the decreased production of TxA2 (potent vasoconstrictor and platelet aggregators). In their most recent meta-analysis of more than 200,000 patients from 287 randomized trials, the Antithrombotic Trialists' Collaboration has documented that aspirin significantly reduce the risk of ischemic vascular events by 22% in patients with cardiovascular disease compared with control groups (with 15% reduction in vascular mortality, 34% reduction in myocardial infarction (MI), and 25% reduction in stroke among high-risk patients with atherothrombotic disease.[1] Although the effectiveness of ASA in reducing ischemic events is well established, ASA may not benefit in all patients equally; there are still a significant proportion of patients experiencing recurrent events despite aspirin treatment. Results of many studies in patients with coronary artery diseases (CAD) showed individual variability in response to antiplatelet medications. Patients with low response to anti-platelet medications may be at higher risk for recurrent cardiovascular events.[2-6] Acetyl salicylic acid resistance may be one of these causes. Despite controversy, ASA resistance refers to the inability of ASA to prevent from ischemic vascular events or laboratory phenomenon of reduced effect of aspirin on tests of platelet function. In addition to disagreement regarding definition, the clinical relevance of ASA resistance is also uncertain. An overview of the literature reveals that prevalence of hypo-responsiveness (namely resistance) to ASA has been reported to vary from 5-60% among patients with atherosclerotic diseases.[1-14] Although much is currently known about ASA's effect on platelets, the mechanism by which some patients' platelets are resistant to this effect has not been established.

Many tests are currently available to assess inhibition of platelet function induced by aspirin including, light transmission aggregometry (LTA), whole blood aggregometry, platelet function analyzer, PFA-100, verify now aspirin, urinary 11-dehydro-thromboxane B.[15] Given the high prevalence of cardiovascular diseases, potential impact of resistance to ASA in the daily practice of physicians and cardiovascular surgeons, we decided to design a study to evaluate ASA resistance in cardiovascular disease patients, to correlate platelet aggregation with parameters linked to cardiovascular risk such as advanced age, gender, diabetes mellitus, hypertension, cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL) levels, hemoglobin level, and smoking in Semnan, Iran.

Methods. One hundred and twenty-four patients with stable CAD were enrolled in this cross sectional study from the outpatient clinic of the Department of Cardiology, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran, between May 2008 and August 2008. All patients had prior history of cardiovascular disease as defined by previous documented coronary stenosis on cardiac catheterization, history of previous myocardial infarction, history of percutaneous coronary intervention (PCI) , and coronary artery bypass graph (CABG). Institutional review board approval and written informed consent were obtained

The study was approved by the local ethics committee and written informed consent was obtained from each patient. Demographic data such as age, gender, and major risk factor (smoking, diabetes mellitus, hypertension, cholesterol, triglyceride, HDL, LDL levels. and hemoglobin level were evaluated. Patients were evaluated for laboratory evidence of ASA resistance by urinary 11-dehydro-thromboxane B. Patients treated with aspirin 80 mg daily for more than 7 days before the test were eligible for enrollment. Compliance on ASA was determined by patient interview both at study enrollment. Exclusion criteria was acute coronary syndrome, revascularization within the last 6 months, concurrent ingestion of non-steroidal anti-inflammatory drugs (NSAID), (including COX-2 selective anti-inflammatory drugs), clopidogrel, ticlopidine, dipyridamole, warfarin, use of non-prescription NSAID or drugs containing aspirin, major surgical procedure within one month of enrolment, platelet count less than 100 or more than 450 x 10^9, hematocrit <25%, chronic renal failure requiring dialysis, administration of heparin or low-molecular-weight heparin within 24 hours before enrollment; myeloproliferative disorders, and history of heparin-induced thrombocytopenia. Urinary 11-dehydro-thromboxane B concentrations were measured using an enzyme immunoassay kit. Concentrations in the range of 10-1000 pg/mL can be measure, with a specificity approaching 100%. Urinary dTxB2 were normalized for creatinine concentrations (ng/mmol of creatinine): ASA resistance was defined if >298 pg/mmol, ASA sensitive if <134 pg/mg, otherwise intermediate response (relative resistance) has been defined.

Statistical analyses were performed using logistic regression analysis by SPSS Version 18. The p-value less than 0.05 was considered statistically significant.

Results. Approximately 59.7% of patients were males and 40.3% were females. The mean ±standard deviation age was 61.8±9.7 (35-84) and 21.8% of them were smoker. Prevalence of diabetes mellitus (fasting blood sugar equal or higher 126) was 28.2%, hypertension (systolic pressure >140 or diastolic pressure >90 mm Hg) was 33.9% (**Table 1**).

Overall, ASA resistance in our study was 49.2%. Of these, 15.3% had relative resistance and 35.5% were sensitive to ASA. Sixty-three percent of smokers and 45.4% of non-smokers were ASA resistant. Association between ASA resistance and smoking was statistically significant odds ratio (OR) =5.24, 95% confidence interval (CI): 1.60-17.15, p=0.006) (**Tables 1 & 2**). Acetyl salicylic acid resistance more common in older age with 37.7% of patients <60 years, 53.7% between 60-69 years, and 63.3% patients with ≥70 years. Chance of ASA resistance (or relative resistance) were 2.77 times in patients 60-69 years (95% CI: 1.12-6.84, p=0.028) and 4.83 times in patients ≥70 years (95% CI: 1.63-14.29, p=0.004) compare to <60 years (**Tables 1 & 2**).

Others variables in this study such as gender, diabetes mellitus, hypertension, cholesterol, triglyceride, HDL, LDL and hemoglobin levels were not significant association with ASA resistance (p>0.05).

Discussion. Low-dose daily ASA is clearly a useful therapy for primary and secondary prevention of cardiovascular events, also in acute event. Acetyl salicylic acid is easy to give, inexpensive, and has relatively few side effects at low doses. Therefore, aspirin is first-line antiplatelet agent in cardiovascular disease. Acetyl salicylic acid resistance in our study was 49.2%, and of these 15.3% have relative resistance and 35.5% were sensitive to ASA. A significant association between age, smoking, and ASA resistance was observed in our study. Acetyl salicylic acid resistance has been reported different in previous studies, including 29% in Cotter et al[2] by TxB2 method, 19% in Pamuckcu et al[3] by PFA-100, 55% in Stejskal et a[l4] by LTA, 13% in Lev et al[8] by LTA, 10% in Poston et al[7] by LTA, and 29% in Yilmaz et al[6] by PFA-100 method. Eikelboom et al[16] performed a nested case-control study on patients with cardiovascular disease (HOPE) trial. Acetyl salicylic acid responsiveness was measured by urinary 11- dehydrothromboxane B2 levels, after 5 years of follow-up, there was a 2-fold increase in the risk of myocardial infarction (MI) and 3.5-fold increase in the risk of cardiovascular death as well.[16] Gum et al[9] enrolled

Table 1 - Acetyl salicylic acid (ASA) resistance status in patients with chronic stable angina according to age, gender, and major risk factor for atherosclerosis.

Characteristic	N	ASA resistance status		
		Resistance %	Relative resistance %	Sensitive %
Age				
<60	53	37.7	13.2	49.1
60-69	41	53.7	17.1	29.3
≥70	30	63.3	16.7	20.0
Gender				
Female	50	36.0	12.0	52.0
Male	74	58.1	17.6	24.3
*Diabetes mellitus**				
Positive	35	37.1	20.0	42.9
Negative	89	53.9	13.5	32.6
*Hypertension***				
Positive	42	45.2	16.7	38.1
Negative	82	51.2	14.6	34.1
Smoking				
Positive	27	63.0	22.2	14.8
Negative	97	45.4	13.4	41.2
High-density lipoprotein				38.3
Abnormal†	47	46.8	14.9	33.8
Normal	77	50.6	15.6	
Triglyceride				
>150	36	50.0	22.2	27.8
≤150	88	48.9	12.5	38.6
Cholesterol				
<200	100	51.0	15.0	34.0
200-240	13	46.2	23.1	30.8
>240	11	36.4	9.1	54.5
Low-density lipoprotein				
<100	93	51.6	14.0	34.4
100-129	13	53.8	7.7	38. 5
≥160	18	33.3	27.8	38.9
Hemoglobin				
Abnormal‡	26	42.3	19.2	38.5
Normal	97	50.5	14.4	35.1

*Fasting blood sugar ≥126, **Systolic pressure >140 or diastolic pressure >90 mm Hg, †<40 for men and <50 for women, ‡<14 for men and <12 for women.

Table 2 - Acetyl salicylic acid (ASA) resistance risk-assessment model patients with chronic stable angina.

Variables	Coefficient	Standard error for beta	*P*-value	Odds ratio (OR)	95% confidence interval* for OR
Smoking					
Positive	-	-	-	1.00	-
Negative	1.66	0.61	0.006	5.24	1.60-17.15
Age			0.002		
<60	-	-	-	1.00	-
60-69	1.02	0.46	0.028	2.77	1.12-6.84
≥70	1.57	0.55	0.004	4.83	1.63-14.29

stable patients with cardiovascular disease treated with ASA 325 mg daily for more than 7 days and defined ASA resistance by optical platelet aggregation. Acetyl salicylic acid resistance was noted in 5.2%. Multivariate analysis demonstrated that, in addition to other risk factors, ASA resistance was an independent predictor of adverse outcomes.[17] Chen et al[18] found that patients with elective percutaneous coronary intervention (PCI) who take ASA had ASA resistant (19.2%).[18]

There are multiple possible mechanisms for this diminished inhibition of platelet aggregation in patients taking ASA. This unpredictable response to aspirin can be attributed to clinical, cellular, and genetic factors.[19-22] Clinical causes of ASA resistance can range from patient's non compliance to physicians who fail to prescribe aspirin appropriately, patients may take ASA but not absorb it, or may have interactions because of other medications. Ibuprofen, for example, can adhere to the COX-1 binding site of ASA and limit its cardio protective function. The dose of ASA may contribute to uninhibited platelet activity depending on the weight and age of patients.[23]

In addition, ACSs and congestive heart failure are associated with increased platelet reactivity,[24] hyperglycemia,[25] hypercholesterolemia, chronic kidney disease inflammation, obesity and bypass surgery,[26] exercise, and the catecholamine surge can also affect platelet responsiveness.[27] Age, gender and smoking also reduce the platelet inhibitory effect of aspirin.[28] Cellular factors influencing ASA efficacy include inadequate suppression of platelet COX-1 and COX-2.[29] Genetics also play a role in patient's response to ASA.[30-32] The clinical importance of biochemical ASA resistance remains poorly elucidated because of the differences in definition, variation in detection methods, and limited study data.[10,33-37] In addition, no consensus exists on the prevalence of ASA resistance, with estimates ranging from 5-60%, depending on the types of patients studied and the use of various laboratory tests (there was not any standard route), or whether ASA dosage use of various dose of ASA (higher dose resulting in lower resistance and resistance is very low in a dose more than 325 mg, duration of treatment, different in prevalence gender distribution male and female in various studies. Genetic factors or patient comorbidities play a role in the development of resistance. Several prospective studies show an association between biochemical ASA resistance and clinical outcomes. These data suggest a possible influence of the age and smoking and mechanisms responsible for ASA resistance that agree with other publications as a extrinsic factor in the loss of platelet factor in the loss of platelet sensitivity to ASA.[37-39] In another study, no (statistically significant) evidence of a relationship between platelet aggregation levels and smoking.[27]

Acetyl salicylic acid is a common drug, that are commonly used for heart disease; thus, we do not have any limitation due to the high prevalence of ASA resistance. We recommended that all patients who are or not resistant to aspirin should follow for cardiac outcomes.

In conclusion, prevalence of ASA resistance in chronic stable angina patients, especially in elderly and smoker, is high. It seem that other treatment modalities such as high dose of ASA or other antiplatelet agents such as clopidogrel and prasugrel is helpful in these patients, that need to be investigated in future study.

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