ASPIRIN RESISTANCE IN PATIENTS PRESENTING TO THE EMERGENCY DEPARTMENT

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[Resistenza all'aspirina in pazienti che si presentano al pronto soccorso]

ABSTRACT

Introduction*: The effect of aspirin is not the same for all patients and some patients can be resistant. Few emergency department (ED) studies have prospectively determined the rate of aspirin resistance in patients presenting to the ED and the most of them consider only specific group of patients. We aimed to evaluate the relation between clinical and laboratory parameters with aspirin resistance in patients presenting to the ED*

Methods*: Using the bed-side point-of-care VerifyNow Aspirin assay (Accumetrics, San Diego, Calif), we sought to determine the rate of aspirin resistance in patients presenting to the ED with any complaint.*

Results*: A total of 97 patients were included in this study. Aspirin resistance was found in 29 (29.9%) of them. There were not any significant differences in age, sex, drug usage, platelet count, ECG changes, heart rate, systolic, or diastolic blood pressure measures between the aspirin-resistant and aspirin-sensitive patients. In addition, patients' aspirin sensitivity and aspirin resistance did not differ significantly with regard to clinic results and diagnoses in the ED. However, patients with renal failure had significantly more aspirin resistance than other patients (p=0.007). Besides, the relationship between aspirin intake <30 time, pulse pressure and aspirin resistance were found out significant.*

Conclusion*: To the best of our knowledge, this second current report of aspirin resistance in patients presenting to the ED pointed-out its presence in 29.9% of patients. In aspirin resistance, renal failure, pulse pressure and aspirin intake time were determined as important factors.*

Key words: Emergency department. aspirin resistance. renal failure. pulse pressure. aspirin intake time.

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Introduction

Aspirin is one of the oldest and most widely used drugs[1,2]. Since Sir John Vane discovered aspirin's antithrombotic potential, it has been widely prescribed as an antiplatelet agent for treatment of several kind of disease[1]. Clinical trials have shown the efficacy of aspirin in the primary and secondary prevention of myocardial infarction, stroke and cardiovascular death[3-5]. However, the effect of aspirin is not the same for all patients and some patients have a resistance to aspirin.

Aspirin resistance has been regarded as the failure of aspirin to inhibit cyclooxygenase-1 and platelet function after stimulation by various agonists ("laboratory aspirin resistance") or the failure to protect from cardiovascular events ("clinical aspirin resistance")[2,6-8]. The prevalence of aspirin resistance reported in the literature varies widely[6-11]. There are a few emergency department (ED) studies that have prospectively determined the rate of aspirin resistance in patients and the most of them have been conducted on special group of patients such as acute coronary syndrome or chest pain patients[11-13]. Using the bed-side point-of-care VerifyNow Aspirin assay (Accumetrics, San Diego, Calif), we sought to determine the rate of aspirin resistance in patients presenting to the ED with any complaints. We also aimed to evaluate the relation between clinical and laboratory parameters with aspirin resistance according to these patients complaints and diagnoses.

Methods

Patients population and study protocol

One hundred consecutive patients (≥ 18 years old) admitted to the ED, Uludag University Faculty of Medicine Hospital, with any complaint and who taken, regularly, aspirin therapy in the last four weeks. Exclusion criteria were: use of other drugs that might influence platelet aggregation (clopidogrel and non-steroidal anti-inflammatory drugs), a platelet count <150000 or >450000 and/or hemoglobin <8 g/dl.

History was taken and physical examination was performed for each patient. Medications of patients were questioned; complete blood count and biochemical tests were studied. In addition, to determine whether aspirin resistance exists or not, venous blood samples were taken. Bedside kits were used for the detection of aspirin resistance (The VerifyNow Aspirin Assay, Accumetrics, San Diego, CA). Testing results are calculated from the change in the optical signal caused by the aggregation and are expressed as aspirin reaction units. Aspirin resistance is defined as a result of greater 550 aspirin reaction units (ARU)[14].

Since the laboratory tests and data collected in this study are part of routine clinical practice, the Institutional Ethics Committe approval was waived. Verbal informed consent was obtained from eligible patients or the relatives of incapacitated patients.

Statistical analyses

Shapiro-Wilk test was used to test the normality of variables. Mean, standard deviation, median and minimum-maximum values were given for continuous variables as descriptive statistics. Mann-Whitney's U-test or t-test was performed for comparing two independent groups. Categorical variables were expressed by counts and percentages. Comparisons between the groups were performed with Pearson chi-square and Fisher's exact chi-square tests for categorical variables.

Analysis of covariance (ANCOVA) was also performed to determine any difference between two groups after controlling for the effects of covariates. Significance level was taken as P>0.05. Statistical analyses were performed with SPSS version 16.0 (SPSS Inc., Chicago, IL).

Results

A total 97 patients (41 female and 56 male) were included in this study. Three patients were excluded due to incomplete data. The overall mean age was 63.0 ± 12.3 years. The distribution of gender was homogeneous in terms of age between groups (P=0.114). Mean ARU was 509.5 ± 81.1 and aspirin resistance was found in 29 (29.9%) patients in all groups. When aspirin resistant and aspirin sensitive groups have been compared in terms of gender and average age values, they did not reveal statistically significant difference (P>0.05). The patients were classified in three groups as 18-40 years, 41-64 years and ≥65 years. Although aspirin resistance rate was found to be highest in groups of 41-64 years and ≥65 years, there was no significant difference among groups (P >0.05). Sixteen of aspirin resistant patients (55.2%) referred to emergency department with cardiac complaints. Even though Electrocardiography (ECG) changes were more in aspirin sensitive group, they were not statistically significant (P>0.05). Besides, there were not any significant differences in heart rate, systolic or diastolic blood pressure (SBP or DBP) measures between the aspirin-resistant and aspirin-sensitive presenting to ED patients. Another drug intake with aspirin was highly common in those who were aspirin resistant. As can be seen, demographic and clinical characteristics of the patients are listed in Table 1.

ANCOVA was also performed to determine any differences between the two groups (aspirin resistance and sensitive groups) in terms of pulse pressure after controlling for the effects of age, GCS and ECG covariates. When the effects of age, GCS and ECG were removed, the effect of the group variable (aspirin resistance) on pulse pressure was found statistically significant (P = 0.019). Estimated marginal means (EMM) adjusted for the effects of covariates were 57.02 ± 3.08 for the aspirin sensitive group and 49.72 ± 4.40 for the aspirin resistant group. Covariates age and ECG were significantly related to pulse pressure (P = 0.027 and P =0.032 respectively), while GCS was not (P = 0.140).

When the duration of aspirin intake was examined in the patients admitted to emergency department, aspirin resistance incidence in the patients who have <30 hours aspirin intake was 34.1% while it was 0% for >30 hours. On the other hand, in aspirin sensitive group of patients with time

Characteristic[a]	Aspirin resistance (n=29)	Aspirin sensitive (n=68)	p value
Years	65.0±13.5	62.2±11.7	0.30
Sex, Male	17	39	1.0
Age Groups			>0.05
18-40 y	1	2	
41-64 y	15	36	
>65 y	13	30	
Complaints			1.0
Cardiac	16	36	
Other	13	32	
EKG changes	8	14	0.442
Systolic blood pressure	128.7± 31.4	118.9±25.9	0.10
Diastolic blood pressure	73.8 ±12.7	70.0 ±13.8	0.064
Pulse pressure	48.6 ±15.7	54.8 ±15.7	0.382
Pulse	83.9±17.6	81.8±13.6	0.458
Glasgow Coma Scale (GCS)b	15 (15-15)	15 (14-15)	0.160
Additional drug use, present	27	64	1.0
Platelet count	269.1±111.5	278.2±178.1	0.516

Table 1. Demographic and clinical characteristics of paitents.
aData for the characteristics are expressed as mean±SD
bData for GCS were axpressed as median (min-max)

course of <30 hours aspirin intake, the rate was 65.9% whereas it was 100% in >30 hours. The rate of aspirin resistance occurrence in those who had <30 hours aspirin intake was more significant (P =0.016).

The categories of primary diseases were classified into cardiovascular diseases (n=39, 40.2%); internal diseases (n=22, 22.7%); stroke/ transient ischemic attack (TIA) (n=5, 5.2%); renal disease (n=4, 4.1%) and others (n=27, 27.8%). Among the cardiovascular diseases, there were 12 acute heart failure (AHF) (12.4%), 10 unstable angina pectoris (USAP)/acute coronary syndrome (ACS) (10.3%), 10 stable angina pectoris (SAP)/coronary artery disease (CAD) (10.3%), 4 arrhythmias (4.1%) and 3 others (3.1%). Among the internal diseases, there were 4 pneumonia (4.1%), 4 pulmonary embolisms (PE) (4.1%), 4 gastrointestinal hemorrhages (4.1%), 3 gastritis/peptic ulcer (3.1%), 3 diabetic ketoacidosis (DKA) and 4 others (4.1%).

In all patients with renal failure, aspirin resistance (n=4) was determined. The rest of the patients had no renal failure (n=93). Patients with renal failure were significantly more aspirin resistant than other patients (P=0.007). When those with renal failure (601.2 ± 33.3) and without renal failure (505.5 ± 80.2) were compared for aspirin level, it revealed significant difference (P =0.014). In contrast, no significant relation was detected between other diagnoses of patients and aspirin resistance (Table 2).

Diagnosis	Aspirin Resistance n (%)	p value
All patients (n=97)	29 (29.9%)	
Cardiovascular diseases	9 (23.1%)	0.329
İnternal diseases	4 (18.2%)	0.271
Stroke/TİA	1 (20%)	1.0
Renal failure	4 (100%)	0.007*
Other	11(40.7%)	0.30

Table 2. The relation between prevalence of aspirin resistance and definite diagnosis.
**p<0.05 between groups*.

Clinical results of the considered patients were: discharge (n=51), hospitalization (n=39) and mortality (n=4) rates were 40.2% and 4.1% respectively. Three of the patients who refused the treatment were all aspirin sensitive. While 16 of aspirin resistant cases (55.2%) were discharged, 11 of them (37.9%) were considered to be hospitalized. 35 patients (51.5%) of aspirin sensitive group were discharged whereas 28 patients (41.2%) were hospitalized. 2 Two patients (6.9%) in aspirin resistant group and 2 patients (2.9%) in aspirin sensitive group died (Figure 1). However, comparison of discharge, hospitalization, and mortality rates of patients revealed statistically insignificant difference between aspirin resistant and aspirin sensitive groups (P >0.05).

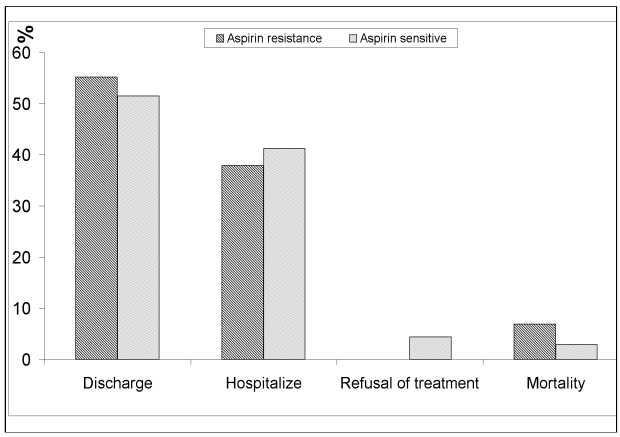

Figure 1: Clinical outcomes of patients.

Discussion

Despite effective and appropriate aspirin intake, thromboembolic occasions were found to be reappeared in patients[6,15]. This case depends on the fact that antiaggregant effect of aspirin it is not equivalent in all patients and some of them might not to benefit from aspirin intake. Those patients are named as aspirin resistant or aspirin non-responsive patients[2,4,7]. Aspirin resistance may cause mortality and morbidity to increase in cardiovascular and cerebrovascular diseases[3,5]. A number of studies have been conducted in different patient groups via same or different methods, which report various rates of aspirin resistance. Yet, the studies related to aspirin resistance in patients admitted to emergency department are few in the literature. Most of the serious thromboembolic cases are admitted to emergency departments. Therefore, in emergency departments, aspirin has been given to patients due to both acute and chronic use.

Besides, in literature, there exist a lot of studies on the frequency of aspirin resistance. To date, according to the results of studies carried out in various patient groups by means of different methods, 5.5-75% frequency of aspirin resistance has been established[4, 6-10,16]. Majority of those studies were in connection with cardiovascular diseases and dissimilar aspirin resistance frequencies were reported in all individuals. Moreover, it was found out that the frequency of aspirin resistance was associated with, to a considerable extent, the laboratory method utilized. While aspirin resistance was found as 8.3% and 33.3% in studies conducted over healthy patients[17,18], higher aspirin resistance frequency was reported in patients with cardiovascular diseases[19,20]. In cerebrovascular diseases, the rate was established as 25-37%[21-23]. In aspirin resistance

studies on individuals with peripheral vascular diseases, it was reported ranging from 40% to 60%[24,25]. The studies conducted in our country revealed that aspirin resistance in healthy individuals was 27.5-28%[11, 26,27], and 23.4-40.3%[7,20] in individuals with coroner artery diseases while it was 4.5-33% in cerebrovascular diseases[28,29]. In our study, aspirin resistance was found in 29 (29.9%) patients in all groups. Aspirin resistant patients (55.2%) were admitted due to cardiac complaints. Nine of aspirin resistant patients suffered from cardiovascular disease, 1 was affected with stroke, and 4 with renal failure.

The present study is the first one conducted in emergency department in our country because in the literature there are considerably few studies about aspirin resistance in patients applying to emergency departments. In this sense, we have encountered with only one study, in which aspirin resistance was detected as 6.5% in patients with acute coronary syndrome[12]. The most highlighted point of our study is the establishment of aspirin resistance in all patients with renal failure. Furthermore, there was significant difference in those patients when compared in terms of aspirin level (P =0.014). Renal failure was included as comorbidity associated with aspirin resistance in a review[4,30]. However, Gum et al[6] reported that the presence of renal disease caused no difference in aspirin sensitivity in patients with cardiovascular disease. A recent meta-analysis has reported that aspirin resistance might be higher in patients with previous renal impairment, and recommended future studies exploring the relation of aspirin resistance with renal failure[10].

In a study carried out in Turkey, aspirin resistance was evaluated in 245 patients with chronic renal failure detecting this condition in 85 patients (34.7%) 53 patients undergoing hemodialysis (46.1%) and in 32 patients (24.6%) with phase 3-4 chronic renal failure)[30]. Significantly high aspirin level was seen in this study, which was similar to our[30].

The mechanisms associated with aspirin resistance are not well known, but some clinical, biological or genetic factors may be responsible. Whereas some studies report that aspirin resistance is influenced by older age, gender, drugs intake (especially statins), and platelet amount[6,10,14,27,29], some other studies find no significant relation between aspirin resistance and those parameters[11,12,16,28]. In line with some studies in the literature, in the present study, statistically significant difference was not established between aspirin resistance and the age, gender, platelet amount of patients, and the drugs used.

Several studies reporting relationships between hypertension and aspirin resistance were conducted in different patient populations like stable coronary artery disease, and association of hypertension with aspirin resistance were shown by either univariate or multivariate analysis. Multivariate analysis also did not reveal any significant association between blood pressure measures and aspirin resistance. Yet, in several studies, high systolic blood pressure was determined in aspirin resistant patients[16,31].

In our study, there were not any significant differences in heart rate, systolic or diastolic blood pressure measures between the aspirin-resistant and aspirin-sensitive presenting to ED patients. Unlike the previous studies, when the variables influencing pulse pressure were excluded, in aspirin resistant patient group pulse pressure was significantly high. In the literature, there have been pretty few studies showing that pulse pressure is related to aspirin resistance. In establishing aspirin resistance pulse pressure might be an independent variable. A number of factors including increased arterial stiffness, shear stress, and endothelial dysfunction might contribute to altered platelet reactivity and lead to relatively high frequency of aspirin resistance among subjects with increased blood pressure[32].

Although aspirin circulation half-life was 20 minutes, since antiaggregant effect irreversibly inhibit COX-1 enzyme, it was stated as effective when used at 24-48 hours intervals[2,4,15]. It was thought that blood platelet inhibition which was complete at the beginning turned into partial inhibition in 6 months due to chronic use or resistance against aspirin was developed[4,33].

In a study by Hobikoglu et al.[34], no relation with aspirin resistance could be determined in spite of quite long aspirin use periods (weeks/months). Besides, in patients who have cerebrovascular experience, in one third of patients resistance was observed in 12th hour though there was total response to aspirin in the 2nd hour[21]. A study by Glauser et al.,[12] revealed that in 6.5% of patients presenting with emergency department due to the suspicion of acute coronary syndrome resistance developed 2 hours later following aspirin administration and also when they re-applied to emergency department after a one-month tracing, the resistance was observed as twice-folded. (12.5%).

In our study, the rate of aspirin resistance occurrence in patients who had <30 hours aspirin intake was significantly more (P =0.016). Independent from clinical conditions, the risk of mortality, morbidity, cardiovascular and cerebrovascular cases are higher in those who are aspirin resistant[6,7,10,12,21,23,29].

On the other hand, the studies claiming that aspirin resistance are not related to cardiovascular endpoints draw attention[8, 33]. Unlike those studies, in the current study, a relation between aspirin resistance and prognosis was not detected. This may derive from less number of patients and having no period of patient tracing.

Conclusion

With medical prescription or over the counter, aspirin has been widely used in our country. In addition, when it is considered how widespread the cardiovascular diseases are, aspirin resistance may generate a crucial risk for society. To the best of our knowledge, this second current report of aspirin resistance in patients presenting to the ED finds this last resistance in 29.9% of patients. Renal failure, pulse pressure, aspirin intake time were determined as important factors in aspirin resistance. Nevertheless, in a wider population, aspirin resistance should be studied in patients with renal failure admitted to emergency department. Knowing aspirin resistance in thromboembolic (cerebrovascular and cardiovascular) patients applying to emergency department might be of clinical importance in mortality, morbidity, and its treatment.

Limitations

The present study has some restrictive parameters. The first one may be the method used. In relation to this, the previous studies reported that the frequency of aspirin resistance could change depending on the method used. However, it was showed that the method used in this study was quite widespread and had a correlation with many studies. Secondly, in the study, in order to report an important relation between aspirin resistance and mortality, morbidity, and prognosis, studies including wider population of patient groups should be conducted and the observation period should be longer. Thirdly, it is not exactly known the amount of aspirin taken and for how long our patients have been using aspirin. Next, although total patient number for aspirin resistance is sufficient, the number of patients in sub-groups is not. For instance, by increasing the number of patients with renal failure, more significant results may be obtained. Finally, whether there are other factors influencing aspirin resistance except from the factors stated in this study, cannot be analyzed clearly.

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