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Aspirin resistance predicts unfavorable functional outcome in acute ischemic stroke patients

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ABSTRACT

Objective: To investigate the prognostic value of aspirin reaction units (ARU) in a 3-month follow-up study in a cohort of Chinese patients with first-ever ischemic stroke.
Methods: Prospective single-center survey of acute ischemic stroke patients receiving aspirin therapy. Two hundred and seventy-five Chinese patients with first-ever ischemic stroke who previously received aspirin therapy were enrolled. ARU was measured using the VerifyNow system. A cutoff of 550 ARU was used to determine the presence of aspirin resistance (AR).
Results: Median age at study entry was 67 years (IQR: 59–75) and 142(51.6%) were male. A total of 52 of 275 enrolled patients (18.9%) were AR. Median regression estimated a statistically significant increase in NIHSS score of 0.033 point for every 1-point increase in ARU (95% CI, 0.024 to 0.068; P < 0.001). The unfavorable outcomes distribution across the ARU quartiles ranged between 11.8% (first quartile) to 64.8% (fourth quartile). After adjusting for other established risk factors, in multivariate models comparing the third and fourth quartiles against the first quartile of the ARU, levels of ARU were associated with unfavorable outcome, and the adjusted risk of unfavorable outcome increased by 145% (OR = 2.45 [95% CI 1.46–3.87], P = 0.011) and 317% (4.17[2.76–6.15], P < 0.001), respectively. Similarly, the adjusted risk of mortality increased by 215% (OR = 3.15 [95% CI 1.98–4.73], P = 0.008) and 429% (5.29[4.02–8.17], P < 0.001), respectively.
Conclusions: The results suggest that AR is a meaningful and independent marker to predict short-term functional outcome in patients with ischemic stroke.

What is known about this topic?

Aspirin is widely used in the treatment of stroke.

Aspirin resistance may lead to aspirin fails to prevent myocardial infarctions and strokes.

What does this paper add?

A total of 52 of 275 enrolled stroke patients were aspirin resistance.

Median regression estimated a statistically significant increase in NIHSS score of 0.033 point for every 1-point increase in ARU.

Aspirin resistance is an independent marker to predict short-term functional outcome in patients with ischemic stroke.

1. Introduction

Aspirin is widely used in the treatment of stroke. It significantly reduces the risk of recurrence (Helgason et al., 1994; Antithrombotic Trialists' Collaboration, 2002) and the severity of stroke (Wilterdink et al., 2001; Sanossian et al., 2006). Long-term aspirin therapy has been estimated to have a cost-effectiveness ratio of $11 000 per quality-adjusted year of life gained (Gaspoz et al., 2002). However, aspirin fails to prevent myocardial infarctions and strokes in a large proportion of people (Mueller et al., 1997; Hayden et al., 2002) and the phenomenon of aspirin resistance (AR) may contribute to this problem. AR could translate into a significant increase in health burden.

One study demonstrates the natural history of AR in a stable

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population, documenting a greater than threefold increase in the risk of major adverse events associated with AR (Gum et al., 2003a). Most recently, Eikelboom et al. (2002) reported an increased risk for cardiovascular death associated with AR in patients with cardiovascular disease or diabetes and AR has been suggested associated with increased risk of recurrent stroke and poor outcome after stroke (Zheng et al., 2013). Yi et al. (2013) found that patients who are detected to be AR were at a greater risk of clinically important vascular events in Chinese stroke patients.

Interestingly, research findings suggested an association of AR with increased stroke severity and infarct size (Zheng et al., 2013; Oh et al., 2016). Even though another study did not demonstrate a substantial positive influence of pre-stroke antiplatelet usage on stroke severity (Agayeva et al., 2016). Stroke severity is significantly linked to a poor neurological outcome (Derex et al., 2002). In addition, infarct volume is strongly correlated with clinical stroke severity and is therefore an important surrogate of stroke outcome (Saver et al., 1999). We hypothesized that AR is risk factor for worse functional outcomes in patients with ischemic stroke. The aim of this study is to determine aspirin reaction units (ARU) at admission and investigate the prognostic value of ARU in a 3-month follow-up study in 275 Chinese patients with first-ever ischemic stroke.

2. Methods and patients

From January 2015 to September 2016, 275 consecutive first-ever acute ischemic stroke patients who were admitted to the Department of Emergency of our Hospital were included. The inclusion criteria were (1) at least 7 days of aspirin therapy (acetylsalicylic acid, 100 mg daily) prior to stroke onset; (2) within 24 h of experiencing a new focal or global neurological event; (3) evidence of ischemic infarct on magnetic resonance imaging (MRI) or Computed Tomography (CT); (4) with informed consents and finished follow-up. Acute ischemic stroke was defined according to World Health Organization recommendations (defined stroke as a "neurological deficit of cerebrovascular cause that persists beyond 24 h or is interrupted by death within 24 h") (Huang et al., 2016). Patients with malignant tumor, renal insufficiency (creatinine > 1.5 mg/dl), severe edema and history of brain trauma and cardiac diseases (CAD) in past 3 months were excluded. In addition, patients who lost blood samples, had platelet function disorders or concurrently taking an additional anti-platelet or anticoagulant also had been excluded. The present study has been approved by the ethics committee of the First Affiliated Hospital of Xinxiang Medical University. All participants or their relatives were informed of the study protocol, and their written informed consents were obtained.

At baseline, demographic data (age, sex and body mass index [BMI]) and the following vascular risk factors: hypertension, diabetes mellitus, hypercholesterolemia, smoking, previous myocardial infarction, and a family history of ischemic stroke or transient ischemic attack (TIA). were collected. Pre-stroke therapy (antihypertensive and/or statins) and acute treatment (IV thrombolysis and/or mechanical thrombectomy) were also recorded. Patients were evaluated with the National Institute of Health Stroke Scale (NIHSS) (Brott et al., 1989) score at their admission, performed by a stroke neurologist certified. The clinical stroke syndrome was determined by applying the criteria of the Oxfordshire Community Stroke Project (OCSP), and strokes were classified according to the criteria of the TOAST (Trial of Org 10,172 in Acute Stroke Treatment) classification. Brain imaging (either CT or MRI) was done routinely within 24 h after admission. MRI with diffusion-weighted imaging (DWI) was available for some patients. The infarct volume was calculated by using the formula $0.5 \times a \times b \times c$ (where a is the maximal longitudinal diameter, b is the maximal transverse diameter perpendicular to a, and c is the number of 10-mm slices containing infarct) (Sims et al., 2009).

From every patient 2 ml blood samples were drawn into tubes containing 3.2% citrate at first morning after admission under fasting. The patients continued to receive aspirin during them in-hospital admission, and the blood samples were drawn prior to administration of aspirin at the hospital. Aspirin-induced platelet inhibition was measured using a commercially available point-of-care device, the Ultegra Rapid Platelet Function Assay-ASA (the VerifyNow System, Accumetrics, San Diego, California). The result is expressed in aspirin reaction units (ARU), taking about 5 min to test one blood sample. The cut-off point is set as 550 aspirin reaction units (ARU) according to the manufacturer's clinical studies using optical aggregometry as the comparison standard. In line with previous definitions, a cutoff of 550 ARU was used to determine the presence of AR (Zheng et al., 2013). An ARU value of ≥550 IU was defined as AR, while < 550IU was defined as aspirin sensitive (AS). Raw ARU scores as continuous variables were also used to indicate the degree of platelet aggregation (Ozben et al., 2011a). Results of the other blood analyses, such as C-reactive protein (CRP), fasting blood glucose (FBG), Platelet (PLT), total cholesterol, LDL cholesterol and white blood count (WBC) were also measured using routine laboratory methods.

The primary end-point was functional outcome on day 90. Functional outcome was assessed by the modified Rankin Scale (mRS) (Bonita, 1998). A favorable functional outcome was defined as a mRS of 0–2 points, whereas an unfavorable outcome was defined as a mRS of 3–6 points. Secondary end-points were all-cause mortality within 90 days. Outcome assessment was performed by two trained medical staff blinded to ARU with a structured interview, if discharged, with telephone interview. The follow-up information was collected by medical personnel blinded to patients' clinical or laboratory data.

2.1. Statistical analysis

All statistical analysis was performed with SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA) and the ROCR package (version 1.0-2). Results were expressed as percentages for categorical variables and as medians (interquartile ranges, IQRs) for the continuous variables. Univariate data on demographic and clinical features were compared by Mann-Whitney *U* test or Chi-Square test as appropriate. Correlations among laboratory parameters were analyzed using Spearman's rank correlation test. In addition, associations between ARU and NIHSS score (infarct volume) were also assessed using ordered logistic regression models in multivariate adjustment for age, sex, BMI, stroke syndrome, stroke etiology, vascular risk factors, acute and pre-stroke treatment, time from stroke onset to ARU test, lesion volumes (NIHSS), and blood levels of WBC, Platelet, total cholesterol, HDL and LDL cholesterol, Hs-CRP, HCY and FBG.

The relation of ARU with the two end points was investigated with the use of logistic regression models. We used crude models and multivariate models adjusted for all significant outcome predictors and report odds ratios (ORs). For multivariate analysis, categorical variables (sex, stroke subtype, stroke syndrome, vascular risk factors, and prior or acute treatment) and continuous variables (age, BMI, time from onset to ARU test, NIHSS score, blood pressure, lesion volumes and blood levels of WBC, PLT, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, Hs-CRP, FBG and HCY) were used as covariates. For a more detailed exploration of the ARU and end points, we also used multivariate analysis models to estimate adjusted OR and 95% CIs of end points for ARU quartiles (with lowest ARU quartile as reference).

Second, receiver operating characteristic curves (ROC) was used to test the overall predict accuracy of ARU and other markers to diagnose unfavorable outcome or mortality, and results were reported as area under the curve (AUC). Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices were calculated to determine the clinical utility of the addition of ARU to established risk factors and the ability of ARU to improve unfavorable outcome or mortality prediction (Pencina et al., 2008). Statistical significance was defined as $P < 0.05$.