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Clinical Study

A pilot study of resistance to aspirin in stroke patients

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Abstract

Aspirin resistance has been shown to be a significant risk factor for recurrent cardiovascular ischaemic events. However, there are a lack of data correlating aspirin resistance and risk of cerebrovascular ischaemic events. This pilot study aimed to determine the prevalence of aspirin resistance in an Australian stroke population and to correlate aspirin resistance with an increased risk of ischaemic stroke. Fifty patients treated with aspirin for 2 years were tested for aspirin resistance using the Ultegra Rapid Platelet Function Assay (Accumetrics, San Diego, CA, USA) on admission to Royal Melbourne Hospital for ischaemic stroke. The 2-year history of ischaemic stroke and transient ischaemic attack (TIA) were assessed. Prevalence of aspirin resistance among our patients was 30%. Univariate analysis suggested a non-significant trend towards increased rate of previous ischaemic stroke or TIA and aspirin resistance (odds ratio, OR = 3.88; 95% confidence interval 0.54–29.87; $p = 0.18$). This study shows that aspirin resistance is prevalent within the Australian ischaemic stroke population.

Keywords: Aspirin resistance; Ischaemic stroke; Transient ischaemic attack

1. Introduction

Aspirin remains the standard first-line therapy in the secondary prevention of vascular events due to underlying atherothrombotic conditions. The Antithrombotic Trialists' Collaboration analysed patient data from 21 randomised controlled studies and concluded that the benefit of aspirin reduced the recurrent odds of stroke by 22% compared to placebo.[1] However, the benefits in a stroke population are even more modest, with a relative risk reduction of only 13%.[2] Therefore, a substantial proportion of patients do not derive the expected benefits of stroke prevention.

Between 5% and 60% of patients treated with aspirin may be regarded as aspirin-resistant, on various laboratory measures of platelet function. This has been independently associated with an increased risk of atherothrombotic vascular events in a wide range of cardiovascular patients.[3–6] Aspirin resistance has been associated with a 4 times increased hazard risk (HR) of adverse events (HR = 4.1 [1.4–12.1]) among stable cardiovascular patients.[3] The increased risk of clinical events is expected to be similarly linked with aspirin resistance among ischaemic stroke patients, given the common underlying pathology of atherothrombosis. If aspirin resistance predicts an increased risk of stroke recurrence, treatment could be individualised.

Few studies have investigated the role of anti-platelet resistance in stroke. Harrison et al. recruited 100 stroke patients and showed that the incidence of aspirin resistance was 17%, using light transmission aggregometry (LTA).[7] This was comparable to the incidence in studies of myocardial ischaemia.[8] However, this study did not address recurrent stroke. The primary objective of our pilot study was to examine the prevalence of aspirin resistance in Australian patients who present with acute ischaemic stroke. The secondary objective was to test the hypothesis that aspirin resistance was more common in those with previous cerebrovascular events.

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2. Materials and methods

2.1. Patients and study design

This study was approved by the Human Research and Ethics Committee (HREC) at the Royal Melbourne Hospital (Melbourne, Victoria) and all subjects provided written informed consent. Over a 7 month period patients presenting consecutively to Royal Melbourne Hospital Comprehensive Stroke Centre with acute ischaemic stroke were screened for enrolment. Inclusion criteria were consenting age >18 and patients who had been taking aspirin for at least 2 years and had presented with an acute ischaemic stroke (excluding transient ischaemic attack, TIA). Patients were excluded if they had an intracerebral haemorrhage on CT scan, significant diseases or abnormalities (terminal cancer, life threatening infection) that might compromise participation. Patients treated with clopidogrel in combination with aspirin were also excluded.

All patients received standard treatment according to Royal Melbourne Hospital Comprehensive Stroke Centre protocol. After a single screening visit to establish eligibility, qualified patients were enrolled in the study. Demographic information (age, gender, race, vascular risk factors) and clinical data which included National Institutes of Health Stroke Scale (NIHSS), Trial of Org 10172 in Acute Stroke Treatment (TOAST) scale[9] and Oxfordshire Community Stroke Project Classification[10] were obtained within 48 hours of admission. Any history of prior ischaemic events was analysed retrospectively for the previous 2 years while taking aspirin and included ischaemic stroke, TIA, myocardial infarction and unstable angina. A single blood sample was obtained per recruited patient to establish the presence of aspirin resistance.

2.2. Blood sampling

Whole blood was obtained via venepuncture into a 2 mL partial fill 3.2% sodium citrate vacuum collection tube using a 21-gauge needle. A tourniquet was used while performing venepuncture. For patients with an in-dwelling cannula, blood was collected after sufficient discard (about 5 mL) had been drawn to clear the line. The tubes were then gently inverted 3–5 times and incubated at room temperature for at least 30 min after collection before testing but for no longer than 4 hours. Blood was taken no less then 2 hours after aspirin ingestion as documented on ward charts.

2.3. Measuring aspirin resistance

Aspirin-induced platelet inhibition was measured using the point-of-care device, the Ultegra Rapid Platelet Function Assay (RPFA) developed by Accumetrics (San Diego, CA, USA). This turbidimetric-based optical detection system measures platelet induced aggregation proportional to changes in light transmission. Modified disposable cartridges containing fibrinogen-coated beads and platelet agonist are inserted into the Ultegra RPFA device to test specifically for aspirin responsiveness. A citrate anti-coagulated blood sample is then gently inverted 4–5 times and placed onto the cartridge. The device automatically dispenses blood, mixing it with the cartridge reagents, thereby no blood handling is required. Fibrinogen-coated beads agglutinate in proportion to the number of activated platelets expressing glycoprotein GP IIb/IIIa receptors, subsequently increasing light transmission through the sample. The result is expressed in Aspirin Reaction Units (ARU), taking about 5 min to test one sample of blood. An ARU value $\geqslant 550$ is consistent with no platelet dysfunction whereas values <550 are consistent with platelet dysfunction. Aspirin resistance based on the Ultegra RPFA is defined as an ARU $\geqslant$ 550 in a patient taking aspirin. The threshold value of 550 ARU was determined by correlation with adrenaline-induced light transmission aggregometry in aspirin-naive patients tested before and then between 2 hours and 30 hours after aspirin ingestion.[11]

Patients received 100 mg aspirin dose as is standard management in the Royal Melbourne Hospital Comprehensive Stroke Centre. Aspirin resistance was recorded as a dichotomous variable, all patients with ARU value <550 and known to be taking aspirin were regarded as aspirin sensitive.

2.4. Analyses

All statistical analyses were performed using STATA 9 (StataCorp LP., College Station, TX, USA). Continuous variables are expressed as median and range. Dichotomous variables are presented as percentages. The relative frequency of dichotomous baseline and clinical variables among aspirin-resistant, compared to aspirin-sensitive, patients was analysed using odds ratios (OR) and their 95% confidence intervals (CIs) with the Fisher's exact test calculated. Logistic regression was used for the continuous variable of age to assess association with aspirin resistance. Statistical significance was defined as $p < 0.05$. However, this pilot study does not have sufficient power to provide statistically significant results because it was designed to provide indications for future research.

3. Results

We studied 50 ischaemic stroke patients admitted to the Royal Melbourne Hospital Comprehensive Stroke Centre during the recruitment period (Table 1). The median age of patients was 77 [51.4–93.6], 74% were male and 98% were Caucasian.

3.1. Prevalence of aspirin resistance

Fifteen out of 50 patients (30%) were found to be aspirin resistant. The distribution of ARU values is shown in