Platelet Function-Guided Modification in Antiplatelet Therapy after Acute Ischemic Stroke is Associated with Clinical Outcomes in Patients with Aspirin Nonresponse

Xingyang Yi, Jing Lin, Chun Wang, Ruyue Huang, Zhao Han and Jie Li

1Department of Neurology, People’s Hospital of Deyang City, China
2Department of Neurology, Third Affiliated Hospital of Wenzhou Medical University, China
3Department of Neurology, the Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University China
4both authors contributed equally

Abstract

Background: Antiplatelet therapy nonresponse is associated with worse clinical outcomes. The aim of this study was to investigate the association of clinical outcomes with platelet function-guided modifications in antiplatelet therapy in patients with ischemic stroke.

Methods: This is a retrospective, multicentre study. From August 2010 to December 2014, 812 patients with ischemic stroke underwent platelet function testing using platelet aggregation. Aspirin nonresponse was defined as a mean platelet aggregation ≥20% with 0.5 mM arachidonic acid and/or ≥70% with 10 μM adenosine diphosphate. Antiplatelet therapy modification was defined as any increase in antiplatelet therapy after testing. Clinical outcomes were compared between patients with and without antiplatelet therapy modifications using univariate and propensity score-adjusted analyses.

Results: Among 812 patients, 223 patients had aspirin nonresponse. 204 patients were modified in antiplatelet therapy after platelet function testing. The incidence rates of ischemic events, death, or bleeding events were not significantly different between the patients with and without antiplatelet therapy modification. However, in patients with aspirin nonresponse, antiplatelet therapy modification was associated with decreased ischemic events (hazard ratio, 0.68; 95% CI, 0.61-0.95; P = 0.01) and ischemic stroke (hazard ratio, 0.71; 95% CI, 0.64-0.99; P = 0.04) compared with no modification in antiplatelet therapy. No differences in bleeding events were observed between two groups.

Conclusions: In patients with aspirin nonresponse, platelet function-guided modification in antiplatelet therapy after an ischemic stroke was associated with significantly lower rate of ischemic events. The platelet function testing is may be useful to guide antiplatelet therapy modification.

Introduction

Stroke is a leading cause of mortality and disability [1]. The risk of recurrent stroke is very high after ischemic stroke in China [2]. After an ischemic stroke or Transient Ischemic Attack (TIA) of arterial origin, antiplatelet therapy, such as aspirin or clopidogrel is currently recommended to reduce the risk of recurrent ischemic events [3,4]. However, the response to aspirin is variable [5,6]. The prevalence of aspirin nonresponse ranges from 5% to 60% [7,8]. Our previous studies showed that nonresponse to aspirin in patients with ischemic stroke is associated with an increased risk of Recurrence Ischemic Stroke (RIS) and worse functional status [6,9].

Despite aspirin nonresponse signifying a risk factor for adverse events, there are no widely accepted standardized treatment recommendations for these patients. Increasing the dose of aspirin might reduce the rate of aspirin nonresponse, and prevent occurrence of vascular events, [10,11] but this may increase the risk of a hemorrhagic event [12]. Adding an additional antiplatelet agent combination therapy may be useful. The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial showed that the combination of clopidogrel and aspirin for the first 21 days is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage in patients with TIA or minor stroke [13]. However, the MATCH (management of atherothrombosis with clopidogrel in high-risk patients with recent transient ischaemic attack or ischaemic stroke) trial found that long-term combination of clopidogrel and aspirin was not more effective than clopidogrel alone in preventing recurrent ischemic events, and the risk of life-threatening or major bleeding is increased [14]. Substitution of aspirin with other antiplatelet drugs is thought to offset the effect of antiplatelet drug resistance,
and may help prevent the occurrence of vascular events [10]. In a trial of patients receiving coronary stents showed no significant improvements in clinical outcomes with platelet-function monitoring and treatment adjustment for coronary stenting [15]. Improvement in clinical outcomes by intensifying antiplatelet therapy has also not been demonstrated in patients with ischemic stroke or TIA [16,17]. A retrospective study showed that platelet function-guided modification in antiplatelet therapy after an ischemic stroke or TIA was associated with significantly increased rates of death, ischemic events, or bleeding events [12]. However, Alberts reported that modification in antiplatelet therapy according to platelet function testing was reasonable [18]. Researchers of the latter studies maintain, however, that more data are required before any firm conclusion can be drawn.

The aim of the present study was to investigate the clinical efficacy and safety associated with platelet function-guided modifications in antiplatelet therapy in patients with acute ischemic stroke.

Materials and Methods

Study population

This retrospective, multicentre study was jointly conducted by the People’s Hospital of Deyang City, the second, and third Affiliated Hospital of Wenzhou Medical University. The study protocol was approved by the Ethics Committee at the participating hospitals.

We consecutively enrolled 812 patients who underwent a first-ever ischemic stroke and were admitted to the participating hospitals within 72 hrs of the onset of stroke between August 2010 and December 2014. The inclusion criteria were: (1) age ≥ 40 years old; (2) all patients underwent platelet function testing; (3) all patients were receiving aspirin monotherapy before the platelet function testing; (4) absence of any endovascular or surgical treatment for stroke. Exclusion criteria were: (1) cerebral embolism or undetermined etiologies of ischemic stroke; (2) patients whose antiplatelet therapy was decreased or who had warfarin added during observational phase; (3) loss to follow-up.

All enrolled patients received standard therapies based on the guidelines for the prevention of stroke in patients with stroke and TIA3. All patient data were obtained through the electronic medical record system and/or paper charts and were independently verified by the authors. Hypertension was defined as the mean of three independent measures of BP ≥140/90 mmHg or the use of antihypertensive drugs. Diabetes mellitus was diagnosed by any one of these criteria: prolonged angina >30 min; total creatinine kinase isoenzyme elevation more than twice the upper limit of normal; electrocardiographic evidence of infarction.

Secondary outcomes included death and bleeding events. Death was defined as all-cause mortality. Bleeding events were defined according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) bleeding classification [20]. GUSTO Severe or life-threatening bleeding was defined as any intracranial hemorrhage or bleeding that causes hemodynamic compromise requiring intervention. Any bleeding that required blood transfusion in the absence of hemodynamic compromise was considered GUSTO moderate bleeding. GUSTO minor bleeding was defined as any bleeding that did not meet criteria for severe or moderate bleeding.

Follow-up was performed by telephone interview and by reviewing the medical charts of each participant regardless of aspirin resistance status. The researchers who performed follow-up interviews were blinded to aspirin sensitivity status. Scheduled follow-up telephone calls were made after discharge to support proper compliance, answer any queries, and record complaints of any side effects. For those patients who reached at least one of the primary end points, a medical chart review was initiated to determine whether the event met the definitions described earlier. The terminal time of follow-up was January 31, 2016.

Statistical analysis

All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Differences between the antiplatelet therapy modification and no modification groups were analyzed by univariate methods. Categorical variables are presented as frequencies and percentages and compared using the Chi-square or Fisher’s exact tests. Continuous variables are expressed as mean ± Standard Deviation (SD) and compared using the Student’s t-test. Survival function estimates for clinical outcomes were evaluated through
There was no significant difference in other risk factors between the patients with aspirin nonresponse than in those with AS (P<0.001). The rate of diabetes mellitus and the level of fasting glucose were higher in patients with aspirin nonresponse and those with AS. The rate of platelet function testing. Table 1 compares the parameters between patients, 223 patients (27.5%) had aspirin nonresponse according to aspirin dosage.

Propensity scores were created for antiplatelet therapy modification and no modification groups. Propensity scores were calculated using Cox proportional hazards model for each outcome was created with and without propensity score adjustment. All tests were two-sided, and the Wald chi-square statistic before and after propensity score adjustment. A Cox proportional hazards model for each outcome was created with and without propensity score adjustment. After adjusting for propensity score, none of the variables used to create propensity score were found to be significantly different between groups. An additional analysis on matched propensity scores was conducted and standardized differences were calculated to determine covariate balance before and after matching. A Cox proportional hazards model for each outcome was created with and without propensity score adjustment. All tests were two-sided, and P values of 0.05 were considered to represent statistical significance.

Results

Characteristics of patients

All patients were administered 200 mg aspirin per day for 14 days after the onset of stroke and 100 mg/day thereafter. Among the 812 patients, 589 patients (72.5%) had aspirin nonresponse according to aspirin sensitivity. Table 1 compares the parameters between patients with aspirin nonresponse and those with AS. The rate of diabetes mellitus and the level of fasting glucose were higher in patients with aspirin nonresponse than in those with AS (P<0.001). There was no significant difference in other risk factors between the two groups.

AntiplATElet therapy modification

Among the 812 patients, 204 patients (25.1%) were modified in antiplatelet therapy after platelet function testing (154 in aspirin nonresponse group, 50 in AS group). Baseline characteristics for the patients with (n = 204) and without (n = 608) antiplatelet therapy modification were shown in Table 2. Patients who underwent antiplatelet therapy modification were older, had higher platelet aggregation with AA or ADP compared with patients without antiplatelet therapy modification. Aspirin nonresponse was significantly higher in patients with antiplatelet therapy modification compared with patients without any modification.

The diverse modifications in antiplatelet regimens used after platelet function testing was at the physician's discretion. The antiplatelet therapy modifications after platelet function testing are shown in Table 3. Changing from aspirin to clopidogrel (n = 126, 61.8%) was the most common modifications. Clopidogrel was added to aspirin in 37 patients (18.1%). 23 patients (11.3%) were changed from aspirin to cilostazol. 18 patients (8.8%) were increased the aspirin dosage.
In aspirin nonresponders (n = 223), antiplatelet therapy was modified in 154 patients by changing from aspirin to clopidogrel (n = 97), adding clopidogrel to aspirin (n = 32), changing from aspirin to cilostazol (n = 15), increasing the aspirin dosage (n = 10). No changes were observed in the distribution of baseline characteristics when compared in patients with and without antiplatelet therapy modification for the aspirin nonresponse subgroups.

**Clinical outcomes**

Clinical follow-up was available for all patients with a mean follow-up period of 3.8 ± 1.4 years (ranged from 1 to 5.1 years). Ischemic events occurred in 159 (19.6%) patients (105 had ischemic stroke, 34 had TIA and 20 had MI). Bleeding events occurred in 77 (9.5%) patients. The incidence rates of ischemic events, bleeding events, and death were not significantly different between the patients who underwent antiplatelet therapy modification compared with patients without modification (all P>0.05, Table 4). With regard to the patients in whom clopidogrel was added, the rate of bleeding was significantly higher than patients without modification (24.3% [95/376] versus 9.2% [56/608], P<0.001). Retesting platelet function at 10 days after antiplatelet therapy modification was performed in 105 patients (51.5%). In patients with aspirin nonresponse, 76% were responsive by adding clopidogrel, 52% were responsive by changing from aspirin to cilostopogrel or cilostazol, and 41% were responsive by increasing the aspirin dosage.

In patients who were nonresponsive to aspirin (n = 223), ischemic events occurred in 45 (20.2%) patients (30 had ischemic stroke, 9 had TIA and 6 had MI). Antiplatelet therapy modification (n = 154) compared with no modification (n = 69) was associated with decreased ischemic events (15.6% versus 30.4%, P<0.001, Table 5), which was primarily due to a decrease in ischemic stroke (9.1% versus 23.2%, P = 0.007, Table 5). Kaplan-Meier estimates of cumulative freedom from ischemic event (log-rank P<0.001, Figure A), and ischemic stroke (log-rank P = 0.008, Figure B) were significantly lower in patients without antiplatelet therapy modification compared with patients who underwent modification in aspirin non-responders. However, there were no significant differences in incidence rates of bleeding events and death between the 2 groups (Table 5). In patients with aspirin response, antiplatelet therapy modification (n = 50) compared with no modification (n = 539) was not associated with ischemic events, bleeding events, or death (all P>0.05).

In patients with aspirin nonresponse, the unadjusted and propensity score-adjusted hazard ratios for clinical outcomes with and without modification of antiplatelet therapy are shown in Table 6. With propensity score adjustment, antiplatelet therapy modification was associated with lower rates of ischemic event (hazard ratio, 0.68; 95% CI, 0.61-0.95; P = 0.01) or ischemic stroke (hazard ratio, 0.71; 95% CI, 0.64-0.99; P = 0.04) compared with no modification. No significant differences were seen in the propensity score-adjusted individual rates of death, or bleeding events between the 2 groups. In additional analyses performed after propensity score matching.

**Table 3: Modification in Antiplatelet Therapy after Platelet Function Testing.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Antiplatelet Therapy Modification (n=204)</th>
<th>No (n = 69)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic events (n, %)</td>
<td>35 (17.2)</td>
<td>124 (20.4)</td>
<td>0.29</td>
</tr>
<tr>
<td>Ischemic stroke (n, %)</td>
<td>24 (11.8)</td>
<td>81 (13.3)</td>
<td>0.53</td>
</tr>
<tr>
<td>Transient ischemic attack (n, %)</td>
<td>7 (3.4)</td>
<td>27 (4.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>Myocardial infarction (n, %)</td>
<td>4 (2.0)</td>
<td>16 (2.6)</td>
<td>0.63</td>
</tr>
<tr>
<td>Any bleeding event</td>
<td>21 (10.3)</td>
<td>56 (9.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>GUSTO minor (n, %)</td>
<td>10 (4.9)</td>
<td>28 (4.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>GUSTO moderate (n, %)</td>
<td>8 (3.9)</td>
<td>20 (3.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>GUSTO severe (n, %)</td>
<td>3 (1.5)</td>
<td>11 (5.4)</td>
<td>0.94</td>
</tr>
<tr>
<td>Gastrointestinal bleeding (n, %)</td>
<td>2 (1.0)</td>
<td>7 (1.2)</td>
<td>0.98</td>
</tr>
<tr>
<td>Intracerebral hemorrhage (n, %)</td>
<td>5 (2.5)</td>
<td>16 (2.6)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

**Table 4: Clinical Outcomes in Patients with or without Antiplatelet Therapy Modification.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR(95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic events</td>
<td>0.65 (0.52-0.86) &lt; 0.001</td>
<td>0.68 (0.61-0.95) 0.01</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.67 (0.58-0.97) 0.003</td>
<td>0.71 (0.64-0.99) 0.04</td>
</tr>
<tr>
<td>Bleeding event</td>
<td>1.32 (0.74-2.35) 0.53</td>
<td>1.38 (0.86-4.24) 0.67</td>
</tr>
<tr>
<td>Death</td>
<td>1.36 (0.62-3.82) 0.55</td>
<td>1.43 (0.92-4.13) 0.61</td>
</tr>
</tbody>
</table>
Kaplan-Maier analysis of cumulative freedom from ischemic
Kaplan-Maier analysis of freedom from ischemic stroke

Discussion

In present study, all patients underwent platelet function testing, antiplatelet therapy was modified in 204 patients after platelet function testing. The incidence rates of ischemic events, death, bleeding events were not significantly different between the patients who underwent antiplatelet therapy modification compared with no modification. However, in patients with aspirin nonresponse, antiplatelet therapy modification was associated with decreased ischemic events and ischemic stroke compared with no modification.

The prevalence of aspirin nonresponse was 27.5% in this study, and was similar to the prevalence reported in our previous studies [6,9,21] and some other studies [7,22]. A very recent systematic review and meta-analysis also showed that the prevalence of High on-Treatment of Platelet Reactivity (HTPR) on ASA was 23% (95%CI: 20-28%), indicates that the patients with HTPR had a significantly higher risk for ischemic stroke recurrence (RR=1.81, 95%CI: 1.30-2.52; P<0.001) [23]. The finding is consistent with our present study. The mechanisms associated with aspirin nonresponse are complex and multifactorial, such as noncompliance, diabetes mellitus, reduced absorption, the biosynthesis of thromboxane A2 from pathways not inhibited by aspirin as well as alternative pathways involved in platelet activation not blocked by aspirin [7,9,21,22]. Several studies have shown that nonresponse to aspirin is associated with more frequent neurologic deterioration, less frequent clinical improvement, and greater risk of recurrent ischemic events in patients with acute ischemic stroke [6,9,24,25]. However, the majority of aspirin nonresponse reported in the literature may be the result of poor adherence and clinical factors that predict aspirin nonresponse are not consistent between different platelet function tests.26 Platelet function testing is not recommended in the current guidelines for management of ischemic stroke [3].

In patients with aspirin nonresponse, preventing recurrent ischemic stroke after ischemic stroke with aspirin therapy remains a challenge. Alberts suggested that modification in antiplatelet therapy according to platelet function testing was reasonable.18 our present data showed that antiplatelet therapy modification was associated with decreased ischemic events and ischemic stroke compared with no modification in patients with aspirin nonresponse. This was inconsistent with other results [12,15]. Collet et al. [15] reported that there were no significant improvements in clinical outcomes with platelet-function monitoring and treatment adjustment for coronary stenting. Depta et al. [12] showed that modification in antiplatelet therapy after an ischemic stroke or TIA was associated with significantly increased rates of death, ischemic events, or bleeding compared with no modification. However, the retrospective study only analyzed 324 patients, the small samples are may be a important cause for the conflicting results.

There are no standardized treatment recommendations for these patients with aspirin nonresponse. In this study, stratified analyses showed that antiplatelet therapy modification was associated with decreased ischemic events and ischemic stroke, and increased platelet inhibition in these patients. Antiplatelet therapy modification included changing from aspirin to clopidogrel or cilostazol, adding clopidogrel to aspirin, and increasing the aspirin dosage in the study. Increasing the dose of aspirin might reduce the incidence of aspirin nonresponse, and prevent occurrence of vascular events [10,11], but higher doses of aspirin may increase the risk of a hemorrhagic event [12]. Dual antiplatelet therapy with aspirin and clopidogrel for the first 21 days or 30 days in patients with acute ischemic stroke can reduce the risk of stroke, and improve 6-month outcome [13,27,28]. However, long-term combination of clopidogrel and aspirin was not more effective than clopidogrel alone in preventing recurrent ischemic events, and the risk of life-threatening or major bleeding is increased [14]. Our results also showed the rate of bleeding was significantly higher in patients in whom clopidogrel was added than
patients without modification. Thus, increasing the dose of aspirin or long-term dual antiplatelet therapy with aspirin and clopidogrel for the secondary prevention of ischemic stroke may be inadequate for these patients. Substitution of aspirin with another antiplatelet drug (like clopidogrel or cilostazol) is thought to optimize regimen, and may help prevent the occurrence of vascular events [29,30]. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial demonstrated that clopidogrel is more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death in patients with atherosclerotic vascular disease [29]. A meta-analysis to estimate the efficacy of antiplatelet agents for secondary prevention of recurrent stroke demonstrated that cilostazol was significantly more efficient than other antiplatelet agents in Asian patients [29]. Our results are consistent with the previous studies [29,30].

Several important limitations of our study should be considered. First, our study is retrospective and observational, and this may limit the generalizability of the results. Additionally, the diverse modifications in antiplatelet regimens used after platelet function testing was at the physician’s discretion. It is unknown what clinical factors led each physician to decide which therapeutic regimen to use after platelet function testing, thus making it very difficult to control for selection bias. Second, several laboratory tests are used to assess the response to aspirin, including LTA, bleeding time, platelet function analyzer-100, the Verify Now Aspirin system. Each method has its own advantages and disadvantages [31]. However, platelet aggregation was only measured using the LTA in this study. Third, retesting platelet function after antiplatelet therapy modification was only performed in 105 patients, the infrequency of retesting limited our ability to determine if responsiveness after antiplatelet therapy modification resulted in any clinical benefit. Furthermore, although careful analysis was performed to account for any differences between patients with and without antiplatelet therapy modification, unknown confounders may have contributed to the differences in clinical outcomes between both groups. Therefore, our findings must be validated in multi-center and randomized-controlled trials.

In conclusion, platelet function testing may be useful as a marker of increased risk for recurrent events after ischemic stroke. In patients with aspirin nonresponse, antiplatelet therapy modification was associated with decreased ischemic events and ischemic stroke compared with no modification. The results of our study indicate that platelet function testing is likely to be useful to guide antiplatelet therapy modification, and optimize clinical outcomes, although our results should be interpreted with caution given the possible confounding role of selection bias. Randomized-controlled trials are needed to determine if a platelet function-guided approach is beneficial and safe to prevent recurrent events after ischemic stroke in future.

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