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Prediction of hemorrhagic transformation in patients with mild atrial fibrillation-associated stroke treated with early anticoagulation: post hoc analysis of the Triple AXEL Trial

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ABSTRACT

Objectives: To investigate the predictors of hemorrhagic transformation (HT) in patients with mild atrial fibrillation-related stroke who were treated with early anticoagulation. We conducted a post-hoc subgroup analysis from Acute Cerebral Infarction Patients with Non-valvular Atrial Fibrillation (Triple AXEL) study.

Patients and methods: The Triple AXEL study was a randomized, multicenter, open-label, blinded end-point evaluation, comparative phase 2 trial. To identify the relationship between the type of HT and risk factors. We analyzed various factors using data from the Triple AXEL study, such as sex, history of hypertension, diabetes, microbleeds, concomitant antiplatelet use, initial infarction volume, initial infarction location, and new intracranial hemorrhage on follow-up gradient recalled echo or susceptibility-weighted imaging.

Results: We analyzed various factors by dividing patients into a new HT group and a no HT group. No correlation was found between HT and risk factors that were significantly associated with HT, including age, sex, history of hypertension, diabetes, microbleeds, concomitant antiplatelet use, and initial infarction volume. When the initial infarction was classified into anterior circulation infarction (ACI) and posterior circulation infarction (PCI), the occurrence of new HT was significantly more associated with PCI than with ACI (57.6% vs 24.0%, P = 0.001). Multivariate logistic regression analysis was performed using HT as a response variable. Only the location of initial infarction according to the vascular territory contributed to the increased risk of HT (OR2.3, 95%CI1.33–3.91, P = 0.003).

Conclusion: PCI is a very important independent risk factor for HT in patients with mild AF-related stroke treated with early anticoagulation.

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1. Introduction

Hemorrhagic transformation (HT) refers to intracerebral hemorrhage following acute cerebral infarction [1]. The estimate of its incidence after acute cerebral infarction ranges from 8.5 to 30% [1,2]. HT develops more frequently in patients with acute cardioembolic stroke than in patients with other stroke subtypes [1,3], and anticoagulation therapy increases the risk of HT [4,5]. Among various etiologies, atrial fibrillation (AF) remains the most common cause of cardioembolic stroke [6,7]. Therefore, the prevention of HT in patients with AF-related stroke who receive anticoagulation is important.

Many previous studies have identified predictors of HT. However, most information on the effect of early HT on clinical outcomes derives from studies on thrombolysis for ischemic stroke [8–10]. Furthermore, predictors of HT have not been sufficiently studied in patients with mild AF-related stroke treated with early anticoagulation. The ability to predict HT can enable safe initiation of anticoagulation therapy, even during the acute phase of cardioembolic stroke, and may improve patient outcomes [11]. Data from the Effects of Rivaroxaban Versus Warfarin on Ischemia, Bleeding, and Hospital Stay in Acute Cerebral Infarction Patients with Non-valvular Atrial Fibrillation (Triple AXEL) study showed that rivaroxaban and warfarin initiated within 5 days of stroke onset in patients with mild AF-related acute ischemic stroke were comparably safe and effective [12]. In terms of new intracranial hemorrhage, there was no difference between rivaroxaban and warfarin on follow-up magnetic resonance imaging (MRI) at 4 weeks. In addition, there were no differences between the 2 groups in the individual components of new intracranial hemorrhage and all cases of intracranial hemorrhage were HT. We analyzed data from those Triple AXEL patients with new intracranial hemorrhage to investigate the prediction of HT in patients with mild AF-related stroke treated with early anticoagulation.

2. Materials and methods

2.1. Study design and participants

We conducted a post hoc subgroup analysis of the Triple AXEL study. The rationale and study design for the Triple AXEL study have been described in detail [12]. Briefly, the Triple AXEL study was a randomized, multicenter, open-label, blinded end-point evaluation, comparative phase 2 trial. The trial was conducted from April 28, 2014, to December 7, 2015, at 14 academic medical centers in South Korea among patients with mild AF-related stroke within the previous 5 days who were deemed suitable for early anticoagulation. Mild stroke was defined by acute ischemic lesion on diffusion-weighted imaging (DWI) of less than one-third of the middle cerebral artery territory, one-half of the anterior cerebral artery territory, one-half of the posterior cerebral artery territory, and one-half of one cerebellar hemisphere [12]. This study was designed and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent from eligible patients or their legally authorized representatives was obtained. The trial was registered with http://www.ClinicalTrials.gov (Identifier: NCT02042534). The trial randomized a total of 195 patients. Participants were randomized 1:1 to receive rivaroxaban 10 mg/d for 5 days, followed by 15 or 20 mg/d, or warfarin with a target international normalized ratio of 2.0–3.0, for 4 weeks. Of 195 randomized patients, 183 (76 women and 107 men; mean [SD] age, 70.4 [10.4] years) completed MRI follow-up and were included in the primary end-point analysis. The primary composite outcome showed that both rivaroxaban and warfarin initiated within 5 days of onset in patients with mild AF-related acute ischemic stroke were safe and effective for preventing early clinical stroke recurrence. The current subgroup analysis sought to identify clinical risk factors or predictors of HT in patients treated with early anticoagulation. This analysis focused on HT risk in 183 patients who completed MRI follow-up.

2.2. Data collection and analysis

Data on the following were recorded: sex, history of hypertension, hyperlipidemia, or diabetes, microbleeds, concomitant antiplatelet use, initial infarction volume, initial infarction location, anticoagulation after stroke, and new intracranial hemorrhage (HT, intracerebral hemorrhage, subarachnoid hemorrhage, subdural hematoma, or epidural hematoma), including symptomatic or asymptomatic hemorrhage on follow-up gradient recalled echo or susceptibility-weighted imaging. To assess the volume of initial infarction, we used the ABC/2 formula (ellipsoid) [13].

To determine the location of initial infarction, we defined 2 initial DWI patterns: (1) cortico-subcortical infarction, cortical infarction, and subcortical infarction, and (2) vascular territories divided according to anterior circulation infarction (ACI), posterior circulation infarction (PCI), and multiple infarcts involving both anterior and posterior circulation (APCI). Anterior circulation includes the anterior cerebral artery, the middle cerebral artery (superior division, inferior division, and lenticulostriate), a single penetrating artery in the deep structure or white matter, the anterior choroidal artery, and watershed; the posterior circulation includes the posterior cerebral artery, circumferential branches of the basilar artery, cerebellar arteries (superior, anterior inferior, and posterior inferior), and cerebellar watershed [14]. MRI was jointly interpreted by two investigators blinded to the clinical data, with interpretation by a third investigator in cases of disagreement.

2.3. Statistical analyses

The chi-square test was used to analyze between-group differences. Differences in continuous variables were assessed using Student's t-test. The Bonferroni correction was used for multiple testing. The relationship between the type of HT and risk factors was assessed using univariate and multivariate logistic regression, with HT as the response variable and related factors as the explanatory variables. All variables were subjected to multiple logistic regression analysis to identify independent predictors of HT. A two-sided P-value < 0.05 was considered statistically significant. To avoid misinterpretations by multiple testing, Bonferroni correction (α/number of comparisons) was used to counteract the problem of multiple comparisons in three types of initial infarct locations, which set the significance at a P value of $0.05/3 = 0.0167$. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient demographics

Of 195 patients registered in the Triple AXEL study from 14 sites in Korea, 183 (93.8%) were included in the main analysis. All 183 completed MRI follow-up and were eligible for inclusion in the host hoc subgroup analysis. In the Triple AXEL study, new intracranial hemorrhage was seen in 30 patients (31.6%) in the rivaroxaban group and 25 of 87 (28.7%) in the warfarin group. There was no statistically significant difference between the rivaroxaban group and the warfarin group (relative risk, 1.10; 95% confidence interval, 0.70–1.71; $P = 0.68$) in the Triple AXEL study. All cases of intracranial hemorrhage showed asymptomatic HT within or adjacent to the qualifying ischemic lesion. Of 55 HT cases, 49 (89.1%) were hemorrhagic infarctions and 6 (10.9%) were type I parenchymal hematomas.

We analyzed various factors by dividing patients into a new HT group and a no HT group. Table 1 summarizes the baseline characteristics of both groups at 4-week follow-up MRI. The analysis of multiple variables, including age, sex, history of hypertension, hyperlipidemia, or diabetes, concomitant antiplatelet agent use, microbleeds, initial infarction volume, and anticoagulation after stroke showed no significant between-group differences.