Short-term Bleeding Events Observed with Clopidogrel Loading in Acute Ischemic Stroke Patients

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Introduction: The Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence trial raised concern that loading doses of clopidogrel may increase hemorrhagic complications. We investigated if similar rates of hemorrhage occur in patients with acute ischemic stroke (AIS) of varying severity. *Methods:* Patients meeting inclusion criteria were divided into 2 groups: the LOAD group and non-LOAD group. The LOAD group was defined as patients who were administered a loading dose of 300 mg or more of clopidogrel with or without aspirin within 24 hours of admission. The non-LOAD group was devised using propensity score (PS): 55 patients who received a loading dose of clopidogrel of 300 mg or more were matched on PS to 55 patients who did not receive loading doses. These patients were taken from a pool of 341 consecutive ischemic patients ineligible for intravenous or intra-arterial fibrinolysis, 162 of whom received a clopidogrel loading dose and the remainder of whom did not. The frequency of hemorrhage was compared between the 2 groups using Student *t* test and chi-square. Logistic regression was used to assess the relationship between loading dose and serious bleeding events (symptomatic intracerebral hemorrhage [sICH] or transfusion for systemic bleeding). *Results:* AIS patients (N = 596) were screened during the 31-month period of this retrospective study. Of this sample, 170 patients were excluded: 149 patients were excluded because they were treated with intravenous tissue plasminogen activator (IV t-PA) alone, 11 were excluded because they were treated with IV t-PA combined with intra-arterial therapy (IAT), and 10 were excluded for treatment with IAT alone. An additional 85 patients were excluded because they were not admitted to the stroke service or because they had an in-hospital stroke. Baseline characteristics of the groups were well matched. There were no significant differences in the rates of sICH, transfusion, hemorrhagic transformation, or systemic bleeding. Clopidogrel loading was not associated with increased odds of serious

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bleeding events in the crude model (odds ratio [OR] .92, 95% confidence interval [CI] .27-3.13) or after adjusting for covariates and confounders of interest (OR 1.06, 95% CI .28-4.04). *Discussion:* Contrary to our original hypothesis, patients with AIS receiving clopidogrel loading doses within 24 hours of symptom onset did not appear to experience a higher rate of new serious bleeding events during acute hospitalization when compared with patients who did not receive loading doses. The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke trial is expected to provide insight into the safety of clopidogrel loading as an acute intervention after cerebral ischemia. **Key Words:** Acute stroke—clopidogrel—loading—antiplatelet—hemorrhage.

Introduction

Given the high incidence of recurrence and progression during the early stages of ischemic stroke, achieving early maximum platelet inhibition may be an important strategy for preventing neurologic deterioration. Although there is evidence to support aspirin therapy within the first 48 hours after the onset of acute ischemic stroke (AIS), the absolute risk reduction for recurrent stroke is less than 1%.[1] Studies support the use of dual antiplatelet therapy (clopidogrel and aspirin) at high "loading" doses in other vascular occlusive diseases (ie, acute myocardial infarction) and with percutaneous coronary interventions.[2-7] However, the benefits of platelet inhibition on reducing major vascular events after stroke may be offset by the risk of hemorrhagic complications.

Although previous studies have reported increased bleeding in stroke patients treated with dual antiplatelet therapy,[8] limited safety data exist for patients treated during the acute period. A small retrospective review comparing patients with AIS or transient ischemic attack (TIA) who received loading doses of clopidogrel and aspirin to historical controls reported low rates of systemic and intracranial hemorrhage.[9] In a pilot study where patients were randomized within 24 hours of symptom onset to placebo or clopidogrel loading, the latter demonstrated a protective effect on stroke recurrence at the cost of increased bleeding.[10] However, this study was conducted in patients with TIA or mild stroke. We investigated rates of bleeding in patients with AIS of varying severity. We hypothesized that clopidogrel loading for more severe strokes would be associated with higher rates of bleeding.

Methods

Study Participants

After approval by our Institutional Review Board, consecutive AIS patients who were admitted to the Tulane Stroke Service within 24 hours of symptom onset between June 2008 and December 2010 were screened. Patients who experienced in-house strokes or patients who were treated with intravenous tissue plasminogen activator (IV t-PA) or intra-arterial therapy (IAT) were excluded. Patients meeting inclusion criteria were divided into 2 groups: the LOAD group and the non-LOAD group. The LOAD group was defined as patients who were administered a loading dose of 300 mg or more of clopidogrel with or without aspirin within the first 24 hours of admission. The aim was to quickly inhibit platelets in patients who presented early, but were not candidates for thrombolysis, and who we thought were at higher risk for stroke progression (suspected small vessel strokes and large vessel occlusions without territorial completed infarcts on baseline imaging). The non-LOAD group was defined as patients who were not administered a loading dose of clopidogrel.

Variables

Data on baseline demographics and clinical and imaging characteristics were collected prospectively as part of the Tulane Stroke Registry.[11] Stroke severity was measured by the National Institutes of Health Stroke Scale (NIHSS). Stroke mechanism was determined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[12] A retrospective review of computed tomography and magnetic resonance imaging scans of the head was conducted by a blinded rater to assess for intracranial hemorrhage according to the European Cooperative Acute Stroke Study criteria.[13] Symptomatic intracerebral hemorrhage (sICH) was defined as a PH-1 or PH-2 with increase in NIHSS greater than or equal to 4 points. Inpatient records were reviewed to determine if systemic bleeding occurred or if transfusion was performed during hospitalization. The composite end point of a new serious bleeding event was defined as either bleeding necessitating transfusion or sICH.

Study Design and Statistical Analysis

Data determined to be missing at random were addressed using multiple imputation techniques. Five data sets were generated. As exposure to clopidogrel loading was not based on random allocation, it was anticipated