Fibrinogen Decrease after Intravenous Thrombolysis in Ischemic Stroke Patients Is a Risk Factor for Intracerebral Hemorrhage

Laura Vandelli, MD,* Marco Marietta, MD,† Mariaelena Gambini, PhD,‡ Milena Cavazzuti, MD,* Tommaso Trenti, MD,§ Maria A. Cenci, MD,§ Federica Casoni, MD,* Guido Bigliardi, MD,* Roberta Pentore, MD,* Paolo Nichelli, MD, PHD,* and Andrea Zini, MD*

Background: Intravenous thrombolysis is an effective treatment in acute stroke patients, but it increases the risk of intracerebral hemorrhages. Our aim is to establish if fibrinogen depletion increases the risk of intracerebral hemorrhage after intravenous thrombolysis for acute ischemic stroke. *Methods:* In 104 ischemic stroke patients, treated with intravenous thrombolysis, we assessed the rate of intracerebral hemorrhages documented by computed tomographic scan at 24 hours and within 7 days post-treatment. Fibrinogen levels were determined at 2 hours after therapy: patients were classified as belonging to "low fibrinogen group" if levels decreased to less than 2 g/L and/or by 25% or more. Fibrinogen levels and other known hemorrhagic risk factors were studied using univariate and multivariate analyses. *Results:* During the first 7 days, an intracerebral hemorrhage was detected in 24 patients (23.1%), and only 6 of these (5.8%) experienced symptomatic bleeding; 41 patients were included in the low fibrinogen group. Among the 24 hemorrhages, 18 occurred in the low fibrinogen group and 6 in the "normal fibrinogen group": the bleeding rate in the low fibrinogen group was significantly higher (43.9%) than that in the normal fibrinogen group (9.5%; odds ratio [OR] 7.43, $P < .001$). Univariate and multivariate analyses revealed that only clinical severity (OR 1.15, $P < .001$) and hypofibrinogenemia (OR 7.47, $P < .001$) were significantly associated with brain bleeding at 7 days and at 24 hours ($P = .008$). *Conclusions:* An early fibrinogen reduction seems to increase the risk of intracerebral hemorrhage after rtPA treatment in ischemic stroke. Fibrinogen assessment could be a rapid, inexpensive, and widely available tool to help the identification of patients at higher risk of bleeding. **Key Words:** Fibrinogen—acute stroke—intracerebral hemorrhage—risk factors—thrombolysis—rtPA.

From the *Stroke Unit, Department of Neuroscience, University of Modena and Reggio Emilia, Nuovo Ospedale Civile S. Agostino-Estense, AUSL Modena, Modena; †Section of Haematology, Department of Oncology and Haematology, Policlinico of Modena, University of Modena and Reggio Emilia, Modena; ‡Environmental Protection Agency, ARPA Emilia Romagna District of Reggio Emilia, Reggio Emilia; and §Clinical Pathology-Toxicology, Nuovo Ospedale Civile S. Agostino-Estense, AUSL Modena, Modena, Italy.

Received March 21, 2014; revision received September 2, 2014; accepted September 6, 2014.

Disclosure: The authors report no conflicts of interest.

Address correspondence to Andrea Zini, MD, Neurology Clinic, Stroke Unit, Department of Neuroscience, University of Modena and Reggio Emilia, Nuovo Ospedale Civile S.Agostino-Estense, AUSL Modena, via Giardini, 1355 Baggiovara, 41100 Modena, Italy. E-mail: andrea.zini@me.com.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.09.005

Introduction

Thrombolytic therapy with administration of intravenous recombinant tissue plasminogen activator (iv rtPA) has been shown to improve long-term functional outcome, and it is recommended for the treatment of eligible acute ischemic stroke patients.[1] This therapy, however, is associated with an increased risk of symptomatic intracerebral hemorrhages (sICH). Symptomatic intracranial bleeding in stroke patients treated with iv rtPA is approximately 6%-8%[2-4] and is associated with a worse clinical outcome. It is, however, not known what proportion of a worse outcome is attributable to sICH as there is an overlap between the risk factors for thrombolysis-associated sICH and those for poor outcome after thrombolytic therapy with no sICH.[2]

Many studies have evaluated sICH risk factors in patients receiving thrombolytic therapy, and 2 recent systematic reviews identified the most relevant ones: hyperglycemia, early ischemic changes on computed tomography (CT)/magnetic resonance imaging scan, clinical stroke severity assessed by the National Institutes of Health Stroke Scale (NIHSS) score on admission, advanced age, and high blood pressure.[2,3,5-10]

The pathophysiological mechanisms of hemorrhagic cerebral transformations could result from the reperfusion of intracranial arteries whose integrity has been disrupted by cerebral ischemia, with an alteration in the blood–brain barrier and an increase in capillary permeability.[3]

Within this complex pathophysiological process, a central role is played by fibrinogen. rtPA binds to plasminogen within the clot, converting it to plasmin that is a proteolytic enzyme capable of breaking cross-links between fibrin molecules and so dissolving clots, releasing fibrin(ogen) degradation products (FDPs). It is important to note, however, that plasmin is fairly nonspecific in its activity and, besides fibrin, will also break down other circulating proteins, including fibrinogen.[11,12] In short, although rtPA is relatively selective for clot-associated fibrin, it can produce a systemic fibrinolytic state (with a secondary hypofibrinogenemia and a D-dimer increase[12]) and bleeding complications, which were first reported in the setting of the treatment of acute myocardial infarction (AMI). The Thrombolysis in Myocardial Infarction trial[13] showed that both streptokinase and rtPA caused a decrease in fibrinogen levels and an increase in FDP and that the rate of hemorrhagic events was higher in patients with increased FDP in both treatment groups and in patients with reduced fibrinogen levels in the rtPA group. Moreover, there were more hemorrhages in patients with greater plasma changes, underlining the importance of coagulation parameters.[13,14] Collen et al[15] analyzed coagulation and fibrinolysis parameters during intravenous rtPA infusions in patients with AMI and showed that the extent of fibrinogen breakdown is occasionally very important, with a decrease of fibrinogen level less than 1.0 g/L observed in 27% of rtPA-treated patients.

Experience and information on the subject of ischemic stroke are poor and sparse. Only 1 recent work by Matosevic et al[16] evaluated the extent of fibrinogen depletion in rtPA thrombolysis in stroke patients and its association with intracranial and extracranial bleeding: they showed that a fibrinogen decrease is a significant predictor for bleeding risk and that a temporal relationship exists with the manifestation of hemorrhage.

For these reasons, we decided to study early modifications in fibrinogen levels pre- and post-thrombolysis, to assess if they are significantly involved in iv rtPA-related ICH in ischemic stroke patients.

Materials and Methods

Study Population

We studied consecutive patients with acute ischemic stroke treated with iv infusion of Alteplase (Actilyse, a tPA produced by recombinant DNA technology) from January 1, 2010, to January 1, 2011, in our stroke unit. Patient's selection was made according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study criteria and the European Cooperative Acute Stroke Study-3 time window (<4.5 hours). A few of treated patients were included in randomized control trials, such as International Stroke Trial-3, Synthesis Expansion, and Thrombolysis in Elderly Stroke Patients in Italy trial, an Italian randomised controlled trial in patients older than 80 years.

The following data were collected on each patient: age, gender, clinical stroke severity assessed by NIHSS pre- and post-thrombolysis, fibrinogen level at admission and 2 hours after the end of rtPA infusion, baseline glycemia, baseline platelet count, and blood pressure levels.

Plasmatic Fibrinogen Dosage

Peripheral blood samples were drawn from each patient, on entry to the emergency room and 2 hours after the end of fibrinolytic infusion. Fibrinogen levels were determined on fresh plasma obtained from blood collected in 5-mL vacuum tubes containing .5 mL sodium citrate (.129 mol/L). The assay was performed using the HemosIL Fibrinogen-C kit assay based on the Clauss method on ACL TOP Coagulation Systems (Instrument Laboratory, Milan, Italy). The Fibrinogen-C kit uses an excess of thrombin to convert fibrinogen to fibrin in diluted plasma. At high thrombin and low fibrinogen concentrations, the rate of reaction is a linear function of the fibrinogen concentration.

Neuroimaging

On admission, all patients underwent a noncontrast brain CT scan, which was repeated about 24 hours and