Serum Uric Acid Is Neuroprotective in Chinese Patients with Acute Ischemic Stroke Treated with Intravenous Recombinant Tissue Plasminogen Activator

Xuan Liu, MD, Ming Liu, MD, Miao Chen, MD, PhD, Qin-Min Ge, MD, PhD, and Shu-Ming Pan, MD, PhD

Background: Exogenous uric acid (UA) is a neuroprotective antioxidant that reinforces the benefits of intravenous recombinant tissue plasminogen activator thrombolysis in animal thromboembolic stroke. However, whether serum uric acid (SUA) also increases the benefits of thrombolysis in Chinese patients with acute ischemic stroke (AIS) has yet to be fully defined. *Methods:* A total of 216 consecutive AIS patients of Chinese origin treated with intravenous thrombolysis were enrolled in a prospective stroke registry. Demographic and clinical characteristics, conventional risk factors, important laboratory data, and neurologic course were prospectively recorded. Functional outcomes were assessed with the modified Rankin Scale (mRS) score on day 90 by telephone calls. Receiver operating characteristic curves and binary logistic regression models were used to examine the performance of SUA in predicting excellent outcomes (mRS, 0-1). *Results:* SUA levels were significantly higher in patients with excellent outcomes than those in patients with poor outcomes (331.46 ± 103.39 versus 277.69 ± 105.62, $P = .008$). SUA had a modest power for predicting excellent outcomes as suggested by area under the curve of .665 ± .052, $P = .003$. In multivariate models, increased SUA levels (adjusted odds ratio, 1.005; 95% confidence interval, 1.002-1.009; $P = .033$) were associated with excellent outcomes independently of the effect of possible confounders. Spearman correlation tests indicated that there was an inverse correlation between SUA levels and stroke severity. *Conclusions:* Increased SUA levels are associated with excellent outcomes in Chinese patients with AIS treated with intravenous thrombolysis, giving additional support to administration of exogenous UA as an adjuvant to thrombolysis. **Key Words:** Acute ischemic stroke—thrombolysis—serum uric acid—neuroprotective.

Introduction

Serum uric acid (SUA) is the end oxidative product of purine metabolism.[1] In humans, the concentration of SUA is higher than that in most other mammals, indicating it may represent an evolutionary advantage owing to its antioxidant properties.[2] These properties include scavenging of hydroxyl radicals, hydrogen peroxide, and peroxynitrite; prevention of the Fenton reaction; chelation of transition metals; and suppression of lipid peroxidation.[3] On the other hand, it has been proposed that SUA may show both antioxidant and pro-oxidant properties depending on levels of other antioxidants, levels of

From the Department of Emergency, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

Received December 10, 2014; revision received January 2, 2015; accepted January 5, 2015.

This work was financially supported by the National Natural Science Foundation of China (no.81000212) and the Health Bureau Scientific Research Foundation of Shanghai (GWDTR201219).

Address correspondence to Shu-Ming Pan, MD, PhD, Department of Emergency, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, 1665 Kongjiang Road, Shanghai 200092, China. E-mail: drshumingpan@hotmail.com.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.01.011

oxidative stress, and time of interaction with the target tissues.[4]

Although a growing body of evidence has shown that exogenous uric acid (UA) may protect neurons against excitotoxic and metabolic insults in vitro[5] and reduce brain damage and improve the benefits of recombinant tissue plasminogen activator (rt-PA) in a rat model of thromboembolic stroke,[6] the relationship between SUA levels and clinical outcomes in acute ischemic stroke (AIS) patients has been discordant until now. Some studies showed high SUA may be an independent predictor of favorable outcomes after AIS[7] and may represent a consumptive and reproducible antioxidant in AIS.[8,9] On the contrary, large population-based studies have indicated that increased SUA is an independent risk factor for cardiovascular disease and stroke,[10–12] and a low SUA concentration is modestly associated with a good short-term outcome.[13] The precise role of SUA in AIS patients treated with thrombolysis is therefore still a matter of ongoing controversy, and this question deserves consideration because the antioxidant capacity of SUA may be promising to improve benefits in situations of oxidative-mediated reperfusion injury.

In the present study, we sought to investigate the association between admission SUA levels and short-term outcomes in a consecutive series of Chinese patients with AIS treated with thrombolytic therapy.

Materials and Methods

Study Population

This prospective trial involved consecutive Chinese patients with AIS treated with thrombolysis admitted to the stroke team of the Department of Emergency, Xinhua Hospital, affiliated to Shanghai Jiaotong University School of Medicine, between January 2011 and July 2014. Medical patients were eligible for thrombolysis if they met the criteria of the National Institute of Neurological Disorders and Stroke trial.[14] A brain computed tomography scan was performed before thrombolytic therapy to rule out the presence of hemorrhagic stroke and repeated at 24 ± 12 hours after thrombolysis or immediately whenever it was required in patients with worsening neurologic condition (at least 4-point increment in the National Institutes of Health Stroke Scale [NIHSS] score). Ten percent of the total calculated dosage (.9 mg/kg) of rt-PA was injected as an intravenous bolus, whereas the remainder was given by continuous intravenous infusion for more than 1 hour according to the National Institute of Neurological Disorders and Stroke trial.[14] All sequences were further confirmed using magnetic resonance imaging scanner with 1.5 T (Magnetom Symphony; Siemens Medical Systems, Erlangen, Germany). Etiologies were determined according to the Trial of ORG 10172 in Acute Stroke Treatment criteria[15] after an initial etiological work-up.

Patients with following conditions were excluded from thrombolysis: (1) intracranial hemorrhage, cerebral stroke of any etiology, or myocardial infarction in the past 3 months; (2) history of alimentary canal or urinary system hemorrhage or trauma in the last 3 weeks; (3) current anticoagulation therapy; (4) personal or family history of hemorrhagic tendency or hemorrhagic disease; (5) history of circulatory failure or uncontrolled hypertension, severe cardiac, renal, or hepatic inadequacy, severe diabetes, or current pregnancy.

The study was approved by Shanghai Jiaotong University Xinhua Hospital Ethics Committee and was carried out in accordance with the Declaration of Helsinki. Informed consents were obtained from all patients.

Blood Measurements

All blood samples for indicators were collected within a median (interquartile ranges [IQRs]) of 18 (14-21) hours of stroke onset and before any treatment was administered to avoid drug-biomarker interference. Venous blood (3 mL) was drawn into an EDTA-containing tube (BD Vacutainer, Becton, Dickinson and Company, Plymouth, UK) and centrifuged at 3000 rpm for 15 minutes at room temperature, and plasma was then frozen at −80°C until analysis. SUA levels were measured using standard laboratory procedures with urate oxidase reagent on a Dax analyzer (Bayer-Technichon) with an interassay coefficient of variation 3%-5%. The normal range of SUA concentration in our laboratory is 149-416 μmol/L.

Study Outcomes

Demographic and clinical characteristics, conventional risk factors, important laboratory data, and neurologic course were prospectively recorded. Neurologic impairment and physical function were evaluated by stroke neurologists on admission and on day 1 and day 7 after admission using the NIHSS score. The short-term clinical progress was defined as the difference between the NIHSS score on admission (NIHSS0) and the NIHSS score on day 7 (NIHSS7) (Δ-NIHSS = NIHSS0 − NIHSS7).[16,17] A positive Δ-NIHSS value indicated clinical improvement, whereas a negative value indicated clinical worsening. Patients who survived the acute phase and were discharged home or to an inpatient rehabilitation facility were further followed up, and their functional outcomes were assessed with the modified Rankin Scale (mRS) score on day 90 via telephone calls.[18] An excellent outcome was defined as an mRS score of 0-1 and a poor outcome as an mRS score of 2-6.

Statistical Analysis

Continuous variables were presented as mean values ± standard deviation or median with IQR, whereas categorical variables were expressed as percentages. The