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Uric Acid Levels Are Relevant in Patients With Stroke Treated With Thrombolysis

Sergio Amaro, MD; Xabier Urra, MD, PhD; Manuel Gómez-Choco, MD; Víctor Obach, MD; Álvaro Cervera, MD, PhD; Martha Vargas, PhD; Ferran Torres, MD, PhD; Jose Rios, BSc; Anna M. Planas, PhD; Álvaro Cervera, MD, PhD

Background and Purpose—Uric acid (UA) is a neuroprotective antioxidant that improves the benefits of alteplase in experimental ischemia. However, it is unknown whether endogenous UA also influences the response to thrombolysis in patients with stroke.

Methods—A total of 317 consecutive patients treated with thrombolysis were included in a prospective stroke registry. Demographics, laboratory data, neurological course, and infarction volume were prospectively collected. Excellent outcome was defined as achieving a modified Rankin Scale score <2 at 90 days. Binary and ordinal logistic regression models were used to analyze modified Rankin Scale score at 90 days.

Results—UA levels were significantly higher in patients with an excellent outcome than in patients with a poor outcome (5.82 [1.39] versus 5.42 [1.81], P=0.029). In multivariate models, increased UA levels (OR, 1.23; 95% CI, 1.03 to 1.49; P=0.025) were associated with an excellent outcome and with an increased risk of shifting to a better category across the modified Rankin Scale (OR, 1.19; 95% CI, 1.04 to 1.38; P=0.014) independently of the effect of confounders. The levels of UA and the volume of final infarction were inversely correlated (r = −0.216, P<0.001) and the inverse correlation remained after adjustment for age, sex, and baseline National Institutes of Health Stroke Scale score (t value = −2.54, P=0.01). Significantly lower UA levels were found in patients with malignant middle cerebral artery infarction and parenchymal hemorrhage postthrombolysis.

Conclusions—Increased UA serum levels are associated with better outcome in patients with stroke treated with reperfusion therapies. These results support the assessment of the potential neuroprotective role of the exogenous administration of UA in patients with stroke treated with thrombolysis. (Stroke. 2011;42[suppl 1]:S28-S32.)

Key Words: alteplase ▪ neuroprotection ▪ oxidative stress ▪ thrombolysis ▪ uric acid

Uric acid (UA) is the end product of purine nucleotides, which are principal constituents of DNA, RNA, and cellular energy stores. In humans, the concentration of UA is higher than in most animals suggesting it may represent an evolutionary advantage owing to its antioxidant properties.1 These properties include scavenging of hydroxyl radicals, hydrogen peroxide, and peroxynitrite; suppression of the Fenton reaction; chelation of transition metals; and prevention of lipid peroxidation.2 UA could also have proinflammatory effects such as stimulation of the synthesis of monocyte chemoattractant protein-1 and increased production by monocytes of interleukin-1β, interleukin-6, and tumor necrosis factor-α.3

The administration of UA is neuroprotective in rats after transient brain ischemia,4 and the benefit is additive to the protection provided by alteplase.5 The relevance of UA levels in patients with cardiovascular disease or stroke is conflicting.6 Some studies showed an association between higher UA and increased cardiovascular mortality,7,8 whereas others9,10 suggested that the apparent worse outcome in hyperuricemic patients was confounded by the effects of more prevalent or uncontrolled risk factors. In patients with acute stroke, higher UA levels have been described in association with improved11 or worse functional outcome.12–14 The generation of UA is increased in the ischemic brain, although there is a gradual exhaustion of the antioxidant capacity that has been correlated with higher lesion volume and neurological impairment in stroke.15 These clashing results could reflect the variable timing of UA assessment in these studies, the inconsistent definition of outcome, the uneven adjustment of comorbidity or initial stroke severity, and the variable use of therapeutic agents.

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The relevance of UA levels in patients with stroke treated with thrombolytic therapy is unknown and this question deserves consideration because the antioxidant capacity of UA could be particularly beneficial in situations of enhanced oxidative-mediated reperfusion injury. In this study, we investigated the association between endogenous UA levels and clinical and radiological outcomes in a consecutive series of patients with stroke treated with thrombolysis.

**Methods**

**Patients**

A total of 317 consecutive patients aged ≥18 years treated with intravenous or endovascular thrombolysis between January 2002 and January 2010 were included in a prospective stroke registry. Demographics, including history of symptomatic cardiovascular disease and prevalence of vascular risk factors, and radiological, clinical, and laboratory data, were prospectively collected, and the neurological function was assessed daily by stroke neurologists using the National Institutes of Health Stroke Scale (NIHSS) from admission to hospital discharge. Functional outcome was assessed with the modified Rankin Scale (mRS) and NIHSS score at Day 90. Diagnostic tests were performed to determine the cause of stroke as lacunar, atherothrombotic, cardioembolic, undetermined, or other specific causes. All patients had conventional laboratory tests including the assessment of UA levels in fasting blood samples obtained within a median (interquartile range) 24 (17 to 42) hours of stroke onset using standard laboratory procedures with urate oxidase reagent on a Dax analyzer (Bayer-Technichon) with an interassay coefficient of variation 3% to 5%.

A brain CT scan was performed before thrombolytic therapy and repeated at 24 (±12) hours or whenever it was required in patients with worsening stroke (at least 4-point increment in the NIHSS score). Once a brain CT scan ruled out the presence of hemorrhagic stroke, intravenous thrombolysis was administered within the first 3 hours of stroke onset from January 2002 to October 2008 and within 4 to 5 hours after October 2008 (n=277). From October 2008 to January 2010, endovascular thrombolysis was used if intravenous thrombolysis was contraindicated (n=13) or as a rescue therapy for occlusions resistant to intravenous thrombolysis (n=27). Infarct volume was measured on the second CT scan using the brain maps of Gado, Hanaway, and Frank16 by investigators blinded to clinical outcome and UA levels. Hemorrhagic transformation on CT scan described any presence of blood regardless of symptoms and was classified according to the European Cooperative Acute Stroke Study criteria as hemorrhagic infarction (HI) and parenchymal hematoma (PH) Types 1 and 2.17 Symptomatic intracerebral hemorrhage defined those bleedings associated with at least a 4-point increment in the NIHSS score. Malignant middle cerebral artery (MCA) infarction was defined as lesions that occupied at least two thirds of the MCA territory with mass effect. Excellent outcome was defined

### Table 1. Main Traits of the Study Population According to Clinical Outcome at Day 90

<table>
<thead>
<tr>
<th></th>
<th>mRS 0 to 1 (n=101)</th>
<th>mRS 2 to 3 (n=103)</th>
<th>mRS 4 to 6 (n=113)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics and risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males, no. (%)</td>
<td>66 (65.3)</td>
<td>63 (61.2)</td>
<td>48 (42.5)</td>
<td>0.020</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>68 (13.3)</td>
<td>71 (11.7)</td>
<td>76 (10.3)</td>
<td>0.000</td>
</tr>
<tr>
<td>Previous stroke, no. (%)</td>
<td>8 (8)</td>
<td>18 (18)</td>
<td>17 (15)</td>
<td>0.043</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>66 (65)</td>
<td>67 (65)</td>
<td>74 (66)</td>
<td>0.990</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>16 (16)</td>
<td>25 (24)</td>
<td>37 (33)</td>
<td>0.013</td>
</tr>
<tr>
<td>Coronary heart disease, no. (%)</td>
<td>18 (18)</td>
<td>18 (18)</td>
<td>20 (18)</td>
<td>0.960</td>
</tr>
<tr>
<td>Dyslipidemia, no. (%)</td>
<td>36 (36)</td>
<td>45 (44)</td>
<td>39 (35)</td>
<td>0.579</td>
</tr>
<tr>
<td>Smokers, no. (%)</td>
<td>40 (40)</td>
<td>40 (39)</td>
<td>32 (28)</td>
<td>0.276</td>
</tr>
<tr>
<td>Atrial fibrillation, no. (%)</td>
<td>19 (19)</td>
<td>67 (66)</td>
<td>63 (57)</td>
<td>0.000</td>
</tr>
<tr>
<td>Prior mRS 0 to 1, no. (%)</td>
<td>94 (93)</td>
<td>67 (66)</td>
<td>63 (57)</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Baseline parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>6 (3–11)</td>
<td>9 (6–17)</td>
<td>18 (13–21)</td>
<td>0.000</td>
</tr>
<tr>
<td>Glucose, mg/dL, median (IQR)</td>
<td>119 (106–145)</td>
<td>128 (109–158)</td>
<td>128 (110–149)</td>
<td>0.114</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg, median (IQR)</td>
<td>155 (142–170)</td>
<td>155 (138–166)</td>
<td>151 (139–166)</td>
<td>0.422</td>
</tr>
<tr>
<td>UA levels, mg/dL, mean (SD)</td>
<td>5.8 (1.39)</td>
<td>5.6 (1.73)</td>
<td>5.2 (1.86)</td>
<td>0.029</td>
</tr>
<tr>
<td>Time of UA measurement since stroke onset, median (IQR)</td>
<td>22 (17–40)</td>
<td>24 (16–43)</td>
<td>25 (18–44)</td>
<td>0.198</td>
</tr>
<tr>
<td><strong>Treatment type, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.780</td>
</tr>
<tr>
<td>IVT</td>
<td>90 (89)</td>
<td>95 (92)</td>
<td>92 (81)</td>
<td></td>
</tr>
<tr>
<td>IVT-EVT</td>
<td>7 (7)</td>
<td>4 (4)</td>
<td>16 (14)</td>
<td></td>
</tr>
<tr>
<td>EVT</td>
<td>4 (4)</td>
<td>4 (4)</td>
<td>5 (4)</td>
<td></td>
</tr>
<tr>
<td><strong>Radiological parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final infarct volume</td>
<td>2 (0–10)</td>
<td>10 (3–26)</td>
<td>60 (20–135)</td>
<td>0.000</td>
</tr>
<tr>
<td>Malignant MCA infarct, no. (%)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>22 (20)</td>
<td>0.000</td>
</tr>
<tr>
<td>PH 1 or 2, no. (%)</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>16 (14)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Excellent outcome (mRS 0 to 1) versus mRS ≥2.

IQR indicates interquartile range; IVT, intravenous thrombolysis; EVT, endovascular thrombolysis.
as a mRS score of 0 to 1 at Day 90. The study was approved by a local ethics committee.

**Statistical Analysis**

Continuous variables are reported as the mean±SD or median with interquartile ranges and were compared with the Student t test, 1-way analysis of variance, Mann–Whitney, or Kruskal–Wallis tests as appropriate. Correlations were assessed with Pearson or Spearman coefficients, and categorical variables were compared with the χ² and Fisher exact tests. Binary and ordinal multivariate logistic regression models were used to assess the effects of UA levels on clinical outcome adjusted for variables showing a P<0.2 in univariate analysis. In binary logistic regression models, mRS was dichotomized (mRS <2 versus mRS ≥2) and a backward stepwise strategy was used to select the variables remaining in the final model. Age, sex, time to treatment, and treatment modality were forced to remain in the final model. We also constructed ordinal regression models to show the results were consistent across levels of the mRS (3 categories: 0 to 1, 2 to 3, 4 to 6) adjusted for factors and covariates related to dichotomized mRS in the binary analysis. Infarct volume was assessed in multiple regression adjusted for age, sex, and baseline NIHSS score. The analysis was performed using PASW Statistics Version 18.0 and the level of significance was established at the 0.05 level (2-sided).

**Results**

**Main Characteristics of the Study Population**

In the study population, mean (SD) age was 72 (12.2) years, 56% of patients were males, median (interquartile range) NIHSS score on admission was 11 (6 to 18) median (interquartile range) delay to thrombolytic treatment was 135 (105 to 172) minutes, and mean (SD) UA levels were 5.5 (1.70). Expectedly, males had higher levels of UA than females, 5.9 (1.60) versus 5.1 (1.72; P<0.001), as well as patients with history of hypertension, 5.8 (1.66) versus 5.1 (1.67; P<0.01) or diabetes, 6.0 (1.77), versus 5.4 (1.65; P<0.05). Age, coronary artery disease, alcohol, smoking, history of prior stroke, or stroke subtype did not significantly modify UA levels (data not shown). Excellent outcome was achieved by 101 (32%) patients at Day 90. Moreover, 52 (16%) patients reached a mRS of 2, 51 (16%) patients a mRS of 3, 61 (19%) patients a mRS of 4, 16 (5%) a mRS of 5, and 36 (11%) patients a mRS of 6.

**Clinical Course and Functional Outcome in Relation to UA Levels**

In the whole study group, there was an inverse correlation between the levels of UA and the severity of stroke (NIHSS score) at baseline (r = −0.16, P = 0.006), at 24 hours (r = −0.24, P = 0.001), at hospital discharge (r = −0.26, P = 0.001), and at Day 90 (r = −0.18, P = 0.001) and with mRS score at Day 90 (r = −0.14, P = 0.013). As shown in Table 1, outcome was associated with male sex; younger age; absent history of stroke, diabetes, or prestroke disability; atrial fibrillation; and baseline NIHSS score. Moreover, UA levels were significantly higher in patients with excellent outcome than in patients with poor outcome, 5.82 (1.39) versus 5.42 (1.81; P = 0.029). As shown in Table 2, increasing UA levels (OR, 1.23; 95% CI, 1.03 to 1.49; P = 0.025) were associated with excellent outcome at 90 days in adjusted models. In ordinal regression analyses, higher UA levels also increased the risk of shifting to a better category across the mRS scale (OR, 1.19; 95% CI, 1.04 to 1.38; P = 0.014).

**UA Levels and CT Scan Findings**

Expectedly, patients with a poor outcome had larger infarctions than patients with an excellent outcome, 24.4 mL (6.00 to 76.72 mL) versus 1.9 mL (0 to 9.97 mL; P<0.001). The levels of UA and the volume of final infarction were inversely correlated (r = −0.216, P<0.001) and the inverse correlation remained after adjustment for age, sex, and baseline NIHSS score (t value = −2.54, P = 0.01). Higher UA levels remained associated with smaller lesions in analyses restricted to patients (n = 234) with MCA infarction (t value = −2.09, P = 0.04). Moreover, significantly lower UA levels were found in patients with malignant MCA infarction (n = 23; 4.72 ± 1.84 versus 5.61 ± 1.67 mg/dL, P = 0.015) and in patients with PH 1 or 2 (n = 22; 4.62 ± 2.16 versus 5.62 ± 1.64, P = 0.008), as shown in the Figure. As shown in Table 1, both malignant MCA infarction and PH 1 or 2 were associated with bad outcomes.

**Discussion**

In this study aimed to analyze the relationship between serum UA levels and outcome in patients treated with thrombolysis, we found that higher UA levels were associated with an increased rate of excellent recovery independently of baseline variables. Moreover, increased serum levels of UA were significantly associated with smaller infarction volumes and lower rates of malignant MCA infarctions or PH (1 or 2) postthrombolysis. Overall, these results support the study of the exogenous administration of UA in patients with acute stroke who receive thrombolytic therapy.
UA is the most important endogenous antioxidant in the human brain and it has shown neuroprotective effects in preclinical studies. The safety and feasibility of UA modulation was recently assessed in 2 small randomized controlled trials that decreased or increased the levels of this natural antioxidant in patients with acute stroke. In the former study, patients received allopurinol within 72 hours of stroke onset and did not experience safety concerns. In the latter, allopurinol was able to reduce the levels of UA and of stroke onset and did not experience safety concerns. In a recent pilot study, patients with stroke were treated with alteplase and then randomized to receive UA or placebo. Active treatment with UA prevented an early fall of endogenous UA levels and treated patients experienced no serious adverse events, disclosed lower levels of lipid peroxidation, and had less activation of active matrix metalloproteinase compared with control subjects. It was argued that UA had impeded oxidation and/or nitrosylation of matrix metalloproteinases after brain ischemia and modulated essential redox-sensitive transcription factors that promote inflammation.

In agreement with previous clinical and radiological observations, the current study found an inverse correlation between the levels of UA and the volume of the infarction at follow-up brain CT scan, and this finding was confirmed in sensitive analyses restricted to patients with MCA territory infarctions. On the contrary, lower UA levels were associated with a greater incidence of malignant MCA infarctions and hemorrhagic transformation (PH 1 or 2). Although the early assessment of infarction size on CT scan may have underestimated the final volume of the infarctions, all CT scans were performed at a similar time delay (24±12 hours) after stroke onset and were evaluated by investigators blinded to clinical and laboratory findings to limit the risk of bias.

The current study is limited by the lack of information regarding the rate and timing of arterial reperfusion and also because UA was measured only once. Hence, it could be argued that inconsistent recanalization rates between the UA groups did influence the rate of recovery or that lower UA levels were the result of larger infarctions. Nonetheless, experiments conducted after transient focal brain ischemia in rats demonstrated that the administration of UA and alteplase resulted in synergic neuroprotective effects. The associations observed in the current study among higher UA levels, better clinical outcome, smaller infarctions, and less bleeding complications at follow-up do not prove causality but strongly suggest that the endogenous levels of UA are of major biological relevance in patients with stroke receiving thrombolytic therapy. These results deserve confirmation in larger prospective studies.

**Conclusions**

Overall, the results of the current study give additional support to the clinical significance of oxidative stress in patients with acute stroke and open new therapeutic avenues aimed to increase the benefits of thrombolytic therapy. One such approach is the dual administration of exogenous UA and alteplase, a strategy recently proven to be feasible and safe. However, the definitive proof of causality between increased UA levels and better stroke outcome requires an appropriately designed therapeutic controlled trial. For this reason, the Spanish Drugs Agency has recently approved a multicenter clinical trial of UA administration in patients with acute stroke treated with alteplase and which is due to start in 2010 (EudraCT 2007-002687-95 and NCT00860366).

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**Disclosures**

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**References**