Systemic Hematologic Status Following Intraventricular Recombinant Tissue-Type Plasminogen Activator for Intraventricular Hemorrhage

The CLEAR IVH Study Group

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**Background and Purpose**—This is the first prospective evaluation of changes in systemic hematologic status following administration of intraventricular recombinant tissue-type plasminogen activator in patients with intraventricular hemorrhage (IVH).

**Methods**—Laboratory data from subjects enrolled onto the Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR IVH) Trials were analyzed. We analyzed pre- and post- recombinant tissue-type plasminogen activator dosing coagulation parameters. Longer-term changes in hematologic status were studied in subjects who received the study agent after blood clot in the third/fourth ventricles had resolved radiologically.

**Results**—Plasma fibrinogen increased significantly in both treatment groups. Dosing did not have a significant impact on any systemic coagulation parameters in either treatment group.

**Conclusions**—Intraventricular recombinant tissue-type plasminogen activator is unlikely to impact systemic coagulation or to compound the effects of systemic anticoagulation for deep venous thrombosis prophylaxis.

**Clinical Trial Registration**—URL: http://clinicaltrials.gov. Unique identifier: NCT00650858.

(Stroke. 2011;42:3631-3633.)

Key Words: coagulation ■ intracerebral hemorrhage ■ thrombolysis

Thrombolytic treatment of intraventricular hemorrhage (IVH) with low-dose intraventricular recombinant tissue-type plasminogen activator (rtPA) has shown significant improvement in 30-day survival. Intravenous rtPA produces a transient systemic hypocoagulable state. Administering intraventricular thrombolytics to hypertensive IVH patients could contribute to a systemic coagulopathy and increase risk for both intracranial and extracranial bleeding. We performed a retrospective analysis of data from a large, placebo-controlled, multisite trial to assess the impact of intraventricular rtPA on systemic coagulation.

**Methods**

The CLEAR IVH Trial study procedures have been published previously. We investigated changes in prothrombin time, partial thromboplastin time, platelets, plasma plasminogen, and plasma fibrinogen in patients who had blood coagulation data both before and within 36 hours after the first dose of the study agent. To explore how longer-term effects of rtPA when dosing may have systemic effects after restoration of normal cerebrospinal fluid resorption, we studied a smaller subgroup; this subgroup received the study agent after blood clot in the third/fourth ventricles had resolved, in whom an additional laboratory draw was performed within 24 hours after a dose was administered following clot resolution in those ventricles. Adverse events were recorded prospectively.

rtPA and placebo groups were compared for demographic and clinical characteristics using \( \chi^2 \) analysis, \( t \) test, and the Kruskal-Wallis 1-way ANOVA as appropriate. Regression analyses were used to compare treatment and placebo groups, adjusting for baseline coagulation parameters, baseline IVH volume, and sex. All results are presented as mean±SD. Probability values less than 0.05 were considered significant.

**Results**

Laboratory data were available for 78 of 100 enrolled subjects. Demographic and clinical characteristics are shown in Table 1. Coagulation data were similar in both treatment groups at baseline and during dosing (Table 2). Percent increase in plasma fibrinogen was statistically associated with time relative to first dose, but there was no statistically significant difference between placebo and rtPA groups (\( P<0.01; \) Figure 1).
Demographic and coagulation data were similar in both treatment groups in the 27 subjects who had laboratory data after clearance of third/fourth ventricles (Supplemental Table I; http://stroke.ahajournals.org), except for time from administration of the first dose to clot resolution in the third/fourth ventricles. After rematching the placebo group to the rtPA group using the time of clearance of the rtPA group to account for time-related change, there were no significant differences between coagulation parameters of the 2 groups.

Deep venous thrombosis occurred in 2.5% of rtPA and 4.5% of placebo patients. One patient had a myocardial infarction. Symptomatic brain bleeding occurred in 8 rtPA subjects and in 1 placebo subject. Coagulation data were similar between subjects who had symptomatic brain bleeding and those who did not. The only non-central nervous system bleeding event reported (gastrointestinal hemorrhage) was in the placebo group. None of 29 subjects who received subcutaneous heparin or coumadin during intraventricular rtPA dosing experienced systemic bleeding.

**Discussion**

In contrast to intravenous thrombolytic administration, patients were exposed to significantly lower doses of intraventricular rtPA (maximum of 3.0 mg every 12 hours for up to 13 days). Our findings show that administration of low-dose intraventricular rtPA does not significantly change systemic

<table>
<thead>
<tr>
<th>Table 2. Baseline and Post-First-Dose Coagulation Parameters</th>
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</thead>
<tbody>
<tr>
<td><strong>Coagulation Parameter</strong></td>
</tr>
<tr>
<td>rtPA Mean±SD (n) Placebo Mean±SD (n)</td>
</tr>
<tr>
<td>Platelet count, plt/mm³</td>
</tr>
<tr>
<td>PTT, s</td>
</tr>
<tr>
<td>PT, s</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
</tr>
<tr>
<td>Plasminogen, %</td>
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</tbody>
</table>

rtPA, recombinant tissue-type plasminogen activator; PTT, partial thromboplastin time; PT, prothrombin time; SD, standard deviation.
hematologic status in patients with IVH either before or after radiographic clearance of the third/fourth ventricles. Following administration of 100 mg intravenous rtPA, there is a decrease (16% to 36%) in circulating fibrinogen.\(^4\) We observed a mean increase in fibrinogen in both groups after the first dose and after ventricle clearance, which we attribute to an acute-phase hematologic response to intracranial hemorrhage.\(^5\)

Systemic hematologic status is an important consideration in the treatment of hemorrhagic stroke, as hemorrhagic stroke is an independent risk factor for deep vein thrombosis.\(^6\) The rates of deep vein thrombosis and pulmonary embolism among all rtPA subjects in the CLEAR IVH trial are consistent with those in other studies,\(^1,7\) suggesting clinically that intraventricular rtPA does not initiate systemic fibrinolysis, and would be unlikely to compound the effects of systemic low-dose anticoagulation for deep vein thrombosis prophylaxis. The effect of local factors on brain bleeding, such as extent of tissue trauma and timing of local tPA delivery in relation to hemostasis, would benefit from additional investigation.

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**Disclosures**

D.F.H. has received research support as principal investigator of the CLEAR IVH trial.

**References**

Online Supplement

Systemic Hematologic Status Following Intraventricular rt-PA for Intraventricular Hemorrhage

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Supplemental Methods
Inclusion criteria into CLEAR IVH included age 18-75 years, admission spontaneous ICH volume ≤ 30cc (by ABC/2 method), admission systolic blood pressure < 200 mmHg, Historical Rankin score 0 or 1, and obstructive hydrocephalus requiring urgent external ventricular drainage. Patients were excluded if they had a suspected or untreated aneurysm or AVM, clotting disorders, a platelet count < 100,000, INR > 1.7, active internal bleeding, current use of heparin, coagulopathy with prothrombin time (PT) or partial thromboplastin time (PTT) outside of normal range, or infratentorial hemorrhage. All patients with an intraventricular catheter (IVC) inserted in the initial 24 hours of illness to treat IVH were considered. Patients were enrolled within 48 hours after diagnostic head CT. Subjects were randomized to receive either intraventricular rt-PA (0.3mg q12h, 1.0mg q12h, 1.0mg q8h, or 3.0mg q12) or placebo (saline). Subjects could not receive intravenous anticoagulants or low molecular weight heparin for deep venous thrombosis prophylaxis or antiplatelet agents until 72 hours post last dose. Use of subcutaneous unfractionated heparin was not specifically restricted. This study was approved by the Institutional Review Boards of all participating centers. Seventy-eight patients had clinical data that allowed for pre/post dosing comparison of coagulation parameters. All patients had occlusion of the 3rd and 4th ventricles prior to first dose administration. For a lab draw to be eligible for analysis, it required at least one of three coagulation parameters: PT, PTT, or platelet count. Plasma plasminogen and fibrinogen concentrations were included when available. Subjects were included if they had data for the same coagulation parameter at all time points necessary for analysis. The use of anticoagulants during treatment, such as heparin and warfarin, was recorded.

The percent change for each outcome was calculated as (post treatment – baseline)/baseline. To compare coagulation states of patients who experienced brain bleeding to those who did not, we compared the maximum and minimum coagulation values during treatment.
## Supplemental Tables

### Table S1. Comparison of Pre- and Post-Ventricle Clearance Coagulation Parameters

<table>
<thead>
<tr>
<th>Coagulation Parameter</th>
<th>Baseline</th>
<th>rt-PA</th>
<th>Placebo</th>
<th>Pre-Ventricle Clearance</th>
<th>rt-PA</th>
<th>Placebo</th>
<th>Post-Ventricle Clearance</th>
<th>rt-PA (%Δ)</th>
<th>Placebo (%Δ)</th>
<th>% Δ in Coagulation Parameter Between Pre- and Post-III/IV Ventricle Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Mean ± SD (n)</td>
<td>Median Range</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Platelet Count (plt/mm³)</td>
<td>231±50 (19)</td>
<td>226±51 (7)</td>
<td>213±57</td>
<td>191±35</td>
<td>216±48</td>
<td>226±68</td>
<td>3.3±13.1</td>
<td>2.74</td>
<td>-21.8 – 24.5</td>
<td>17.1±15.9</td>
</tr>
<tr>
<td>PTT (Sec.)</td>
<td>29.0±3.3 (19)</td>
<td>30.4±4.5 (6)</td>
<td>29.2±3.6</td>
<td>30.6±5.1</td>
<td>29.3±4.9</td>
<td>29.4±4.6</td>
<td>-0.05±9.3</td>
<td>1.57</td>
<td>-26.9 – 12.5</td>
<td>-2.6±16.0</td>
</tr>
<tr>
<td>PT (Sec.)</td>
<td>12.4±2.0 (19)</td>
<td>12.2±2.0 (7)</td>
<td>13.2±4.3</td>
<td>11.7±1.7</td>
<td>12.2±2.1</td>
<td>11.6±2.0</td>
<td>-4.8±11.6</td>
<td>-2.31</td>
<td>-48.3 – 7.2</td>
<td>-1.7±4.1</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>464±145 (12)</td>
<td>430±110 (6)</td>
<td>574±174</td>
<td>532±166</td>
<td>685±180</td>
<td>508±138</td>
<td>24.1±24.8</td>
<td>20.7</td>
<td>-24.4 – 66.8</td>
<td>0.05±23.9</td>
</tr>
<tr>
<td>Plasminogen (%)</td>
<td>103±17 (7)</td>
<td>114±23 (3)</td>
<td>107±27</td>
<td>123±32</td>
<td>109±14</td>
<td>139±50</td>
<td>4.9±16.9</td>
<td>4.27</td>
<td>-23.9 – 29.2</td>
<td>11.5±11.5</td>
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