Efficacy of Intravenous Tissue-Type Plasminogen Activator in Central Retinal Artery Occlusion Report From a Randomized, Controlled Trial

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Background and Purpose—Central retinal artery occlusion is caused by a platelet-fibrin thrombus or embolic occlusion and is a stroke of the eye. Observational studies suggest that thrombolytics may restore ocular perfusion and visual function. We hypothesized that intravenous tissue-type plasminogen activator (tPA) administered within 24 hours of symptom onset might restore ocular perfusion and visual function.

Methods—A placebo-controlled, randomized trial of intravenous tPA versus intravenous saline was performed in patients with clinically defined central retinal artery occlusion within 24 hours of symptom onset. tPA was administered at a total dose of 0.9 mg/kg, with 10% given as a 1-minute bolus and the remainder over 1 hour. An improvement of visual acuity of 3 lines or more was considered significant.

Results—Twenty-five percent (2 of 8) of the tPA group experienced the primary outcome at 1 week after tPA versus none of the placebo group. One patient had an intracranial hemorrhage. The visual acuity improvement of these 2 patients was not sustained at 6 months. In both patients, tPA was administered within 6 hours of symptom onset.

Conclusions—Although essentially a negative study, it does add to the evidence base of reperfusion in central retinal artery occlusion by showing that the time window for intervention is likely to be <6 hours. Reocclusion is a potential problem and may require adjuvant anticoagulation. Future studies should concentrate on determining the efficacy of thrombolytics in the <6-hour time window.

Clinical Trial Registration—URL: http://www.anzctr.org.au. Unique identifier: 83102.

Key Words: ophthalmology ■ retinal ischemia ■ thrombolysis ■ thrombolytic agents ■ tPA

Central retinal artery occlusion (CRAO), or an ocular stroke, results in sudden, painless vision loss whereby 80% of affected persons have a final visual acuity (VA) of counting fingers or worse.1–3 Unlike ischemic cerebral stroke, randomized, controlled trials (RCTs) of acute reperfusion therapies are lacking in CRAO. Acute therapies, such as paracentesis, carbogen inhalation, ocular massage, and carbonic anhydrase inhibitors, have a widely varied success rate of restoring vision in 6% to 49% of subjects.4,5 Owing to the observational nature of the data, some studies report a superior outcome,6 but most have found that they are no better than placebo.1,2,6–8

Intravenous tissue-type plasminogen activator (IV tPA) is standard therapy in ischemic stroke patients presenting within 4.5 hours of symptom onset.9 Despite similarities between the ocular and cerebral circulations, the effect of thrombolysis in CRAO has been investigated only in observational studies and a single RCT. These studies delivered therapy intra-arterially. Meta-analyses of observational studies suggests that thrombolytics may improve vision in CRAO,10–12 whereas an RCT of intra-arterial thrombolytics showed no benefit and a high rate of adverse events, including cerebral hemorrhage.5

An alternative route of administering thrombolysis is intravenously. In contrast to the intra-arterial approach, IV thrombolysis is more accessible, as there is no requirement to have a neurointerventional laboratory and the procedure is noninvasive, reducing the risk of complications.13 A systematic review of all observational studies of IV tPA in acute CRAO showed that 48.5% of subjects had a VA improvement of 4 lines or more with fewer complications when compared with intra-arterial administration.12

The optimal time window for CRAO treatment is unknown. Animal models have suggested that recovery of

Received January 22, 2011; accepted February 8, 2011.
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© 2011 American Heart Association, Inc.
Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.111.613653

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retinal function can be seen up to 4 hours from induction of ischemia. In humans, interventional case series have observed an improvement of visual function if thrombolysis is administered within 24 hours of symptom onset. The recent European Assessment Group for Lysis in the Eye (EAGLE) randomized patients within 20 hours of CRAO onset.17

We therefore hypothesized that IV tPA administered within 24 hours of CRAO onset would result in an improvement of VA. Given the rare occurrence of concurrent cerebral and ocular ischemia, we also hypothesize that the risk of intracranial hemorrhage (ICH) would be small and was estimated at 0.3%, based on studies of systemic tPA in myocardial infarction.18

Methods

A phase II, placebo-controlled RCT of IV tPA in the treatment of CRAO was conducted at the following participating hospitals in Australia: Flinders Medical Centre, South Australia, and the Royal Victorian Eye and Ear Hospital/St. Vincent’s Hospital, Melbourne, Victoria, Australia. The study protocol has been described previously13 and is registered with the Australian and New Zealand Clinical Trial Registry (ACTRN12608000441314). The study was approved by the ethics committees of each recruiting hospital.

All patients were assessed by an ophthalmologist, who confirmed the diagnosis of acute CRAO according to standard clinical criteria of monocular vision loss associated with an ipsilateral relative afferent pupillary defect and diffuse, pale swelling of the retina with a macular “cherry-red” spot and attenuation of retinal vessels by ophthalmoscopy. The use of other therapies such as acetazolamide or carbogen inhalation was left to the discretion of the diagnosing ophthalmologist and was not a contraindication for study enrollment. After consent was obtained, eligible patients were referred promptly to the stroke thrombolysis team. Immediate neuroimaging and blood tests were performed as outlined in the inclusion and exclusion criteria.

The inclusion criteria were as follows: patients age ≥18 years with acute CRAO presenting within 24 hours of symptoms onset and CRAO of a presumed thromboembolic cause, with no evidence of temporal arteritis by clinical assessment or laboratory studies (for example, elevated erythrocyte sedimentation rate). Before randomization, a noncontrast computed tomogram (CT) of the brain was obtained, demonstrating no acute ICH, infarction, or mass lesion, and a CT angiogram demonstrated no ipsilateral carotid artery occlusion.

The exclusion criteria were factors known to increase the risk of hemorrhage after thrombolysis. These included a history of ICH at any stage, a history of ischemic stroke or systemic hemorrhage within the last 3 months, major surgery or trauma within 2 weeks, gastrointestinal or urinary bleeding within 3 weeks, and an arterial puncture or lumbar puncture within 7 days. Those patients from whom we were unable to obtain informed consent or who were pregnant were excluded from the study. All patients had baseline blood pressure and blood tests for full blood count, coagulation, and biochemistry studies. Those with a platelet count <100 000/mL or who had heparin administered within the last 48 hours or a vitamin K antagonist with an international normalized ratio of >1.6, systolic blood pressure >185 mm Hg and/or a diastolic blood pressure of >110 mm Hg, or a serum glucose value >22 mmol/L were excluded.

Recruitment and Allocation

Patients were randomized 1:1 in a block design via a Website run by the coordinating center at Flinders Medical Centre. A concealed printout of the treatment allocation was passed on to a trial nurse at the recruiting site, with instructions for the dose of tPA or placebo that needed to be prepared. Thus, the treating stroke team was blinded to treatment allocation.

Those who were randomized to the treatment arm were weighed and given alteplase, 0.9 mg/kg IV (maximum, 90 mg). A 10% bolus was given over 1 minute, followed by the remaining dose over 1 hour. Those who were randomized to placebo received 10 mL of...
normal saline in a syringe administered over 1 minute, followed by 50 mL of normal saline given as an infusion over 1 hour. Antiplatelet therapy was commenced 24 hours after infusion in both groups after a CT brain scan was obtained to exclude cerebral hemorrhage.

Clinical data collected included age, sex, vascular risk factors, medications, VA at presentation, ophthalmologic and neurologic findings, time from onset of symptoms to presentation, treatment received, and visual outcomes. Data were entered via a secure Website and transferred to a study coordinator at Flinders Medical Centre.

Follow-Up
Patients were admitted to the stroke unit for the first 24 hours after treatment and received standard investigations and management to address vascular risk factors. Participants were examined by an ophthalmologist blinded to treatment allocation on day 1 to document VA. Visual field testing was performed when the VA was better than 20/400, and a fundus fluorescein angiogram (FFA) was performed after treatment. All participants were followed up clinically at 1, 3, and 6 months in the neurology and ophthalmology outpatient clinics. All adverse events, in particular hemorrhagic complications, were documented. Subjects were allowed access to the principal investigators to discuss any concerns.

Primary Outcomes
The primary outcome was defined as improvement in Snellen VA by ≥3 lines between baseline and 6 months, equating to a >0.3 change in the logMAR vision score.

Secondary Outcomes
The secondary outcomes were the mean improvement in VA stratified according to the following time intervals from symptom onset to treatment: 0 to 6 hours, 6 to 12 hours, and 12 to 24 hours. An analysis of the time course of visual recovery (at 1 week, 1 month, and 3 months) was plotted. All serious adverse events were reported to the data safety and monitoring board. In the event of an ICH, immediate review of the outcomes was initiated.

Sample Size Calculation and Statistical Analyses
Bioussé et al22 performed a meta-analysis of acute CRAO treated with IV thrombolysis. They found that 48.5% had 4 lines or more of VA improvement. In the “standard therapy” group, the GISSI Study Group22 showed that only 4.8% achieved a VA improvement of 3 lines or more. With these figures (48.5% in treatment versus 4.8% in placebo), a sample size of 25 in each group was required to demonstrate an absolute difference of 43.7% in the proportion of subjects achieving a 3-line improvement in Snellen VA with tPA compared with controls at an α of 0.05 and power of 80%.

A Mann-Whitney U test was used for analyzing continuous ordinal, nonparametric variables owing to the nonhomogeneity of the variances between the 2 groups in the sample population. The dichotomous variables were analyzed by Fisher exact test. An α=0.05 was considered statistically significant.

Results

Table 1. Trial Demographics

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>tPA</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, years</td>
<td>73±8</td>
<td>67±9</td>
<td>0.18</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>6 (75)</td>
<td>5 (62.5)</td>
<td>0.59</td>
</tr>
<tr>
<td>Time to presentation, hours</td>
<td>9.1±6.1</td>
<td>3.9±2.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Time to treatment delivery, hours</td>
<td>14.4±6.5</td>
<td>7.3±3.0</td>
<td>0.01</td>
</tr>
<tr>
<td>NIHSS at randomization</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>VA at baseline, No.</td>
<td>0</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>NLP</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>LP</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>HM</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>CF</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>VA improvement, No. (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

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Secondary Outcomes
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Results

Study Patients
From July 1, 2008, to April 1, 2010, 21 patients presented with acute CRAO. Five of these individuals were ineligible for the study on the basis of exclusion criteria: 2 were taking vitamin K antagonists and had an international normalized ratio >1.7, 1 had suspected giant-cell arteritis, later confirmed by a temporal artery biopsy, and in 2 patients, the time of symptom onset could not be determined. Sixteen patients were eligible for the study, and all gave consent. The mean±SD age was 70±9 years. There were 11 men and 5 women. Eight were randomized to IV tPA therapy and 8 received placebo, consisting of an IV saline infusion (Figure 1).

No subject in either the treatment or placebo group received additional therapies.

There were no significant differences between the mean age of the 2 groups, the sex distribution, or vascular risk factors (Table 1). The baseline VA between the groups was comparable, with vision of counting finger or worse at presentation (P=0.25). The mean±SD time to presentation was 6.5±5.2 hours. Subjects who were assigned to the placebo group had a shorter mean time to presentation compared with the tPA group (P=0.04). The average time from the onset of CRAO to the patient receiving treatment was 10.8±6.1 hours from onset, and there was no difference between the 2 groups. No patient in either the tPA or placebo group had neurologic deficits before randomization.

Visual Outcomes
At 1 week, 2 of the 8 patients (25%) among the tPA subjects had an improvement in their VA of 3 lines or more. One patient improved from seeing hand movement to 6/24 (logMAR 1.6 to 0.8). There were no changes in VA in the other 6 patients receiving tPA. The mean change at 1 week was −0.275±0.53 logMAR in the tPA group compared with 0.05±0.14 in the placebo group (P=0.144). The changes in VA at 1 and 3 months are shown in Table 2. There were no significant differences in the VA at 6 months between the tPA and placebo group (P=0.535).
The vision of the patient that changed from ability to detect hand movement to 6/24 at 1 week decreased to 6/38 (logMAR 0.8) at 1 month. At 3 months, the vision was counting fingers (logMAR 1.6) at the scheduled visit, and a vitreous hemorrhage was seen. FFA showed retinal neovascularization. The other patient had initial improvement in vision but noted sudden vision deterioration. Immediate ophthalmologic examination showed no ocular hemorrhage, and FFA showed delayed arterial filling. In both cases, there was a relatively short symptom to tPA delivery time of 6 and 4.5 hours, respectively. By contrast, none of the patients receiving placebo had an improvement of their VA. Secondary outcome analysis of time to tPA showed that only those presenting from 0 to 6 hours had VA improvement (Figure 2).

Safety and Adverse Effects

One subject, age 64 years, had an ICH within 45 minutes of starting the tPA infusion. A pretreatment CT brain scan showed no lacunar infarcts or white matter disease, and no protocol violations were detected. The hemorrhage and subsequent edema were of sufficient severity to cause a significant midline shift, and he required intubation. He subsequently had a hemicraniectomy and evacuation of the hematoma and was given prothrombinex and recombinant factor VII with platelet infusion to reverse the effects of thrombolytic. He has made a good recovery with minimal right-sided pyramidal deficits with a modified Rankin score of 2 on discharge. He had no recovery of vision from his CRAO.

There were no deaths or retinal or systemic hemorrhages. Two patients developed neovascularization of the retina, including the patient who had a vitreous hemorrhage with deterioration in vision at 3 months. The other patient received placebo treatment and had neovascularization of the disc seen at the 1-month review. The patient was asymptomatic and did not have increased intraocular pressure from neovascular glaucoma. Both were treated successfully with panretinal photocoagulation.

Discussion

CRAO as a stroke of the eye is analogous to ischemic cerebral stroke, and the CRA and retina are homologous to the branches of the circle of Willis and the brain parenchyma, respectively. Indeed, based on the American Heart Association–endorsed definition of stroke and transient ischemic attack, retinal ischemia constitutes a part of the broader definition of “stroke.” Thus, stroke physicians in conjunction with ophthalmologists will have an integral role in the management of CRAO.

Unlike ischemic cerebral stroke, wherein there are guideline-based recommendations for treatment with tPA within 4.5 hours of symptom onset, the same robust data are lacking in CRAO, despite the fact that both share a common

<table>
<thead>
<tr>
<th>Mean Visual Acuity (logMAR)</th>
<th>Baseline</th>
<th>1 Wk</th>
<th>1 Mo</th>
<th>3 Mo</th>
<th>6 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>tPA</td>
<td>1.85±0.21</td>
<td>−0.275±0.53</td>
<td>−0.10±0.46</td>
<td>0±0.21</td>
<td>0.1±0.18</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.2±0.44</td>
<td>0.05±0.14</td>
<td>0.05±0.14</td>
<td>0.05±0.14</td>
<td>0.05±0.14</td>
</tr>
<tr>
<td>P value</td>
<td>0.061</td>
<td>0.144</td>
<td>0.589</td>
<td>0.540</td>
<td>0.535</td>
</tr>
</tbody>
</table>

tPA indicates tissue-type plasminogen activator.

Figure 2. Change in visual acuity (logMAR) of patients with acute central retinal artery occlusion treated with intravenous tissue-type plasminogen activator (tPA), stratified by time of treatment (0 to 6, 6 to 12, and 12 to 24 hours from the onset of central retinal artery occlusion).
pathophysiology. Data on the optimal time window for intervention are lacking.

Observational studies to date have provided modest evidence for the efficacy of tPA, but this is the first RCT of IV tPA in the treatment of CRAO. Our results demonstrated an early improvement in VA of 3 lines or more in 2 of 8 tPA subjects but in none of the placebo subjects. This improvement was evident during the first week after tPA but was not sustained at 6 months, and thus, the primary outcome measure was not achieved. Both subjects were given tPA within 6 hours of symptom onset, and this suggests that the human retina has an ischemic tolerance time of 6 hours, matching the maximum time window for reperfusion in ischemic brain tissue.25

Even though the study protocol allowed for so-called "standard therapies" to be used, such as ocular paracentesis, carbogen inhalation, and ocular massage in addition to either tPA or saline placebo, in none of the 16 subjects were additional therapies used. Thus, any improvement in visual function in the current study is attributable to the use of tPA. The EAGLE study enrolled patients within 20 hours of symptoms with a mean time to treatment of 10.99 hours. Whereas EAGLE did not show an improvement in VA after thrombolysis, like our study, it suggests that a delay between symptom onset and treatment renders thrombolysis ineffective. On the other hand, if thrombolytics are administered earlier, then there is an increased chance of better visual outcomes. Hattenbach et al26 showed a VA improvement when tPA was administered within 6.5 hours of symptom onset. Similarly, Aldrich et al27 demonstrated that a third of their CRAO subjects had a VA improvement of 3 lines or greater when intra-arterial tPA was administered within 3 hours of symptom onset.

The main reason for the deterioration of vision in the 2 patients who had an initial recovery of VA after tPA is CRA reocclusion. This is supported by the FFA performed at the time of vision deterioration, showing delayed arterial filling and a persistent cherry red spot. In our study, heparin anticoagulation was not used after tPA, and this may have contributed to an increased risk of reocclusion.

There was 1 serious adverse event of an ICH in the tPA group. This triggered an immediate review of the results by the data safety monitoring board. The study was halted because of 2 factors: (1) there was no sustained improvement in VA in those patients receiving tPA and (2) the single ICH. It was deemed unethical to proceed further with the current protocol, given the lack of benefit and the potential of further harm from either systemic or intracranial bleeding. To date, the point estimate of ICH after CRAO tPA treatment has been reported as negligible and similar to the rate seen in cardiac thrombolysis.18 The EAGLE study showed that thrombolytic use in CRAO is not without risk, with 3 of 42 (7.1%) of their tPA group developing either intracranial or systemic bleeding.5

Although from a primary outcome measure this was a negative study, its value lies in adding further information on the response of the eye to ischemia and the potential benefits and risks of thrombolytic therapy. Our study and that of the EAGLE investigators emphasize that the time window for intervention is far narrower than the 24 hours postulated by some investigators and is probably closer to a ~6-hour time window. Our study also suggests that adjunctive anticoagulation therapy may be needed to prevent vessel reocclusion in the same way low-molecular-weight heparins are used in acute coronary syndromes.27

In light of the potential for vision recovery if tPA is delivered earlier, future RCTs should concentrate on delivering tPA as early as possible, with a maximum therapeutic time window of <6 hours. Such studies should be saline placebo controlled, given the lack of efficacy of "standard therapies" in CRAO. Until such time as a multicenter study is completed, tPA for CRAO cannot be considered standard therapy, although it does show promise.

Acknowledgments

The authors wish to thank Professors Douglas J. Coster and Keryn A. Williams for their review and helpful comments on the manuscript and Marie Therese Lan Kelly for statistical assistance.

Source of Funding

The study received research grant support from the Perpetual Trustee The Lindsay & Heather Payne Medical Research Charitable Foundation.

Disclosures

A.W.L. was supported by a National Health and Medical Research Council, National Insitutes of Clinical Studies Fellowship.

References

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Stroke. published online July 14, 2011;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2011/07/14/STROKEAHA.111.613653