Local Intraarterial Fibrinolysis Administered in Aliquots for the Treatment of Central Retinal Artery Occlusion

The Johns Hopkins Hospital Experience

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Background and Purpose—Central retinal artery occlusion results in acute visual loss with poor spontaneous recovery. Current standard therapies do not alter the natural history of disease. Several open-label clinical studies using continuous infusion of thrombolytic agents have suggested that local intraarterial fibrinolysis (LIF) is efficacious in the treatment of central retinal artery occlusion. The aim is to compare the visual outcome in patients with acute central retinal artery occlusion of presumed thromboembolic etiology treated with LIF administered in aliquots with that of patients treated with standard therapy.

Methods—We conducted a single-center, nonrandomized interventional study of consecutive patients with acute central retinal artery occlusion from July 1999 to July 2006.

Results—Twenty-one patients received LIF and 21 received standard therapy. Seventy-six percent of subjects in the LIF group had a visual acuity improvement of one line or more compared with 33% in the standard therapy group ($P_{H11005}=0.012$, Fisher exact). Multivariate logistic regression controlling for gender, history of prior stroke/transient ischemic attack, and history of hypercholesterolemia showed that patients who received tissue plasminogen activator were 36 times more likely to have improvement in visual acuity ($P_{H11005}=0.0001$) after adjusting for these covariates. Post hoc analysis showed that patients who received tissue plasminogen activator were 13 times more likely to have improvement in visual acuity of 3 lines or more ($P_{H11005}=0.03$) and 4.9 times more likely to have a final visual acuity of 20/200 or better ($P_{H11005}=0.04$). Two groin hematomas were documented in the LIF group. No ischemic strokes, retinal or intracerebral hemorrhages were documented.

Conclusions—LIF administered in aliquots is associated with an improvement in visual acuity compared with standard therapy and has few side effects. (Stroke. 2008;39:000-000.)

Key Words: retinal artery occlusion ■ thrombolytic therapy ■ tissue plasminogen activator

Central retinal artery occlusion (CRAO), a cause of acute visual loss, occurs in one per 10,000 ophthalmology outpatient visits.¹ The visual prognosis of CRAO is poor with 61% of patients having a final visual acuity (VA) of 20/400 or worse.² This degree of severe unilateral visual impairment is associated with limitations in social functioning, poor mental health,³ and is a risk factor for becoming dependent.⁴ Most CRAOs are thought to be caused by thrombosis or embolism.⁵ Standard therapies for acute CRAO include ocular massage, paracentesis, and other methods of reducing intraocular pressure as well as inhalation of a mixture of 95% oxygen and 5% carbon dioxide (carbogen). These treatments have not been shown conclusively to improve visual acuity beyond the natural history of disease.⁶,⁷ Systemic and intraarterial thrombolysis have been successful in restoring perfusion to ischemic tissue by fibrin–platelet clot lysis in ischemic stroke and myocardial infarction.⁸–¹⁰ In several open-label studies, local intraarterial fibrinolysis (LIF) was efficacious in the treatment of CRAO, with up to 60% to 70% of treated subjects experiencing an improvement in VA.¹¹–¹⁵ Most studies of LIF therapy in CRAO have used a continuous infusion of the thrombolytic agent.¹² Despite the efficacy of LIF in restoring VA in CRAO, concerns remain
with its use in clinical practice. First, it is an invasive procedure that can cause embolic stroke and second, thrombolytic agents may result in either intracranial or systemic hemorrhages.14–16

An alternative to the continuous infusion of thrombolytic is its administration in small aliquots until patency of the central retinal artery is clinically established. There are 2 theoretical advantages of this approach. First, titration of the thrombolytic agent may result in a reduction in the total dose that is administered, thus potentially reducing the risk of hemorrhage. Second, the titration approach may reduce procedural time. Given that the duration of cerebral angiography is correlated with the risk of periprocedural stroke, reduced angiography time might be expected to reduce the incidence of complications.17–19

We hypothesize that the treatment of acute CRAO with LIF administered in aliquots may achieve a better visual outcome than standard therapy alone and with a lower complication rate.

Methods

We performed a retrospective analysis of a consecutive cohort of 42 patients admitted to the Johns Hopkins Hospital with acute CRAO from July 1999 to July 2006. All patients gave informed consent for the off-label use of tissue plasminogen activator (tPA) by intraarterial administration.

Ophthalmic Examination

All patients were assessed by an ophthalmologist who confirmed the diagnosis of acute CRAO using 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.

VA at presentation was measured by Snellen chart at 20 feet for all patients whose VA in the affected eye was 20/400 or better. Patients with VA less than 20/400 in the affected eye were assessed on an ordinal categorical scale progressing from counting fingers, to hand movement, to light perception and finally to no light perception. Fluorescein angiography was performed whenever possible. Demographic details and vascular risk factors on admission were recorded.

Two therapeutic procedures were compared in this study: standard therapy alone (control group) or LIF in addition to standard therapy (LIF group). The decision for a subject to undergo LIF was made by the treating ophthalmologist and neurologist if the patient was eligible.

The inclusion criteria for LIF were: (1) time to presentation of CRAO within 15 hours of symptom onset; (2) a presumed thromboembolic cause; (3) no evidence of vasculitis by clinical assessment or laboratory studies (eg, erythrocyte sedimentation rate); and (4) no evidence of hypoperfusion of the ipsilateral internal carotid artery as a cause of CRAO documented either angiographically or with duplex ultrasonography. Exclusion criteria included uncertain time of CRAO within 15 hours of symptom onset; (2) a presumed thromboembolic cause; (3) no evidence of vasculitis by clinical assessment.

Standard therapy of CRAO included ocular paracentesis, carbogen inhalation, topical intraocular pressure-lowering agents, or a combination of these. All patients eligible for LIF underwent CT or MRI with a fluid-attenuated inversion recovery sequence to exclude cerebral hemorrhage.

A diagnostic 4-vessel angiogram was performed under local sedation to assess the intracranial vasculature with an emphasis on the patency of the ipsilateral carotid and ophthalmic arteries. All angiograms and LIFs were performed by K.M. or P.G. LIF was performed by advancing a guide catheter using a fluoroscopic roadmap of the internal carotid artery ipsilateral to the affected eye, after which 3000 U of heparin was infused to prevent periprocedural thrombosis. A 1018 microcatheter (Boston Scientific, Natick, Mass) steamed to the shape conforming to the ophthalmic artery siphon was then advanced to the origin of the ophthalmic artery and aliquots of 3 mg tPA, in 3 cc normal saline increments, were infused over 5 minutes each. Aliquot infusion was stopped if there was a clinical VA improvement or a prespecified maximum dose of 20 mg of tPA was reached, at which time the guiding and microcatheters were removed. All patients were admitted to an intensive care unit and partial thromboplastin time was measured every 2 hours. Once the partial thromboplastin time value had dropped below 1.5 times the normal value, an infusion of intravenous heparin was begun, without a bolus, using a weight-based nomogram. Once the therapeutic range of a partial thromboplastin time value of 1.5 to 2.5 times normal was reached, the partial thromboplastin time was checked every 6 hours. The intravenous heparin infusion was stopped after 24 hours.20 All adverse events were recorded.

In both standard and LIF groups, VA was assessed on day 1 postprocedure and then daily until discharge. The final VA for all patients was obtained from the patients’ ophthalmologists for the most recent follow-up and the duration of follow-up recorded.

Outcome Measures

The primary outcome was defined as a one-line improvement in VA on the Snellen chart for patients with initial VA of 20/400 or better at 24 hours postadmission. For patients with initial VA worse than 20/400, a improvement was considered to have occurred if VA improved from no light perception to light perception, from light perception to hand movement, from hand movement to counting fingers, and from counting fingers to 20/400 or better at 24 hours after LIF.11 Secondary outcomes included improvement in VA of 3 lines or more, signifying a doubling of visual angle22 and achieving a VA of 20/200 or better, signifying the US definition for legal blindness.22 Any adverse effects related to LIF were recorded.

Statistical Methods

Statistical analyses were performed with Stata statistical software, version 9.0 (StataCorp, College Station, Texas). Univariate comparisons between baseline categorical characteristics in the 2 groups were made using Fisher exact test. Comparisons between continuous characteristics were made using a Student t test with adjustment for unequal variances when appropriate. Simple logistic regression was used to compare the primary outcome in the 2 groups, and multivariate stepwise logistic regression was performed including other covariates thought to be potential confounders. These variables were selected for clinical reasons or because they were found to have univariate associations with either the outcome or the use of LIF.

Although the initial analyses were performed using an automated stepwise comparison, subsequent decisions were made based on clinical importance, variables with an adjusted probability value (by likelihood ratio testing) <0.10, those that moderately changed the point estimate for the primary variable of interest (LIF group), or those variables that were believed to be clinically significant despite nonsignificance and probability values and were included in the final model. Goodness of fit was assessed using the Hosmer-Lemeshow statistic. Probability values for regression analyses are reported using likelihood ratio testing results. In addition, for analysis of the primary outcome, multinomial logistic regression was performed with a 3-level outcome (worsening/no change/improvement in VA) and appropriate adjustment for potential confounders. Unless otherwise specified, an alpha <0.05 was considered to be statistically significant.

Results

Demographics and Vascular Risk Factors

Twenty-one subjects with a mean age of 65.1±13 years and 56.6±15 years were in the LIF and standard treatment
Table 1. Demographic Parameters

<table>
<thead>
<tr>
<th></th>
<th>LIF Group (n=21)</th>
<th>Control Group (n=21)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>65.1±13</td>
<td>56.6±15</td>
<td>0.07</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>52.4%</td>
<td>33.3%</td>
<td>0.35</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, %</td>
<td>80.9%</td>
<td>61.9%</td>
<td>0.31</td>
</tr>
<tr>
<td>Black, %</td>
<td>19.1%</td>
<td>33.3%</td>
<td></td>
</tr>
<tr>
<td>Asian, %</td>
<td>0</td>
<td>4.8%</td>
<td></td>
</tr>
<tr>
<td>Vascular risk factors at admission, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>71.4%</td>
<td>65%</td>
<td>0.74</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28.6%</td>
<td>23.8%</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>28.6%</td>
<td>33%</td>
<td>1.00</td>
</tr>
<tr>
<td>Current smoker</td>
<td>28.6%</td>
<td>38.1%</td>
<td>0.74</td>
</tr>
<tr>
<td>Prior cerebrovascular events (either transient ischemic attack or cerebrovascular accident)</td>
<td>28.6%</td>
<td>23.8%</td>
<td>1.00</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>19.1%</td>
<td>19.1%</td>
<td>1.00</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>4.8%</td>
<td>4.8%</td>
<td>1.00</td>
</tr>
<tr>
<td>Mean time to presentation, mean±SD hours</td>
<td>3.3±2.0</td>
<td>25.8±20</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*Statistically significant at an alpha=0.05.

The mean time between the onset of CRAO to presentation to an ophthalmologist or emergency room was 3.4±2.0 hours in the LIF group compared with 25.8±20 hours in the control group (95% CI: 13.5 to 31.4 hours; P<0.001.). In 76% of control subjects, time of presentation after 15 hours was the main reason for not receiving LIF. Six patients presented within 15 hours but were not given tPA. Of these, 2 patients refused LIF treatment; 2 patients had significant medical comorbidities and were deemed unsuitable for LIF; one patient had an elevated erythrocyte sedimentation rate, raising the clinical suspicion of giant cell arteritis. The patient underwent a temporal artery biopsy that was negative and thus is included in our analysis. Finally, one patient had an ipsilateral internal carotid artery occlusion on angiography and the microcatheter could not be passed through the occlusion for LIF. These patients all received standard therapy.

The mean time from onset of visual loss to LIF was 9.3±2.9 hours. The mean time of the LIF procedure was 96.3±28.3 minutes. The mean dose of tPA was 11.25±3.5 mg.

Visual Outcome
VA at presentation was 20/400 or worse in all patients. There was no statistically significant difference in the distribution of VA at presentation between the 2 groups (Table 2). In the LIF group, 71.4% experienced a one line or more of improvement in VA within 24 hours after completion of LIF compared with baseline versus 9.5% in the control group (P<0.001). At final examination, 76.2% of subjects in the LIF group had an improvement in VA of one line or more (mean follow-up, 15 months) versus 33.3% in the control group (mean follow-up time, 11 months; P=0.018; Table 3).

Univariate logistic regression for the primary outcome showed that patients who received LIF were 6.4 times more likely to have an improvement in VA compared with the control group (95% CI: 1.65 to 24.77; P=0.0045). Adjusted analysis (including adjustment for gender, prior history of stroke/transient ischemic attack, and history of hypercholesterolemia) yielded an OR for an effect of LIF of 36.0 (95% CI: 3.09 to 417.6; P=0.0001; Table 4). We assessed for

Table 2. Visual Acuity at Admission*

<table>
<thead>
<tr>
<th>Initial Acuity</th>
<th>LIF Group (n=21)</th>
<th>Control Group (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No light perception</td>
<td>4.8%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Light perception</td>
<td>9.5%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Hand movement</td>
<td>47.6%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Count fingers</td>
<td>28.6%</td>
<td>28.6%</td>
</tr>
<tr>
<td>20/800</td>
<td>0</td>
<td>9.5%</td>
</tr>
<tr>
<td>20/400</td>
<td>9.5%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

*Percentage distribution of subjects in each visual acuity category for the LIF and control groups. There was no statistically significant difference between the groups using Fisher exact test (P=0.31).

Table 3. Visual Acuity Within 24 Hours After LIF or Standard Therapy and At Final Examination

<table>
<thead>
<tr>
<th></th>
<th>LIF Group (n=21)</th>
<th>Control Group (n=21)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate vision change at 24 hours postadmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual improvement by ≥ 1 line</td>
<td>71.4%</td>
<td>9.5%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>No change in vision</td>
<td>28.6%</td>
<td>71.4%</td>
<td></td>
</tr>
<tr>
<td>Visual worsening by ≥1 line</td>
<td>0%</td>
<td>19.1%</td>
<td></td>
</tr>
<tr>
<td>Vision change at final follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual improvement by ≥1 line</td>
<td>76.2%</td>
<td>33.3%</td>
<td>0.018*</td>
</tr>
<tr>
<td>No change in vision</td>
<td>19.0%</td>
<td>38.1%</td>
<td></td>
</tr>
<tr>
<td>Visual worsening by ≥1 line</td>
<td>4.8%</td>
<td>28.6%</td>
<td></td>
</tr>
<tr>
<td>Follow-up time, months±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/400 9.5% 9.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/800 0% 9.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/400 0% 9.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant.

Table 4. Multivariate Logistic Regression Analysis With Adjusted OR for Visual Acuity Improvement

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIF</td>
<td>36.0</td>
<td>P=0.0001*</td>
</tr>
<tr>
<td>History of elevated cholesterol</td>
<td>0.10</td>
<td>P=0.0195</td>
</tr>
<tr>
<td>Prior transient ischemic attack or stroke</td>
<td>0.11</td>
<td>P=0.054</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.08</td>
<td>P=0.025</td>
</tr>
</tbody>
</table>

*Multivariate stepwise logistic regression adjusting for gender, history of stroke/transient ischemic attack, and history of hypercholesterolemia shows that LIF is the most statistically significant factor associated with VA improvement.
interaction between use of LIF and prior conservative measures as well as between LIF and baseline acuity. No significant interaction was found (OR: 1.97, \( P = 0.57 \) and OR: 4.5, \( P = 0.19 \), respectively).

Secondary analyses were performed using a 3-level outcome measure. The reference group was no change in visual acuity. Using the same set of covariates described in the multivariate model, subjects were 22 times more likely to experience improvement in VA and 86% less likely to experience worsening of VA if they received LIF (adjusted; \( P = 0.0003 \)). In addition, a history of hypercholesterolemia impacted negatively on visual outcome, although only in the adjusted models (adjusted OR: 0.10, 95% CI: 0.012 to 0.85; \( P = 0.02 \); Table 4).

A post hoc analysis was performed using a visual acuity improvement of 3 lines or more. One third of the group receiving LIF had an improvement of VA by 3 lines or more compared with 4.8% of the standard therapy group (\( P = 0.018 \)). On multilogistic regression analysis, subjects undergoing LIF had a 13 times increased likelihood of achieving a VA improvement of 3 lines or more compared with those receiving standard therapy (OR: 13, 95% CI: 1.2 to 145; \( P = 0.03 \)). In addition, subjects in the LIF group were 4.9 times more likely to have a final VA of 20/200 or better (OR: 4.9, 95% CI: 1.05 to 23.4; \( P = 0.04 \)).

Complications

Two patients in the LIF group had groin hematomas that resolved without long-term sequelae. No intracerebral, intraocular, or orbital hemorrhages occurred.

Discussion

Patients with presumed thromboembolic CRAO have a poor visual outcome with 78% having no spontaneous visual recovery.2 Current standard therapies do not alter the natural history of disease, whereby 0% to 30% may have spontaneous improvement.6,23 In contrast, case series of patients with CRAO who undergo LIF report an improvement in final VA in 40% to 74% of subjects, and retrospective, nonrandomized studies of LIF treatment in CRAO document an improvement of VA in 20% to 70% of LIF subjects.11,12,24

In our study, 71% of subjects in the LIF group had an improvement of VA within the first 24 hours and 76% at final examination. In contrast, 9.5% and 33.3% of patients in the standard therapy cohort experienced improvement in VA at 24 hours and final examination, respectively. These point estimates are in keeping with previous studies and more importantly demonstrate a significant therapeutic advantage over the proportion of subjects who have a VA improvement either spontaneously or with standard therapy alone.6,23 This is reflected in the regression analyses in which the use of tPA was associated with a 36-fold greater likelihood of recovery of VA versus standard therapy. In addition the benefit of tPA was also found using a more stringent outcome measure of an improvement in VA of 3 lines or more.

LIF is not without potential risk. Cerebral ischemia, intracerebral hemorrhage, and bleeding at the site of femoral catheterization have been documented.15 The hemorrhage risk is related to the dose of thrombolytic, whereas the ischemic stroke risk may be related to the procedure duration.17–19 Our study was unique in that we used a dose titration of tPA in aliquots until clinical improvement of CRAO occurred. Using this approach, the mean tPA dose of 11.3 \( \pm 2.5 \) mg was smaller compared with a range of 30 to 70 mg of tPA used in previous studies.11,14–16 The duration of LIF of 96.3 \( \pm 28.3 \) minutes was within the range of procedural times of 70 to 150 minutes previously cited.11,16

An important consideration in determining the risk–benefit ratio of LIF in CRAO is regular clinical practice is the severity of adverse events. In contrast to thrombolysis in cerebral ischemia in which the rate of hemorrhage varies from 3% to 20%,8,25,26 there are no reports of intraocular hemorrhage to date. The thrombolytic-related intracranial hemorrhage risk, according to the myocardial infarction literature, is 1%.10,27

The rationale for thromboembolic CRAO fibrinolysis is the assumption of a fibrinoplatelet clot composition that may be thrombolytic-responsive. Criticism of this assumption revolves around the fact that in one study of CRAO due to emboli, 57% (40 of 70) were found to be of the cholesterol type.2,28,29 It is commonly thought that the site of occlusion in CRAO is at the level of the lamina cribrosa and as such is not visible on funduscopic examination.7,20 The study by Arruga et al28 demonstrating the high proportion of patients with cholesterol emboli was a study of visible emboli and does not necessarily reflect the distribution of emboli types in CRAO and thus does not invalidate the use of thrombolysis.

In internal carotid occlusion primate models of ischemic stroke, relief of the occlusion results in recovery of cortical action potentials by salvaging cells in the ischemic penumbra.31 Similarly, reperfusion after occlusion of blood flow in CRAO primate models also results in restoration of retinal and visual evoked potentials.32,33 These findings, and the observation in permanent CRAO of the presence of a sluggish retinal circulation on fluorescein angiography, suggests the presence of collateral blood supply and a retinal penumbra.2,29 Reperfusion of this retinal penumbra could explain the marked VA improvement after LIF.

A potential limitation of this study is its nonrandomized nature that is subject to selection bias. In our study, the time to presentation was much shorter in the LIF group as compared with the standard therapy group. The fact that subjects arriving earlier were selected for LIF reperfusion therapy, compared with those who arrived later and were treated with standard therapy, could skew the results in favor of thrombolysis. Nevertheless, the point estimate of the efficacy of thrombolysis corresponds with previous studies and is above that of the rate of spontaneous recovery in CRAO.

Another limitation is the lack of fluorescein angiography and visual field assessment in all patients, making it impossible to subclassify our subjects with the same degree of detail as previous studies.2 Although it is possible that the apparent efficacy of LIF in our study reflects the spontaneous recovery rate described in transient CRAO, transient CRAO comprise approximately 16% of all CRAOs.2 We believe that the probability that we enrolled consecutive transient CRAO subjects in our LIF group is low and our sample likely reflect
the majority of CRAO cases that are thromboembolic in origin.

Conclusion
Our results support the hypothesis that the treatment of acute thromboembolic CRAOs with LIF administered in aliquots results in a better visual outcome than standard therapy alone and has few complications. It is a biologically plausible therapy modeled on the treatment of similar conditions such as stroke and myocardial infarction. Nevertheless, because of the nonrandomized nature of this and previous studies, LIF use cannot be recommended as standard therapy in daily clinical practice pending the publication of randomized clinical trials.34 Such a trial is already underway in Europe, and a further trial in North America may be warranted in light of these findings.

Disclosures
None.

References
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