EDITORIALS

Thrombolysis for Acute Central Retinal Artery Occlusion: Is it Time?

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CENTRAL RETINAL ARTERY OCCLUSION (CRAO) TYPically results in severe and permanent visual loss.[1,2] Even if visual acuity (VA) spontaneously improves in up to 22% of patients with nonarteritic CRAO,[2] less than 10% of patients report a meaningful recovery of vision.[1] CRAO is a relatively rare disorder with a frequency of approximately one per 10,000 outpatient visits in the United States,[3] and the incidence in the general population is probably less than 3.5 per 100,000.[4] Patients with CRAO are rarely seen acutely, and there is no consensus regarding management. None of the "conservative" treatments classically offered to patients with acute CRAO (such as reducing intraocular pressure (IOP), ocular massage, vasodilators, hemodilution, hyperbaric oxygen, steroids, heparin, or aspirin) has proven effective, and their use is only based on anecdotal reports or small case series.[1]

Thrombolytic agents and mechanical thrombectomy are now routinely used for numerous acute arterial and venous occlusions, including cerebral infarctions.[5] At present, the use of intravenous tissue plasminogen activator (tPA) in cerebral infarction is restricted to selected patients treated within three hours of symptom onset (the recommended dose is 0.9 mg/kg [maximum of 90 mg] infused over 60 minutes). Intra-arterial thrombolytic therapy delivered during a selective catheter angiogram either by regional or by local infusion directly into the thrombus can be administered up to six hours after stroke symptom onset.[5] Intra-arterial approaches have the potential advantages of increased recanalization rates, and perhaps enhanced safety because of a reduction in the total dose of drug administered. Disadvantages include the limited availability of facilities and of personnel who are capable of performing intra-arterial therapy, and the inherent delays in drug administration related to the logistics in assembling an appropriate team and performing an angiogram.[5–8]

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IS IT TIME TO CONSIDER ALSO TREATING ACUTE CENTRAL RETINAL ARTERY OCCLUSION PATIENTS WITH THROMBOLYTICS?

OVER THE PAST YEAR, TWO LARGE REVIEWS[1,9] AND TWO studies[10,11] have suggested that thrombolytics in the treatment of acute CRAO may improve the visual outcome with very few serious complications. Although the treatment of CRAO with thrombolytics remains debated,[1,9,12] more and more investigators are using this treatment in selected patients with acute CRAO.[13] Although the trend has been to offer intra-arterial thrombolytics directly into the internal carotid artery or into the ophthalmic artery,[1,11,13] in this issue of THE JOURNAL, Hattenbach and associates [10] suggest that intravenous thrombolysis may be an easier and efficient alternative. The published literature includes at least 122 CRAO cases treated with intravenous thrombolytics[1,13] and nearly 300 cases treated with intra-arterial thrombolytics.[1,11,13] Hattenbach and associates[10] add 28 CRAO cases treated with intravenous tPA. These enthusiastic publications have emphasized a "significant" visual improvement in treated cases and have also demonstrated that serious complications of thrombolysis are relatively rare among CRAO patients. However, major methodological flaws in most of these studies, as well as the absence of a well-designed randomized controlled study, have made the use of thrombolytics in acute CRAO the subject of major controversy.[1,9,12]

ARE WE CORRECT TO ASSUME THAT THROMBOLYSIS SHOULD WORK IN ACUTE CENTRAL RETINAL ARTERY OCCLUSION?

MOST DATA ON THE TREATMENT OF ACUTE CRAO WITH thrombolytics have been extrapolated from studies evaluating the use of thrombolytics for the treatment of myocardial and cerebral infarction.[1] Acute CRAO with retinal ischemia shares numerous similarities with acute intracranial arterial occlusion and cerebral infarction, and coronary arterial occlusion and myocardial infarc-

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tion. The rationale for thrombolytic therapy is based on the recognition that the majority of ischemic events are caused by thrombotic or thromboembolic arterial occlusions. There is currently no effective neuroprotective agent in acute ischemia, and most therapeutic interventions are aimed at opening the occluded artery before irreversible tissue damage from ischemia occurs. Administration of thrombolytics, sometimes with mechanical thrombectomy, has proven successful in the majority of patients with acute myocardial ischemia and in selected patients with acute cerebral ischemia.[5] So, why not in CRAO?

ARE RETROSPECTIVE STUDIES OR INTERVENTIONAL CASE SERIES SUFFICIENT TO DEMONSTRATE THE EFFICACY AND SAFETY OF THROMBOLYSIS IN ACUTE CENTRAL RETINAL ARTERY OCCLUSION?

OBVIOUSLY, ONLY TREATMENTS EVALUATED IN RANDOMized controlled clinical trials should be recommended in clinical practice.[6] Such trials are currently lacking in acute CRAO. Even the long-awaited prospective multicenter study of the European Assessment Group for Lysis in the Eye (EAGLE)[14] is likely not to give us definite answers. This European study, initiated in 2002, randomized acute CRAO patients to either intra-arterial tPA or "conservative treatment alone," which included nonproven therapies such as ocular massage, decrease of IOP, isovolemic dilution, single-dose heparin, and aspirin 100 mg/day. Recruitment was difficult and slow, and the study was terminated a few months ago after only 80 patients were included. The rarity of CRAO,[3,4] and common delays in diagnosis, with very few patients presenting to the ophthalmologist within a few hours of visual loss, explain why recruitment was a major limiting factor in the EAGLE study. Unfortunately, there is no reason it should be easier for any study performed in the United States.

Despite their limitations, previous studies have suggested that intra-arterial thrombolysis with tPA or urokinase infused at the origin of the ophthalmic artery (dose based on recanalization seen during the angiogram), sometimes associated with heparin, results in major improvement of visual function in about 35% of patients, while intravenous thrombolysis with tPA results in major improvement of visual function in about 50% of patients.[1,10,11] This is probably better than the visual prognosis of untreated CRAO patients, although measurements of visual outcome vary from study to study.[1,2,9,12]

WHAT HAVE WE LEARNED FROM PREVIOUS STUDIES EVALUATING THE TREATMENT OF CENTRAL RETINAL ARTERY OCCLUSION WITH THROMBOLYTICS?

UNFORTUNATELY, THE HETEROGENEITY OF THERAPEUTIC regimens, pretreatment and posttreatment evaluations, and therapeutic window (time from visual loss to drug infusion) make it very difficult to draw conclusions from previously published studies.[1,12] Prior studies have used various thrombolytic agents (most often tPA or urokinase), administered by different routes (intra-arterial or intravenous), either continuously (infusion) or by aliquots, and at various doses (usually similar to those used for cerebral infarction). Thrombolytics have been prescribed in isolation, or with heparin, and were administered within a few hours to a few days after visual loss. The EAGLE Study[14] used intra-arterial tPA administered by aliquots of 15 mg (maximum dose of 50 mg) within 24 hours of visual loss, followed by heparin for five days. A detailed evaluation, including ocular examination with VA measurement by Early Treatment Diabetic Retinopathy Study (ETDRS), slit-lamp examination, tonometry, funduscopic examination, Goldmann visual field, retinal fluorescein angiography, blood pressure (BP), laboratory testing, and electrocardiogram was performed prior to treatment, thereby delaying the administration of thrombolysis. A study at Johns Hopkins[11] used intra-arterial tPA administered by aliquots of 3 mg (maximum dose of 20 mg) within 15 hours of visual loss, and followed by heparin for 24 hours. Interestingly, in the Hopkins series, the mean time from visual loss to diagnosis of CRAO was 3.4 hours ± 2 hours (range, 45 minutes to 7.5 hours), while intra-arterial thrombolysis was administered only from 4.15 to 15 hours (mean, 9.2 hours ± 2.9 hours) after visual loss, suggesting that intra-arterial administration delayed the treatment by a mean of 5.8 hours ± 2.1 hours (range, 2.75 to 8.5 hours). Pretreatment evaluation included Snellen VA, tonometry, funduscopic examination, BP, laboratory testing, electrocardiogram, and brain computed tomography or magnetic resonance imaging to exclude cerebral hemorrhage. In the current study by Hattenbach and associates,[10] time of onset of visual loss to treatment was dramatically reduced by limiting pretreatment evaluations. Only Snellen VA, tonometry, funduscopic examination, BP, and laboratory testing were obtained prior to administering tPA intravenously in a manner similar to that recommended for patients with myocardial or cerebral infarction. However, in order to limit hemorrhagic complications, they chose a lower dose of thrombolytics (50 mg tPA over 60 minutes, instead of 0.9 mg/kg for cerebral infarction), which was started within 12 hours of visual loss. However, they also gave heparin for five days and aspirin 100 mg/day (unlike

the recommendations for cerebral infarction, which discourage the early combination of intravenous thrombolytics with anticoagulants or aspirin).

These recent studies emphasize the lack of agreement regarding treatment strategies, as well as the need to standardize protocols. Adequate pretreatment documentation of visual function, and limited tests to screen for potential contraindications, are necessary, but should be kept to the strict minimum in order to reduce delay in treatment.[6] The therapeutic window for rescuing ischemic but still viable tissue is challengingly brief.[1,15] Neuronal death and retinal infarction evolve progressively in a time-dependent fashion determined by both the duration and severity of the ischemic insult. Early reperfusion of ischemic tissue has the potential to limit the cellular, biochemical, and metabolic consequences of retinal ischemia that ultimately lead to irreversible visual loss.[5–7] Animal model studies have suggested that the ideal therapeutic window for CRAO is less than four hours.[12] However, it is likely that six hours is acceptable for many patients with incomplete CRAO. Hattenbach and associates[10] showed that patients treated within 6.5 hours of visual loss had a better visual outcome than those treated within 6.5 and 12 hours after onset of visual loss. This is much shorter than what was accepted in the EAGLE[14] and Hopkins[11] studies and may not be compatible with intra-arterial administration of thrombolytics.[6,7] This is why administration of intravenous tPA to patients presenting within three hours of stroke onset, followed by a catheter angiogram and possible additional intra-arterial tPA into the thrombus when there is residual arterial occlusion, seems attractive to some investigators, and is currently under investigation for cerebral infarction.[8] Perhaps the combination of intravenous tPA administered within three hours of visual loss, followed by an angiogram and intra-arterial tPA in those CRAO patients with no retinal reperfusion after intravenous tPA, should also be considered and evaluated.[7]

DO WE REALLY NEED A RANDOMIZED CLINICAL TRIAL EVALUATING THROMBOLYTICS FOR ACUTE CENTRAL RETINAL ARTERY OCCLUSION?

IT IS TRUE THAT IN THEORY, WE NEED A WELL-DESIGNED randomized, controlled, double-masked clinical trial evaluating the effect of thrombolysis in CRAO.[6] The Hattenbach study[10] confirms that at least three arms would be necessary, including intra-arterial vs intravenous thrombolysis, and placebo. A fourth arm could include combined intravenous and intra-arterial thrombolytics. The optimal dose of thrombolytics and the mode of administration (infusion or aliquots) remain unknown and may require separate studies. Whether adjuvant therapies such as heparin or aspirin are helpful and safe also remains unknown. It should be kept in mind that administering placebo with intra-arterial intervention would be risky, and that double-masked trials using thrombolytics are costly and challenging.[6] Finally, the ideal therapeutic window is probably less than three hours and likely not longer than six hours. Only a large multicenter clinical trial including a few hundred patients would be able to answer all these questions. Given how rarely acute CRAO is diagnosed within a few hours of visual loss, it is unlikely that such a clinical trial will ever become a reality.

Thrombolysis is not without potential risk. Cerebral ischemia, intracerebral hemorrhage, systemic hemorrhages, and bleeding at the site of catheterization for intra-arterial administration have been documented.[1] However, in a patient preference survey,[16] 37% of CRAO patients with one residual seeing eye, and 80% of CRAO patients with no residual seeing eye, were willing to accept some risk of stroke or life-threatening complication to triple the chances of recovering 20/100 VA in an eye with CRAO. Treatment of CRAO with thrombolysis cannot just be dismissed because "there is no randomized clinical trial." There are now enough data to consider it in patients seen within a few hours of visual loss from CRAO. In the absence of an ongoing clinical trial, this treatment for selected patients should be discussed with institutional stroke and interventional radiology teams. Patients treated very acutely seem to have a better chance of recovery, and the study by Hattenbach and associates[10] emphasizes that intravenous tPA administered in the emergency department by a stroke neurologist can be efficient and safe in selected patients. The first step toward a multicenter trial may be the development of consensus guidelines with specific recommendations regarding treatment protocols, and pretreatment and posttreatment evaluations of acute CRAO patients. Data collected into an international registry would provide the necessary pilot data prior to deciding whether a complex and costly clinical trial will ever be possible. Most importantly, because acute therapeutic interventions are emerging, the ophthalmologic community must develop strategies to get patients with acute visual loss to emergency departments where acute treatments can be administered.

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