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Thrombolytic Treatment of Central Retinal Artery Occlusion (CRAO)

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Abstract

This review focuses on the literature available for the treatment of CRAO with thrombolysis including intra-arterial and intravenous approaches. Although CRAO is an ocular emergency that can lead to disabling blindness, no consensus treatment guidelines currently exist. Based on review of the current literature, further clinical trials are indicated to investigate the safety and efficacy of early thrombolytic therapy for CRAO.

Keywords: CRAO; Thrombolysis; Central retinal artery occlusion; tPA; Intra-arterial thrombolysis

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Central retinal artery occlusion (CRAO) is a cause of acute vision loss, which can lead to irreversible blindness. The natural history is not well understood but one large study suggests the potential for some spontaneous improvement within the first 7 days from symptom onset [1]. Nevertheless the prognosis remains quite poor, with more than half of CRAOs resulting in a final visual acuity of 20/200 or worse [2]. Conservative treatments including oral acetazolamide, ocular massage, paracentesis of the anterior chamber, and topical beta blockers have not been shown to alter visual outcome [3]. As with cerebral stroke, timing is critical for the treatment of CRAO. Results from primate studies showed no evidence of vision loss for the first 97 minutes of occlusion, variable partial vision loss after 105-240 minutes of occlusion, and irreversible retinal and optic nerve damage after 240 minutes of occlusion [4], suggesting that any successful treatment would need to be delivered within 4 hours of onset. Despite the time-sensitive nature of CRAO, risk of disability from resulting monocular blindness, and association with stroke risk factors, no CRAO-specific treatment guidelines currently exist. Given the suspected embolic mechanism of nonarteritic CRAO [5], the use of intra-arterial thrombolysis (IAT) and intravenous tissue plasminogen activator (IV tPA) have been used to treat CRAO. This review will focus on the use of IAT and IV tPA for the treatment of CRAO.

IAT was first used to treat CRAO in 1984 [6]. Since then, several studies have demonstrated that IAT may be an effective treatment of CRAO [7-12]. In 2000, a meta-analysis was published reviewing 16 retrospective, nonrandomized studies. These studies included 100 patients who were treated with intra-arterial tPA or urokinase ranging from 3-60 hours from symptom onset. In patients treated with IAT, there was a mean improvement of three lines on the Snellen chart. Overall, 14% of patients achieved 20/20 or better visual acuity and 37% of patients achieved 20/200 or better. Mean time of treatment after onset of symptoms was 11.6 hours and complications included transient hemiplegia, hypertensive crisis and puncture site hematomas for an overall complication rate of 6% [10]. In 2002, a retrospective study was published comparing 62 patients treated with IAT (tPA or urokinase) versus 116 patients treated conservatively (including paracentesis, acetazolamide, anticoagulation and/or antiplatelets). Time from symptom onset to treatment ranged from 1-312 hours with median time to treatment of 9 hours for both groups. They reported that 58% of the IAT group compared with 29% of the control group demonstrated improved visual acuity defined as 1 line of improvement on the Snellen chart (p=0.002). Notably, 77% of patients who were treated within 6 hours showed visual improvement as compared to only 26% of patients who were treated conservatively. Only 2 patients had complications (transient aphasia and transient hemiparesis)-both occurred in patients >80 years old [11]. Subsequently, a retrospective case-control study was performed evaluating IAT with urokinase within 6 hours of vision loss. Improvement in visual acuity was more likely in the IAT group and there was a trend towards better outcomes when patients were treated within 4 hours of vision loss, though the results were not statistically significant. There were 3 complications reported – 2 TIAs and 1 minor stroke [12]. In 2008, a systematic review of 8 studies from 1991-2005 once again demonstrated overall improvement in visual acuity after IAT (13% with 20/20

or better and 41% with 20/200 or better). However, the overall complication rate for these 8 studies was 4.5% including local hemorrhage, TIA, hypertensive crisis, symptomatic intracerebral hemorrhage (ICH), and stroke [13].

In an effort to reduce the complication rate of IAT, Aldrich and colleagues treated patients with intra-arterial tPA in small aliquots rather than continuous infusion for a smaller total dose of tPA. The mean time to treatment was less than 4 hours in IAT group. Significant visual acuity improvement (at least 1 line on the Snellen chart) was reported in 76% of patients treated with IAT versus 33% of patients in the control group (p=0.012). The IAT group was 13 times more likely to have improvement in visual acuity of 3 lines or more and 4.9 times more likely to have a final visual acuity of 20/200 or better. Complications included puncture site hematomas but no strokes/TIAs or symptomatic ICH [14].

The EAGLE trial, a prospective randomized multicenter trial, randomized 82 patients to treatment with intra-arterial tPA versus maximum conservative treatment. In contrast to previous CRAO studies, both groups were also treated with low dose heparin twice daily for 5 days and aspirin 100 mg daily for 4 weeks. Mean symptom onset to treatment time was 13 hours in the IAT arm. Severe complications in the IAT arm were limited to two symptomatic ICHs. Minor complications included groin hematoma, headache and troponin increase. There was no significant visual improvement with IAT and a higher rate of complications in the IAT group, which led to early termination of the study [15].

Notably, the overall complication rates for these retrospective and case control studies ranged from 4.5-8% with few cases of symptomatic ICH reported [10-14]. The EAGLE trial was discontinued after 2 sICHs, though these patients were concurrently treated with aspirin and heparin [15]. In comparison, the NINDS trial that led to the approval of IV tPA for the treatment of acute stroke reported symptomatic ICH in 6% of patients [16].

Literature supporting the use of IV tPA for the treatment of acute CRAO is limited to case reports and case series, which have also suggested efficacy of IV tPA for CRAO [17-19]. One case series evaluated 12 patients who were treated with IAT 2-18 hours from symptom onset. Standard dose IV tPA was used followed by treatment with anticoagulation 24-hours later. Ten of the 12 patients demonstrated improved visual acuity (2-8 lines of improvement on Snellen chart), which was maintained through the first 3 months. Complications reported included neovascular glaucoma, but there were no reports of hemorrhage [18]. Hattenbach and colleagues reported a series of 28 patients treated with 50 mg IV tPA, IV heparin bolus of 1200 units followed by continuous infusion (aPTT goal 60-80), and aspirin 100 mg within 12 hours of vision loss. Visual acuity improved (3 lines or more on Snellen chart) in 9 of 28 patients (32%). These 9 patients were all treated within 6.5 hours of vision loss. None of the patients treated after 6.5 hours demonstrated a similar degree of visual acuity improvement. Despite combined antiplatelet-anticoagulant therapy following IV tPA, no hemorrhagic complications were reported [19].

Subsequently, a placebo-controlled randomized trial investigating IV tPA versus normal saline within 20 hours of symptom onset was performed. Two of the 8 patients treated with IV tPA demonstrated transient improvement of visual acuity. Both patients were among those treated within 6 hours suggesting a possible benefit to early treatment. However, the study was terminated after a symptomatic intracerebral hemorrhage occurred [20].

As reviewed here, there have been multiple observational studies suggesting efficacy of both IAT and IV tPA in the treatment of acute CRAO [7-14,17-19]. Unfortunately, the two randomized controlled trials were terminated early due to safety concerns and neither demonstrated a significant improvement in visual acuity with thrombolytics [15,20]. Of note, both of these trials had a mean time to treatment greater than 6 hours. The actual therapeutic window for CRAO in humans is unknown but available clinical data suggest that it may be less than 6 hours [11,12,19] while primate studies indicate that the window may be less than 4 hours [4].

Although nonarteritic CRAO is recognized amongst ophthalmologists and neurologists as an ocular emergency, no consensus treatment guidelines currently exist. Future clinical trials are needed to investigate the safety and efficacy of early thrombolytic therapy (administered at least within 6 hours of vision loss). Early treatment with IV tPA has the advantages of emergency room familiarity allowing for quicker administration, as well as low complication rates. Early IAT has shown the most clinical improvement in previous studies, though its use may be limited since it is invasive and requires quick access to an endovascular facility. One major barrier to the completion of such trials is that patients commonly present beyond the therapeutic window unaware of the emergent nature of their vision loss. Increased public awareness that sudden onset loss of vision is a stroke to the eye could encourage earlier presentation to the emergency department, similar other stroke syndromes. An increased awareness of outpatient practitioners, first responders, and emergency medicine staff is also essential for proper triage and potential treatment of CRAO.

Conflicts of Interest: The authors do not report any potential conflicts of interest.

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