Thrombolytic therapy in central retinal artery occlusion: cutting edge therapy, standard of care therapy, or impractical therapy?

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Purpose of review

Numerous therapeutic options have been suggested for the treatment of central retinal artery occlusion (CRAO) such as ocular massage, anterior chamber paracentesis, physical exercise, and medication-induced reduction of intraocular pressure. Because of the lack of a proven effective treatment for CRAO, there has been a strong effort to develop alternative therapies. Recently, thrombolytic therapy has been suggested as a viable therapy for CRAO. The aim of this review is to provide an update on the progress of thrombolytic therapy for CRAO.

Recent findings

Although there is no consensus on a standardized treatment regimen for CRAO, emerging evidence suggests that thrombolytic therapy may be effective if administered promptly. Despite the benefit of thrombolytic therapy, on the basis of the results of case reports and case series, randomized controlled studies are necessary to ultimately prove the effectiveness of the treatment.

Summary

Thrombolytic therapy has yet to be validated as an effective treatment of CRAO. The execution of randomized, controlled trials is greatly needed to establish whether thrombolytic therapy can be considered standard of care therapy for CRAO.

Keywords

central retinal artery occlusion, emboli, thrombolytic therapy, tissue plasminogen activator

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Introduction

Central retinal artery occlusion (CRAO) is an acute vascular event characterized by painless unilateral visual impairment. The incidence of CRAO is relatively low, approximately 1–15 people per 10 000 [1–3]. Clinically, CRAO presents with acute-onset and profound visual loss very often associated with a poor visual prognosis [2,4]. CRAO is a serious ophthalmologic emergency that possibly with timely treatment can minimize the degree of visual compromise [5,6]. A thromboembolic event of the central retinal artery is felt to be the primary cause in most cases of CRAO [1,2]. Approximately 20% of patients with CRAO have concomitant carotid artery disease, which may present as transient monocular visual loss (amaurosis fugax) or transient hemispheric ischemic attack prior to the permanent loss of vision [5,7]. In older individuals (more than 55 years of age), CRAO may be the result of giant cell arteritis (GCA) [8,9].

CRAO results in infarction of the inner retina leading to a quantifiable reduction in the thickness of the inner retinal layers [10]. Although spontaneous recovery is possible, it is uncommon and unpredictable [11]. In addition to visual compromise, a serious ocular complication of CRAO is iris neovascularization, which can ultimately lead to neovascular glaucoma in approximately 5% of cases [12]. Patients with CRAO are also at a high risk of heart disease and acute ischemic stroke [1,13]. Individuals with visible retinal emboli (regardless of whether occlusion is present) have a 56% mortality rate over 9 years and those with CRAO carry a shorter life expectancy when compared with non-CRAO controls [14].

Epidemiology

As mentioned above, the incidence of CRAO is low and there appears to be no age, sex, race, or ethnic bias [1,11]. Typically, CRAO is unilateral but can occur in both eyes simultaneously in 1–2% of cases [1,2].

Risk factors and associations

Thromboembolic disease is believed to be the most common cause of CRAO [2,13]. Patients with CRAO often share the same risk factors as those with

atherosclerotic disease [1–3]. In particular, systemic diseases more commonly seen in patients with CRAO are as follows [1–9,11]:

(1) diabetes mellitus;
(2) collagen vascular disease;
(3) hyperuricemia;
(4) blood dyscrasia (i.e. antiphospholipid syndrome, hemophilia, protein C deficiency, antithrombin III deficiency);
(5) chronic smoking;
(6) hyperlipidemia;
(7) hypercoagulopathies;
(8) cardiac valvular disease;
(9) carotid artery disease;
(10) atrial fibrillation;
(11) systemic arterial hypertension.

Individuals with cardiovascular disease (valvular heart disease, endocarditis, aortic arch disease, and carotid artery disease) are at a higher risk for developing CRAO [6,9,11]. A recent study [11] evaluating 1379 patients with CRAO noted 9% of patients had atrial fibrillation, 18% had carotid artery disease, and 19% had an ischemic stroke. Other vasculitides that can cause CRAO aside from GCA include systemic lupus erythematous, polyarteritis nodosum, Henoch–Schönlein purpura, Wegener's granulomatosis, and Kawasaki's disease [6,15–18].

Clinical presentation

CRAO typically presents as sudden, painless, unilateral loss of vision. The visual loss is often severe (worse than 20/200) but patients seldom exhibit absence of light perception [19–21]. Some patients may experience amaurosis fugax prior to the visual loss, suggesting carotid artery disease or GCA [2,5,9].

Occlusion of the central retinal artery leads to compromised blood supply to the retina, resulting in arterial attenuation and retinal opacification associated with a 'cherry red spot'. Sludging of red blood cells can be seen in the retinal arterial circulation, a process known as boxcarring. In some cases, there may be single or multiple emboli visible throughout the retinal arterioles [11,19], and occasionally there may be optic disc edema [9]. Retinal hemorrhages are seldom seen.

A prospective study [22] of 2000 normal eyes found 14.6% of eyes have a cilioretinal artery. Cilioretinal artery has a greater predilection for occlusion in the setting of CRAO because of its lower perfusion pressure compared with the central retinal artery [22]. Twenty-five percent of eyes with CRAO have a cilioretinal artery [23].

Table 1 Classification of central retinal artery occlusion

Nonarteritic CRAO	'Classic' type presenting with a cherry red spot, boxcarring, and severe visual loss
Nonarteritic CRAO with cilioretinal artery sparring	Central visual acuity is relatively preserved because of the continued perfusion of the cilioretinal artery
Arteritic CRAO	In the setting of inflammatory vasculidities such as giant cell arteritis
Transient nonarteritic CRAO	Reversible visual loss lasting minutes to hours

CRAO, central retinal artery occlusion. Adapted from [9,20,23].

CRAO has been subdivided into four clinical categories according to observable changes in the retina, optic disk, and retinal vessels (Table 1) [9,20,21,23].

Diagnostic evaluation

The fundus appearance of CRAO (see above) is often diagnostic of the disease and few ancillary tests are required to confirm the clinical findings. Intravenous fluorescein angiography (IVFA) and optical coherence tomography (OCT) can be useful as confirmatory tests in the setting of an uncertain diagnosis [2,9,10]. IVFA characteristically shows delayed or restricted retinal arteriole filling [24], whereas OCT displays increased inner retinal layer thickness in the acute phase [10]. Additional clinical evaluation is directed toward determining the underlying cause of CRAO. The presence of systemic symptoms (such as headaches, scalp tenderness, and arthralgias), optic disc edema, and involvement of the posterior ciliary arteries as seen by IVFA should raise the concern for GCA, and an immediate erythrocyte sedimentation rate and C-reactive protein should be obtained [23,25].

A number of paraclinical tests may be necessary to determine the source of the embolus. Evaluation of the extracranial carotid system can be performed by ultrasonography, magnetic resonance angiography (MRA), or computed tomography angiography (CTA) [10]. An ECG can identify an underlying cardiac arrhythmia. Transesophageal echocardiography (TEE) is effective in detecting cardiac valvular and great vessel (aortic arch) disease [26]. Blood cultures and hypercoagulable tests may be warranted to evaluate for bacterial endocarditis and blood dyscrasias, respectively.

CRAO is associated with an increased mortality rate; therefore, patients should undergo a complete medical evaluation in addition to aggressive modification of any and all cardiovascular risk factors [11].

Acute treatment

Currently, there is no proven effective treatment for CRAO [2,16,19]. There are several important factors in

the determination of visual prognosis from CRAO. The subtype of CRAO appears to be an important factor for spontaneous visual recovery. In a study by Hayreh and Zimmerman [23], 82% of eyes with transient CRAO had an improvement in vision, compared with 67% of patients with cilioretinal artery sparing and 22% with complete CRAO. Overall, 6.5% of patients in the study achieved a vision of 20/20 or better, 16% achieved 20/40 or better, and only 29% achieved 20/200 or better. When visual recovery occurred, it did so within the first week from the onset of the visual loss. The duration of the occlusive event in CRAO is also another important determinant of visual morbidity. Experimental studies of CRAO induced in atherosclerotic, hypertensive monkeys have shown that the retina sustains minimal damage if the vascular occlusion is less than approximately 90 min, but irreversible and profound ischemic retinal damage occurs if the occlusion exceeds 4 h [23,27].

'Conservative' strategies to treat CRAO include ocular massage, physical exercise, reduction of intraocular pressure (IOP), and increasing the carbon dioxide concentration in the blood (Table 2) [1–3,19,28–30]. In theory, these treatments work by dislodging the embolus distally down the arterial system thereby minimizing the area of retinal ischemic damage. Other conservative treatment strategies such as hemodilution, hyperbaric oxygen treatment, and supine positioning presumably work by increasing the delivery of oxygen to the retina [3,19,28]. A recent Cochrane review [31] concluded that the currently available conservative treatments do not significantly alter the natural course of CRAO.

Thrombolytic therapy

Thrombolytic therapy involves the use of clot-dissolving medications to lyse thrombi in the arterial vasculature. Some common thrombolytic therapy agents include tissue plasminogen activator (t-PA), reteplase, tenecteplase, anistreplase, streptokinase, and urokinase. Clot lysis occurs because these agents convert plasminogen to plasmin, the active molecule for fibrin degradation (fibrinolysis). Thrombolytic therapy can be administered intravenously (i.v.) or intraarterially. The i.v. route is often preferred because it is quick and relatively easy to administer in a nontertiary setting. Although effective in initiating local clot lysis, i.v. thrombolytic therapy can result in widespread activation of plasminogen and a generalized hypocoagulable state [32••,33–35]. In comparison, intraarterial thrombolytic therapy is a more targeted and relatively better tolerated method because it involves selective catheterization of the effected vessel allowing localized delivery of the thrombolytic agent.

The swift restoration of retinal blood flow is vital for the preservation of retina [36]. Thus, successful treatment of CRAO with thrombolytic therapy hinges on its ability to effectively restore near normal circulation as soon as possible [36,37]. On the basis of the clinical trials of acute ischemic stroke, it would appear that thrombolytic therapy should be administered within 4.5 h of the onset of symptoms because the potential for neurological rescue declines beyond this time period [35].

Thrombolytic therapy was first proven effective in the treatment of ischemic heart disease (IHD) [38]. The favorable results of thrombolytic therapy in the treatment of IHD led to its study in acute ischemic stroke [39–41]. On the basis of the results of the National Institutes of Neurological Disorders and Stroke (NINDS) trial [41], t-PA is the only thrombolytic agent approved for treatment of acute ischemic stroke. Three hundred and three patients were treated with i.v. t-PA within 3 h of the onset of symptoms. Using a global test statistic to assess clinical outcome, patients treated with t-PA were at least 30% more likely to have minimal or no disability at 3 months compared with patients who received placebo. The promising results in IHD and acute ischemic stroke

Table 2 Conventional treatment options for central retinal artery occlusion

Treatment	Mechanism of action
Intravenous mannitol	Hyperosmotic agent – decreases vitreous volume
Intraocular pressure-lowering agents	Beta-adrenergic blockers – block beta-2 receptor in the ciliary process decreasing aqueous humor production Carbonic anhydrase inhibitors (e.g. acetazolamide) – inhibit ciliary body carbonic anhydrase resulting in decreased rate of aqueous humor formation
Vasodilating agents (e.g. prostaglandin E1, calcium-channel blockers, nitroglycerin, and papaverin)	Enhance vasodilation of ocular blood supply
Anterior chamber paracentesis	Acute reduction of intraocular pressure by decompressing the anterior chamber
Hemodilution	Increase retinal artery perfusion by increasing cerebral blood flow
Panretinal photocoagulation	Reduce leakage of retinal vessels
Carbogen (95% oxygen and 5% carbon dioxide)	Vasodilation
Nd:YAG laser (0.5–1.0 mJ)	Lyse and dislodge embolus
Ocular massage	Improve retinal artery circulation by dislodging arterial emboli
Intravenous methylprednisolone	Decrease retinal edema
Pentoxifylline	Improve retinal artery circulation

Nd:YAG, neodymium-doped yttrium aluminium garnet. Adapted from [1,2].

coupled with the theoretic similarities of the thromboembolic event within the retinal circulation led to the application of thrombolytic therapy for CRAO [34].

Recent studies of thrombolytic therapy

Thrombolytic therapy has been suggested as a promising alternative therapy to conservative treatment for CRAO [11,42–47]. Thrombolytic therapy for CRAO can be delivered either i.v. or intraarterial. Despite numerous publications studying the effectiveness of both i.v. thrombolytic therapy and intraarterial thrombolytic therapy for CRAO [11,37,42–47], the benefits remain uncertain with no current consensus on its use [11,34,37].

Intravenous thrombolytic therapy

Intravenous thrombolytic therapy has been used in the treatment of CRAO since the 1960s [48]. Although there have been a number of case reports and retrospective case series published [48–56], there have been only two nonrandomized prospective studies on the treatment of CRAO with i.v. thrombolytic therapy. In the first study involving 12 patients with CRAO, Kattah *et al.* [36] observed visual improvement in 10 patients after i.v. thrombolytic therapy. Four patients had eight lines of visual improvement and six patients had two to four lines of visual improvement 3 days after thrombolysis (nine of these patients maintained their visual improvement 3 months after thrombolysis). The second study focused on examining whether the visual prognosis after i.v. thrombolytic therapy was related to the time of administration. A low dose (50 mg) of i.v. recombinant t-PA (rt-PA) and concomitant i.v. heparinization was given to 28 eyes with CRAO [32••]. Seven of 17 eyes (41%) that received i.v. thrombolytic therapy within the first 6.5 h after onset of symptoms achieved a final visual acuity of 20/50 or better, compared with no eyes in the subgroup that was treated more than 6.5 h from the onset of their symptoms [32••].

Intraarterial thrombolytic therapy

Because of the potential systemic complications associated with i.v. thrombolytic therapy, some investigators have studied the use of intraarterial thrombolytic therapy for CRAO [11,21,57,58]. In a recent nonrandomized, single-center study [59•], the visual outcome of 42 patients with CRAO who received 3 mg aliquots of intraarterial t-PA was compared with 21 patients who received conventional therapy. Seventy-six percent of patients in the intraarterial t-PA group experienced visual improvement of at least one line compared with only 33% of patients in the conventional therapy group. Furthermore, 33% of the patients who received intraarterial t-PA experienced three lines or more of visual improvement compared with only 4.8% of patients in the conventional therapy group. Although these results are promising, the small patient population and lack of randomization limit the recommendation strength of the study.

Arnold *et al.* [57] examined the efficacy of intraarterial thrombolytic therapy in 37 patients with CRAO. Intraarterial thrombolytic therapy was administered within 6 h of symptom onset in all patients, but only 22% demonstrated improved vision as compared with the conventional treatment group [57]. The study found that younger patients had an improved chance of achieving better visual recovery than their older counterparts [57]. Schumacher *et al.* [60] studied intraarterial thrombolytic therapy with urokinase and rt-TPA given within 6–8 h of symptom onset and found 26% of patients demonstrated significant improvement in visual acuity. The authors also found little effect on vision when thrombolytic therapy was administered 20 h or more after the onset of symptoms [60].

Although no defined window of opportunity for using thrombolytic therapy in CRAO has been established, some experts maintain a goal of 3 h from the onset of symptoms [57]. In addition, CRAO has been equated to an anterior cerebral circulation stroke and, thus, should possibly follow similar guidelines recommended for the treatment of acute ischemic stroke [32••,61]. Existing institutional treatment protocols for thrombolytic therapy in acute ischemic stroke, such as at the Duke University Medical Center, may offer an instructive framework upon which to devise an effective treatment algorithm for the diagnosis and treatment of CRAO (Table 3) [62].

Complications and disadvantages of thrombolytic therapy

Although i.v. thrombolytic therapy administration is, from a logistical point of view, a relatively straightforward process, the administration of intraarterial thrombolytic therapy involves a multispecialty approach requiring careful inpatient monitoring of vital functions and coagulation factors during and after treatment [37]. Intraarterial thrombolytic therapy requires a trained interventional neuroradiology team, which may not be available in all hospitals. Even with the appropriate available infrastructure, it can be difficult to streamline patient care to administer thrombolytic therapy within the proposed therapeutic window period. In addition, many patients often fail to recognize or may present many hours after the onset of their symptoms precluding them from thrombolytic therapy.

Thrombolytic therapy may predispose patients to potentially fatal intracerebral hemorrhaging, adverse allergic reactions, or other systemic side effects [41]. In fact, agents with shorter half-lives, such as t-PA, are preferred as administering them locally can reduce the risk of adverse reactions when compared with other longer acting thrombolytic therapy agents [58]. The complication rate of i.v. thrombolytic therapy for CRAO is not known.

Table 3 Duke University t-PA Stroke Protocol

Inclusion criteria for i.v. t-PA for ischemic stroke	Ischemic stroke in any circulation
	Ability to unambiguously establish the time of onset (the last time the patient was known to be symptom free)
	Ability to start t-PA within 3 h of symptom onset
	Head CT scan without any evidence of hemorrhage or other complicating disease
	Age 18 or older
Exclusion criteria for i.v. t-PA for ischemic stroke	Stroke or serious head trauma within 3 months
	Past history of any type of brain hemorrhage
	CT scan showing evidence of hemorrhage, arteriovenous malformation, tumor, or aneurysm
	SBP more than 185 mmHg or DBP more than 110 mmHg (on three occasions, 10 min apart), not responding to therapy
	Seizure preceding or during the current stroke
	Active internal bleeding
	Coagulopathy with elevated PT (>15), INR more than 1.7, elevated PPT, or platelet count less than 100 000
	Rapidly improving or minor symptoms[a]
	Coma or stupor[b]
	Major surgery or invasive procedure within the prior 2 weeks[b]
	Gastrointestinal or genitourinary hemorrhage within the prior 3 weeks[b]
	Noncompressible arterial puncture or biopsy within the past week[b]
	Glucose less than 50 mg/dl or more than 400 mg/dl[b]
	Evidence of active pericarditis, endocarditis, septic emboli, recent pregnancy, inflammatory bowel disease, or lactation[b]
	Active alcohol or drug abuse[b]
	Note: Patients with early ischemic changes on head CT and those with an NIHSS score above 20 may be at increased risk of bleeding. However, this group of patients still benefit from t-PA.
Assessment	Identification of patient experiencing stroke symptoms and activation of stroke code per Duke University Hospital Stroke Code Procedure (above)
	Assess and document baseline neurological status and vital signs
	Note: Monitor vital signs every 15 min before administering t-PA.
	Stat CBC with platelet count, glucose, PT/INR/PTT, and type and screen should be sent and laboratory notified of the stroke code
	Noncontrast brain CT is required prior to the administration of t-PA for stroke, patient is to be accompanied to radiology
	Written MD/neurologist order for t-PA infusion should include (verbal orders are not permitted and may not be accepted for systemic thrombolytics): medication name, recent weight (not stated weight), dose to be delivered (see below), contact information for MD/Neurologist
	Assess patient/family knowledge of risk/benefit and initiate and document patient teaching
Administration	Establish at least two i.v. lines prior to infusing t-PA for stroke: one site for the t-PA infusion, a second catheter of sufficient gauge to administer blood, i.v. fluid, or both if needed, and ideally a third site for withdrawal of blood for labs
	Place any additional lines or tubes such as Foley catheter or nasogastric tube if needed prior to infusing t-PA
	Obtain tPA from pharmacy or Pyxis in the ED
	Time out! Double-check total t-PA dose (0.9 mg/kg) with second registered nurse (RN)/MD and against MD order and the patient identification, maximum dose not to exceed 90 mg
	Begin administration of t-PA via a dedicated i.v. access, do not mix t-PA or infuse through a Y-site with other medications
	Administer 10% of t-PA dose via an i.v. bolus over 2–3 min
	Administer the remainder (90%) t-PA dose as a primary infusion over 60 min
	Stop infusion for signs of neurologic deterioration or serious bleeding occurs, notify MD
	Maintain patency of all i.v. lines with KVO isotonic saline if not being used for an active infusion
	Total t-PA dose is given only once, do not administer t-PA in excess of the established total dose
Patient monitoring	Prior to administration, monitor BP every 15 min
	Following t-PA administration, assess neurologic status and monitor vital signs for 24 h as follows: every 15 min for 2 h; then every 30 min for 6 h; then every 1 h and obtain neurological examination every 2 h for the remaining 16 h of the 24-h period post-t-PA infusion
	Monitor PT, aPTT, and CBC as ordered
	Monitor BP (goal is less than 185 mmHgSBP and less than 110 mmHg DBP or within prescribed parameters), notify MD/neurologist if parameters are exceeded by patient
	Apply external pressure to any bleeding sites until bleeding ceases and notify MD/neurologist
	Do not administer anticoagulants (i.e. heparin and coumadin), heparinoids, low-molecular-weight heparins or antiplatelet agents [i.e. aspirin, plavix, and Aggrenox (Boehringer Ingelheim Pharma KG, Biberach, Germany)] for the first 24 h following t-PA infusion
	Avoid invasive procedures (i.e., Foley catheter insertion, nasogastric tube placement, arterial puncture, venipuncture, intramuscular injection, per rectal medications etc.) for the first 24 h after t-PA infusion unless emergent

Documentation	Document physical assessment, including vital signs and neurological status, prior to, during, and following administration of t-PA; tolerance to therapy; disposition; education and communication to patient/family regarding interventions
	Document NIH Stroke Scale as per unit routine
	Initiate ischemic stroke/TIA clinical pathway
Post-t-PA therapy	The patient should be transferred/admitted to the Neurosciences Step Down/Stroke Acute Care Unit or the Neurosciences ICU as appropriate; if a bed on these units is not available, or if in the judgment of the patient's physician, transfer to these units is not appropriate because of other medical conditions, the patient should be transferred to a similar level care unit
	Consult with operations administrator to facilitate patient placement
	Prior to or following t-PA administration, patient should be transported with RN, MD/neurologist, or both
	Noncontrast CT scan obtained 24 h post-t-PA administration; if neurological deterioration occurs, then contact MD/neurologist and consider an emergent CT as indicated
Reportable conditions	Tachycardia
	Hypertension (SBP > 185 mmHg, DBP > 110 mmHg)
	Hypotension (SBP < 100 mmHg, DBP < 60 mmHg)
	Pallor
	Restlessness
	Changes in baseline neurologic status
	Marked decrease in hematocrit/hemoglobin
	Bleeding

aPTT, activated partial thromboplastin time; BP, blood pressure; CBC, complete blood count; DBP, diastolic blood pressure; INR, international normalized ratio; i.v., intravenous; KVO, keep vein open; NIHSS, National Institutes of Health Stroke Scale; PT, prothrombin time; PTT, partial thromboplastin time; SBP, systolic blood pressure; TIA, transient ischemic attack; t-PA, tissue plasminogen activator.

[a] These represent general guidelines. Children were not included in the NIH randomized clinical trial and there may be an increased risk of hemorrhage. Dosages of 0.5 mg/kg have been suggested. The risk of bleeding may be higher in patients more than 80 years old; however, this is based on very limited data.

[b] These are not absolute contraindications; however, they should be considered when deciding to treat.

In the largest case series of i.v. thrombolytic therapy for CRAO (23 patients), four developed cerebral hemorrhage and one developed cardiovascular shock [51]. There have been at least two other cases reported in the literature of fatal cerebral hemorrhage following i.v. thrombolytic therapy for CRAO [48,55].

In general, intraarterial thrombolytic therapy appears to be better tolerated than i.v. thrombolytic therapy. Suri *et al.* [11] conducted a meta-analysis of 1379 patients with CRAO and found intraarterial thrombolytic therapy was not associated with an increase in mortality rate or risk of intracranial hemorrhage. Another meta-analysis by Noble *et al.* [21] regarding intraarterial thrombolytic therapy found an overall complication rate of 4.5% (10/220), including one local hemorrhage, five transient ischemic attacks (TIAs), one hypertensive crisis, one intracerebral hemorrhage, and two completed ischemic strokes. Similarly, a meta-analysis by Biousse *et al.* [34] noted that intraarterial thrombolytic therapy yielded a complication rate of 10% (25/249), with 12 TIAs, six minor cerebral infarctions, two serious cerebral infarctions, two cerebral hemorrhages, and two groin hematomas. There are several absolute contraindications to the use of thrombolytic therapy in acute ischemic stroke [1–3,11,20,28–30,32••]:

(1) chest pain,
(2) recent head trauma or surgery,
(3) gastrointestinal ulceration or hemorrhage within past 3 months or active peptic ulcer disease,
(4) cerebrovascular ischemia or any history of intracranial bleeding within past 12 months,
(5) bacterial endocarditis,
(6) pregnancy or recent obstetric delivery (14 weeks or earlier: assess maternal vs. fetal risk),
(7) severe hypertension (systolic blood pressure more than 160 mmHg/diastolic blood pressure more than 100 mmHg),
(8) hypertensive retinopathy,
(9) GCA,
(10) proliferative diabetic retinopathy,
(11) current anticoagulant use [international normalized ratio (INR) more than 2–3 has increased risk for bleeding events),
(12) recent (within 3 months) hemorrhagic stroke or TIA,
(13) suspected aortic dissection,
(14) intramuscular injection within past week,
(15) active internal bleeding,
(16) intracranial neoplasm,
(17) documented hypersensitivity.

Furthermore, the effects of thrombolytic therapy may be potentiated in individuals taking medications such as aspirin, anticoagulants, antiseizure medications (e.g. valproic acid and divalproex sodium), and cephalosporin antibiotics [2,63–65]. Given its propensity for adverse reactions, careful screening of eligible patients is warranted prior to the administration of thrombolytic therapy.

Future prospects

Despite recent widespread enthusiasm surrounding the use of thrombolytic therapy in CRAO, the absence of randomized clinical trials calls into question the proven efficacy of such a treatment paradigm at this time [23]. Framme *et al.* [47] found no statistically significant visual

improvement in CRAO patients treated with thrombolytic therapy when compared with those treated with other common treatments. Some experts have concluded that despite its efficacy in treating acute ischemic stroke, conflating the management of CRAO with that of acute ischemic stroke is erroneous [23,66]. This notion is underscored by the finding that over 80% of emboli in CRAO consist of cholesterol or calcified material, which are not theoretically treatable with thrombolytic therapy [23]. It is also worth noting that the vast majority of studies examining thrombolytic therapy in CRAO have not only been retrospective and nonrandomized but have failed to account for the various classifications of CRAO [23].

The absence of conclusive studies supporting thrombolytic therapy in CRAO is particularly important when one considers the potentially catastrophic neurological complications associated with thrombolytic therapy [11,34,37]. The multicenter study of the European Assessment Group for Lysis in the Eye (EAGLE) represents the first randomized, prospective clinical trial to compare conventional treatment with intraarterial thrombolytic therapy in patients with CRAO. Although the final results of this study have not yet been published, the authors are enthusiastic that their findings will 'enable ophthalmologists and neuroradiologists to improve the therapy of patients with acute CRAO' [67]. However, this enthusiasm has been dampened by the comments of some experts regarding the validity of the study describing its protocol as 'sketchy and vague' and noting that the study fails to prevent important selection biases [68].

In the event that future randomized studies unambiguously and convincingly demonstrate the efficacy and safety of thrombolytic therapy in CRAO, ophthalmologists and healthcare providers should consider the following issues and potential hurdles to the successful implementation of thrombolytic therapy as a standardized treatment for CRAO:

(1) Development of an organizational infrastructure that facilitates the well tolerated administration of i.v. thrombolytic therapy, intraarterial thrombolytic therapy, or both in a timely manner.
(2) A systematic institutional approach with the integral involvement of ophthalmologists, stroke specialists, emergency physicians, and neuroradiologists.
(3) Development of a specific thrombolytic therapy protocol to maximize benefit and minimize complications.
(4) A consensus on who will be responsible for the administration of i.v. thrombolytic therapy (e.g. emergency physician, ophthalmologist, neurologist, etc.). Currently, most hospitals allow emergency physicians to administer i.v. thrombolytic therapy for an acute ischemic stroke [69–71], a situation that may not necessarily be appropriate for patients with CRAO.
(5) The medicolegal ramifications of thrombolytic therapy associated with CRAO [69].
(6) Lack of public awareness of CRAO resulting in a delay in seeking medical care. To overcome this problem, it will require extensive public education and awareness programs.
(7) The large financial cost of thrombolytic therapy [11]. In a recent study involving 1379 CRAO patients, Suri *et al.* [11] showed the mean hospital cost of not receiving thrombolytic therapy was dramatically less than the hospital cost of thrombolytic therapy ($14 500 vs. 32 500–37 800, respectively).

Conclusion

CRAO is a clinical emergency leading to abrupt and, in most cases, irreversible loss of vision. Although no consensus exists on a standardized treatment strategy, emerging evidence suggests that thrombolytic therapy may be an effective strategy for CRAO if administered within what appears to be a narrow window of time. However, further studies are needed to better analyze the benefit, risk, and cost of thrombolytic therapy in CRAO. At this time, it is the authors' opinion that thrombolytic therapy in CRAO is a cutting edge therapy that may prove to be standard of care therapy; but it remains to be seen whether it will be a practical therapy outside of the controlled environment of a clinical trial.

Acknowledgement

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 237).

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