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Running head: Trends in CRAO treatment

Title: Current treatment of central retinal artery occlusion: a national survey

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Current treatment of central retinal artery occlusion: a national survey

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Abstract

Background: Central retinal artery occlusion (CRAO) is an ophthalmological emergency, the retinal analog of a stroke. To date there is no consensus or national guidelines on how this disorder should be managed. As academic neurologists and ophthalmologists treat CRAO frequently, we set out to understand how these clinicians approach patients with CRAO with a national survey.

Methods: We identified university-associated teaching hospitals offering vascular neurology, neuro-ophthalmology and/or retina fellowships in the United States and asked the directors of the programs to respond to questions in an open response format to profile the acute management of CRAO at their institution.

Results: We found remarkable heterogeneity in the approach to acute treatment of patients with CRAO among the 45 institutions that responded to the survey. Only 20% had a formal policy, guideline or white paper to standardize the approach to treatment. The primary treating physician was an ophthalmologist, neurologist, or neuro-ophthalmologist 44, 27, and 4% of the time, respectively; 24% were co-managed acutely by neurology and ophthalmology. Intravenous fibrinolysis was offered to selected patients in 53% of institutions, and was the preferred initial treatment in 36%. When the acute treatment team involved a vascular neurologist, fibrinolysis was more likely to be considered a first-line treatment ($p<0.05$). Anterior chamber paracentesis, ocular massage and hyperbaric oxygen therapy were offered 42%, 66% and 7% of the time respectively, while 9% of institutions offered no treatment. Anterior chamber paracentesis was more likely to be offered at programs where neurologists were not involved in treating CRAOs ($p<0.001$). At 35% of institutions, patients with acute CRAO were not routinely referred to a general emergency room for initial evaluation and treatment. Carotid imaging was routinely obtained by 89% of programs, magnetic resonance imaging of the brain by 69%, echocardiogram by 62%, laboratory screening for an inflammatory state by 27% and retinal angiography by 30%. The thoroughness of vascular risk-factors screening was greater in programs that routinely referred acute CRAO cases to the emergency department.

Conclusions: This survey shows that there is significant variability in treatment practices for acute CRAO in the United States. Because of the high cerebrovascular and cardiovascular risk reported in this population of patients, it is notable that the approach to risk factor screening is also highly variable and many programs do not routinely refer patients to an emergency department for urgent evaluation. Finally, there appears to be equipoise among treatment teams regarding the efficacy of systemic fibrinolysis, as 53% of programs report a willingness to treat at least some patients with this modality.

Introduction

Central retinal artery occlusion (CRAO) is an ophthalmologic emergency and an important cause of acquired blindness. Occlusion of the central retinal artery is usually secondary to one or more serious systemic diseases, often carotid artery or cardiac valvular disease, although hypercoagulability, atrial fibrillation and autoimmune diseases are significant contributors as well.[1,2] A minority of patients (approximately 17%) have meaningful improvement in visual acuity without any treatment, presumably due to spontaneous reperfusion of the retina prior to the onset of permanent damage.[3] Usually, however, patients develop permanent blindness.

Despite being a topic of research for nearly 150 years, there is still no treatment proven to restore visual acuity and no consensus for how these patients should be managed. Empiric treatments for this terrible disease include chemical fibrinolysis or transluminal neodymium-doped yttrium aluminum garnet (Nd:YAG) laser assisted thrombectomy in an effort to lyse the offending thrombus, anterior chamber paracentesis, ocular massage and/or intraocular pressure lowering medications in an effort to encourage a clot to propagate more distally and hyperbaric oxygen delivery in an effort to oxygenate ischemic retinal tissue until the vascular obstruction resolves.[4,5] These treatments have varying levels of support from existing literature, but none have yet been convincingly demonstrated to improve visual acuity outcomes. We and others have found that, similar to ischemic stroke treatments, early intervention appears to be necessary to improve outcomes.[3]

Because of the lack of a clearly effective treatment, clinical approaches to acute CRAO have evolved based on local experience and/or beliefs regarding the pathophysiology of this disease. The purpose of the current study is to evaluate how patients with CRAO are treated at academic teaching hospitals in the United States including how often treatment is standardized with a formal protocol, the setting of care (emergency department versus clinic), the various treatments employed and what screening is done to evaluate for systemic disease and vascular risk factors.

Methods

Survey

A focused questionnaire was drafted and reviewed by MS, TY and DG; the final version is included in supplementary figure 1. The questionnaire was e-mailed to the directors of clinical fellowships in vascular neurology, neuro-ophthalmology and retina at university associated medical centers with training programs in both stroke neurology and neuro-ophthalmology or retinal ophthalmology. When necessary, a follow-up e-mail was sent to the director and/or another member of the faculty. Phone calls and in person meetings were used as needed. No patient information or data on outcomes was solicited, so this portion of the study was exempt from Institutional Review Board oversight. All questions were open-ended. Responses were reviewed by three authors (MS, TY and MP); individual responses were kept anonymous and data was presented only as summary statistics.

Statistics

Results of the survey were tabulated and presented both as a single group and as subgroups of respondents, divided into those managed or co-managed with neurology and those managed with only ophthalmological expertise. Also, results were sub-grouped by the site of treatment (general emergency department or any other site). Comparison of treatment preferences by specialty was accomplished with the "N-1" Chi-squared test.[6] $P<0.05$ was accepted as a significant result.

Results

Survey

The questionnaire was sent to at least two individuals at 58 university hospitals in the United States that have both vascular neurology and retina or neuro-ophthalmology fellowship programs. Responses were obtained from one or more representatives at 43 hospitals, for a response rate of 74%. In two cases the responses from affiliated vascular neurology and ophthalmology departments were highly divergent and because they provided care in separate, independent sites we included them as separate responses for a total of 45 responses.

Twenty percent of programs had a formal approach to the management of acute CRAO through a protocol or white paper, and one-third of programs explicitly stated that there was no consensus within their own

Table 1: Acute management of CRAO by primary provider type

	All respondents (n=45)*	Primary management included stroke neurology (n=23)	Primary management by ophthalmology (n=20)	p-value
Does your institution have a CRAO protocol?	20% yes	26% yes	14% yes	0.19
Which team(s) treat CRAO?		NA	NA	
Neurology and ophthalmology jointly	24%			
Ophthalmology primary	44%			
Neurology primary	27%			
Neuro-ophthalmology	4%			
Where are patients referred for treatment?				0.0002
General emergency department	65%	87%	35%	
Ophthalmologic emergency department	7%	4%	10%	
Clinic	28%	9%	55%	
Preferred first-line treatment**				
Systemic fibrinolysis (for appropriate patients)	36%	52%	20%	0.034
Ocular massage	19%	9%	25%	0.17
Anterior chamber paracentesis	14%	0%	30%	0.006
No treatment	9%	13%	5%	0.38
No consensus approach	33%	26%	40%	0.34
Treatments offered at least "occasionally"				
Systemic fibrinolysis	53%	61%	50%	0.48
Intra-arterial fibrinolysis	14%	22%	5%	0.12
Ocular massage	66%	57%	80%	0.12
Anterior chamber paracentesis	42%	21%	70%	0.002
Hemodilution	2%	4%	0%	0.32
Hyperbaric oxygen	7%	0%	15%	0.063
Acute anticoagulation	5%	4%	5%	1.0
Acetazolamide	7%	4%	10%	0.54
Breathing into bag or carbogen inhalation	9%	0%	20%	0.03
Topical intra-ocular pressure lowering drops	12%	4%	20%	0.14
Nd:YAG-laser thrombectomy	2%	0%	5%	0.29

* Ns in subsequent columns do not total to 45 because in two programs neuroophthalmologists primarily managed acute CRAOs
** columns do not add to 100% because numerous groups apply a combination of treatments as first-line therapy
CRAO= central retinal artery occlusion, Nd:YAG=neodymium-doped yttrium aluminum garnet

departments on the initial approach to these patients. Nine percent of programs explicitly opposed using any treatments for CRAO in the acute phase due to lack of efficacy. Only 65% of programs routinely referred patients to a general emergency room for evaluation; 7% referred to a specialty ophthalmology emergency center, and 28% managed patients with CRAO in a clinic.

Fibrinolysis/thrombolysis

Systemic fibrinolysis with intravenous tissue plasminogen activator (tPA) was offered to selected patients with acute CRAO at 53% of programs, although it was considered the first-line treatment at only 36%. The majority of programs offering tPA treated CRAO as a retinal stroke and used the tPA administration approach used for ischemic stroke: treatment only within 4.5 hours of onset and the same tPA dosing (0.9 mg/kg up to 90 mg, 10% administered as a bolus, the rest as an infusion over 1 hour). One program offered treatment only within 3 hours of onset, another within 4. Two programs offered a reduced dose at later time points (one 50 mg within 6.5 hours of onset, another 0.3 mg/kg as late as 24 hours from onset). Of the groups that routinely referred patients to a conventional emergency department for evaluation, 64% offered fibrinolysis which was significantly higher than groups that did not routinely refer to an emergency department (31%, p=0.037). While not a question on the formal survey, several programs indicated that they obtained formal, written consent from

Table 2: Diagnostics and screening obtained by academic hospitals to evaluate CRAO

What other diagnostic / risk evaluation studies are routinely obtained?	All respondents (n=45)	Management included stroke neurology (n=23)	Management by only ophthalmology (n=20)	p-value	Managed in clinic or specialty ED (n=17)	Managed in general ED (n=28)	p-value
Carotid imaging	89%	96%	85%	0.23	76%	96%	0.04
CT head	66%	83%	55%	0.049	41%	82%	0.005
MRI brain	69%	87%	45%	0.003	47%	86%	0.006
Echocardiogram	62%	65%	60%	0.72	59%	64%	0.85
ESR/CRP, other autoimmune surveillance	27%	17%	35%	0.19	41%	18%	0.09
"Stroke labs" (at least LDL, Hgb A1c)	22%	39%	5%	0.008	6%	36%	0.02
Long-term cardiac monitoring	33%	43%	25%	0.20	29%	36%	0.67
Fluorescein angiogram or ocular Doppler	30%	22%	40%	0.19	41%	25%	0.25

ED=emergency department, CT=computed tomography, MRI=magnetic resonance imaging, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, LDL=low density lipoprotein, HgbA1c=hemoglobin A1c.

patients prior to offering fibrinolysis. All programs offering IV tPA obtained a CT head prior to administration. Six programs offered intra-arterial fibrinolysis at least occasionally, although many program reported having abandoned this treatment after the publication of the results from the EAGLE trial (reviewed in the discussion).[7] One program offered transluminal Nd:YAG laser thrombectomy in patients with visible emboli on fundoscopy; this technique attempts to lyse emboli visible on fundoscopy using a high-energy laser.

Ocular massage, anterior chamber paracentesis, hemodilution and other treatments

Ocular massage continues to be widely practiced; about two-thirds of programs use ocular massage at least occasionally and it is the first-line treatment for CRAO at 19% of programs. It is often used in conjunction with other treatments. We asked programs to describe how the procedure is performed, how long it is continued and how long from the onset of CRAO it would be tried; the responses were remarkably variable. Some programs treated all patients with CRAO with ocular massage; others only within 30 minutes, 1 hour, 2 hours, 4.5 hours, 12 hours or 24 hours from onset. Additionally, one program used ocular massage only when intra-ocular pressure was elevated and stopped the treatment when the globe felt soft. A typical description of the procedure was the thumb or palm of the hand applied to the closed eyelid and firm pressure applied and released every few seconds. Treatment duration ranged from 1 to 10 minutes, or "until other treatments could be administered." A few groups opposed this treatment, one describing it as "old fashioned and silly." Anterior chamber paracentesis (ACP) was the first line treatment for 14% of programs and was offered at least occasionally in 42%. It was offered much more commonly in programs where neurologists were not involved in the management of patients with acute CRAO (70% versus 21% respectively, p=0.002). Most programs offering ACP attempted it up to 12 or 24 hours from symptom-onset, although a few used shorter intervals, one as short as 90 minutes from onset. Two programs specifically indicated that they would not offer ACP to a patient who had or might have tPA treatment.

Hyperbaric oxygen was offered at three hospitals, while several others reported placing patients on high-flow oxygen and continuing it as long as necessary if it seemed to improve visual acuity. Only one program offered hemodilution as a treatment for CRAO. Carbogen inhalation (or breathing into a paper bag), acetazolamide administration, topical intra-ocular pressure lowering drops, and acute anticoagulation were all offered occasionally as described in table 1.

Approach to risk stratification

There was general consensus about the importance of carotid artery screening, with 89% of respondents indicating patients with CRAO were screened routinely. The screening rate was lower for those evaluated in a clinic setting than for those evaluated in the emergency department (p=0.04). Rates of obtaining neuroimaging were highly variable, with higher rates when neurologists were involved (83% versus 55% for CT head, and 87% versus 45% for MRI brain). Neuroimaging was more likely to be obtained when patients were evaluated in the emergency department than when they were evaluated in a clinic (p=0.005). Echocardiograms were routinely obtained by 62% of respondents, and this rate did not vary appreciably based on the specialty of the provider or site of evaluation. Rates of obtaining other screening and diagnostic tests are shown in Table 2. Treatment and risk stratification practices differed based on the specialties of the providers involved and on the location of service.

Discussion

CRAO is an ophthalmologic emergency that often results in devastating or complete loss of vision, and there is no accepted standard of treatment. We found that there was a high rate of variability in the approach to the management and care of patients with CRAO in academic teaching hospitals in the United States. Our survey benefited from a good response rate, but is limited to being representative only of academic teaching hospitals. Never-the-less, the pattern of variability observed here is likely representative of non-academic setting as well. Intravenous fibrinolysis is offered to selected patients in 53% of teaching hospitals, and is considered the treatment of choice in appropriate patients in 36% of hospitals. This finding suggests there is equipoise among treating academic neurologists and ophthalmologists regarding the efficacy of systemic fibrinolysis. The available clinical data on the topic is not conclusive. Intra-arterial fibrinolysis for CRAO was evaluated in a randomized clinical trial and not found to be effective, although the mean time from symptoms onset until treatment was 11 hours and none of the subjects enrolled in that trial were treated within 4.5 hours.[7] In a subgroup analysis, the authors noted better outcomes in patients treated at earlier further emphasizing the importance of early treatment.[8] For this reason we conducted a subject level meta-analysis of observational studies of intravenous fibrinolysis for CRAO to try to define an effective time window. We found that intravenous fibrinolysis within 4.5 hours of symptom onset in CRAO appeared to be effective in this non-randomized and observational dataset.[3] Despite the established efficacy of tissue plasminogen activator in acute ischemic stroke, treatment of acute CRAO with fibrinolysis presents some specialized challenges, not the least of which is that the initial evaluation of a patient needs to include a thorough ophthalmologic examination to exclude other differential diagnoses prior to the initiation of fibrinolysis.[9] Never-the-less, due to its widespread use and potential efficacy in non-randomized studies, the efficacy of this intervention should be assessed in a high quality clinical trial.

ACP and ocular massage are antiquated treatments for CRAO, having been first suggested over 130 years ago,[10,11] but they have never been demonstrated to have a positive effect on visual acuity outcome. Never-the-less, we found both treatments were still in frequent use. A recent meta-analysis suggested these treatments may in fact be harmful.[3,12,13] Inducing huge swings in intra-ocular pressure could adversely impact the survival of ischemic retinal neurons. A retrospective study of ACP failed to demonstrate any benefit of this treatment, and this effect was independent of the timing of the treatment.[13] Another recent study found that treatment with ACP correlated with worse visual acuity outcomes, similar to our results.[14] In the absence of any compelling data supporting their efficacy, and given the concerns about safety, we advocate abandoning ocular massage and anterior chamber paracentesis in treating acute CRAO. Hemodilution has a long history as a CRAO treatment, but likewise there is minimal evidence to support its efficacy.[3] Hemodilution appears to have been largely abandoned in the United States as a CRAO treatment as only one respondent in our survey indicated this modality was still in use.

A final important finding of our study was that in 35% of institutions patients with acute CRAO were treated in an outpatient clinic or a specialized ophthalmologic hospital rather than in a traditional emergency room. This is important because patients with acute CRAO are at significant risk of further cardiac and cerebrovascular events.[15,16] This risk is highest in the first week after CRAO, so risk factor evaluation should not be

delayed.[15] The major causes of CRAO are cardiac and artery-to-artery emboli, which are also common causes of stroke and the shared underlying risk factors are often modifiable.[17] This survey permitted us to see the difference in the quality of diagnostics obtained in different treatment settings. We found that institutions that treated acute CRAO outside of a traditional emergency room and without the involvement of neurologists performed less comprehensive screening for systemic diseases with lower rates of carotid imaging, MRI scans of the brain to detect clinically silent lesions, stroke labs and cardiac monitoring. Modern CRAO management should be primarily directed at evaluation and management of cardiovascular and cerebrovascular risk factors. Collaboration between neurologists and ophthalmologists in managing these complicated patients is likely to improve outcomes and it may be helpful to produce consensus multidisciplinary guidelines to lay out a clear strategy to managing acute CRAO.

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Supplementary figure 1: Questionnaire sent to US fellowship program directors

1. Does your institution have a policy or protocol to standardize the treatment of acute central retinal artery occlusion? If so, would you share this protocol with us? (If the protocol addresses the following questions, feel free to skip them.)

2. Are cases of acute CRAO routinely referred to the ER for evaluation? Which service provides the initial treatment for acute CRAO at your institution – ophthalmology, neurology/stroke, neuro-ophthalmology, internal medicine or ER physicians?

3. In a patient with painless unilateral vision loss, what is the minimal diagnostic evaluation which you feel is necessary before treating for CRAO? What is the preferred first treatment for acute CRAO at your institution?

4. Are patients with acute CRAO at your institution offered intravenous tPA and if so, what dose is used and is there a time-from-onset cut-off after which treatment is not offered?

5. Are patients with acute CRAO routinely treated with ocular massage and if so, for what duration of time and is there a time-from-onset cut-off after which treatment is not offered?

6. Are patients routinely treated with anterior chamber paracentesis and is there a time-from-onset cut-off after which treatment is not offered?

7. Are any other treatment modalities offered? (i.e., acetazolamide, hemodilution, intra-arterial fibrinolysis, steroids, hyperbaric oxygen, etc)

8. What additional diagnostic studies are routinely obtained for patients with CRAO? Is an MRI brain routinely obtained? CT head? Carotid imaging? Retinal angiography?