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INTRAVITREAL INJECTION OF TISSUE PLASMINOGEN ACTIVATOR FOR CENTRAL RETINAL VEIN OCCLUSION*

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ABSTRACT

Purpose: This pilot study evaluated the feasibility of intravitreal injections of tissue plasminogen activator (tPA) in eyes with central retinal vein occlusion (CRVO).

Methods: Between August 1997 and October 2000, 9 eyes with CRVO were treated with intravitreal injection of tPA, 100 μg (50 μg/0.1mL), and paracentesis. After the injection, each patient was placed at strict bed rest in the supine position for 6 hours. Each patient was administered one baby aspirin daily. Best corrected visual acuity with Light House charts was obtained at each visit. A change of 3 or more lines of vision from pretreatment levels at 6 months' follow-up or a change in one level (ie, counting fingers to hand motions) was deemed significant.

Results: All patients were followed up for at least 6 months. Four of 9 eyes (44%) showed 3 or more lines improvement at 6 months. In this group, the average improvement was 7 lines. Two eyes showed 6 or more lines loss of vision at 6 months. Four eyes showed dramatic improvement in visual acuity within 1 month of injection. There were no adverse effects related to treatment. Three eyes subsequently developed retinal or anterior-segment neovascularization requiring panretinal photocoagulation; all were graded as ischemic CRVO on fluorescein angiography at baseline.

Conclusion: Intravitreal tPA can be injected safely and easily. Local injection of tPA should spare the patient the serious systemic risks of intravenous tPA administration, such as stroke. Given the morbidity of CRVO, further investigation with this therapy to establish both efficacy and safety seems warranted.

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INTRODUCTION

Central retinal vein occlusion (CRVO) is a common retinal vascular problem that frequently can devastate vision.[1-3] Histopathologic studies implicate thrombosis at the central retinal vein at the level of the lamina cribrosa retrolaminal optic nerve as the cause of CRVO.[4-7] Intravascular pressure is thought to increase from resistance to blood flow from the thrombus, leading to breakdown of the blood retinal barrier and extravasation of blood and fluid throughout the retina, with the typical "blood and thunder' appearance of CRVO. Continued extravasation can lead to a self-perpetuating spiral of increased edema and capillary closure. Should sufficient damage to the capillary bed ensue, retinal ischemia may liberate vasoproliferative factors, which stimulate the development of anterior- or posterior-segment neovascularization.

Several investigators have reported on systemic treatment with thrombolytic agents in CRVO.[8-12] Because of systemic risks, this approach has not been widely adopted or definitively studied. To limit the systemic side effects, investigators have used other approaches to deliver the thrombolytic agent locally, such as intravitreal injection and intravenous retinal cannulization.[13-15] Lahey and associates[14] and Glacet-Bernard and colleagues[15] first reported on the intravitreal injection of tissue plasminogen activator (tPA) for CRVO. This pilot study was designed to evaluate the effects of intravitreal injection of tPA in eyes with acute CRVO.

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PATIENTS AND METHODS

We reviewed the records of all patients treated with intravitreal injections of tPA for CRVO. All patients were treated within 1 month of the onset of symptoms, or within 1 month of a documented worsening of visual acuity and fundus presentation of the CRVO. All patients were treated between August 1997 and October 2000 and were followed for a minimum of 6 months. Patients were examined 1 day, 1 week, and 1 month after tPA administration and then monthly thereafter until 6 months postinjection. Examinations at each visit included ocular and medical history, visual acuity measurement on a Lighthouse (ETDRS) chart, slit-lamp biomicroscopy, tonometry, dilated biomicroscopic fundus examination, fluorescein angiography, and fundus photography. For analysis, the denominators of the visual acuities were converted to their logarithm

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using the logMAR method.[16] Counting fingers vision was deemed to be equivalent to 20/800, hand motions to 20/1600, and light perception to 20/3200. Thus, a change in level of vision from hand motions to counting fingers was deemed to be equivalent to doubling of the visual angle, or equal to 0.3 log units.

Intravitreal tPA was administered in each patient in the minor operating room of an adjacent community hospital. The tPA was prepared by the hospital pharmacy and diluted to a dose of 50 μg in 0.1 mL volume in a sterile tuberculin syringe. The patients were placed in the supine position and the affected eye anesthetized with a retrobulbar injection of 2% lidocaine. Topical ciprofloxin drops were administered before and immediately after the procedure. After the periorbital skin was cleansed with povidone-iodine (Betadine) solution, a sterile drape was placed over the involved eye. With a 30-gauge needle on an open barrel syringe, a paracentesis was performed to remove 0.2 mL of aqueous. With a caliper, a distance 3.5 mm posterior to the limbus was marked on the inferior temporal conjunctiva. At the marked spot, the conjunctiva and sclera were perforated, aiming for the center of the vitreous, with a 30-gauge needle on the tuberculin syringe containing the tPA. A total of 0.2 mL (100 μg) of tPA was injected into the vitreous with the bevel up. As the needle was withdrawn from the eye, a cotton-tipped applicator was placed on the injection site for 1 minute to provide tamponade against subconjunctival bleeding. The injection site and the fundus were inspected for complications using indirect ophthalmoscopy with scleral depression. Thereafter, 5% homatropine drops and ciprofloxin drops were instilled on the cornea and an eye patch was placed. Each patient remained at strict bed rest in the supine position for the next 6 hours in the recovery room to facilitate pooling of the tPA over the posterior pole. Prior to discharge, the patch was removed and the patient examined with a near vision acuity card, tonometry, and indirect ophthalmoscopy. At discharge, each patient was started on a regimen of 1 enteric-coated baby aspirin daily.

RESULTS

Nine eyes in 9 patients were treated with intravitreal tPA injections. The pertinent data are summarized in Table I. The mean patient age was 65.5 years and the median age was 66 years.

None of the eyes sustained any complications related to the injection, such as vitreous hemorrhage, choroidal hemorrhage, retinal detachment, or endophthalmitis. Three eyes (cases 7, 8, and 9), all ischemic, subsequently developed ocular neovascularization, which regressed in all eyes in response to panretinal photocoagulation.

Table I shows the pretreatment and 6-month post-treatment visual acuities, with the change in lines of visual acuity 6 months after treatment. Four of 9 eyes (44%) showed 3 or more lines improvement at 6 months. In this group, the average improvement was 7 lines. Two eyes showed 6 or more lines loss of vision at 6 months. Four eyes showed dramatic improvement in visual acuity within 1 month of injection (cases 3, 4, 5, and 6). In each, the injection was administered within 2 weeks of the onset of symptoms. Each of these eyes was also judged to be perfused on the pretreatment fluorescein angiogram. In contrast, none of the ischemic eyes improved beyond 20/400, although 2 of 4 eyes (cases 7 and 8) showed significant improvement of 3 or more lines from pretreatment vision. Two eyes (cases 2 and 8) received tPA in response to marked worsening of clinical appearance and visual acuity. In case 2, initial visual acuity was 20/80, the angiogram showed a perfused CRVO, and there was no afferent papillary defect. One month later, the vision dropped to counting fingers, the angiogram showed conversion to the ischemic variant, and an afferent papillary defect was detected. Despite the tPA injection, the vision did not improve beyond counting fingers. In case 8, initial vision measured 20/40 and remained stable for 3 months. At that point, the vision suddenly dropped to counting fingers, the fluorescein angiogram converted from perfused to ischemic, and the fundus appearance dramatically worsened. The tPA was injected within 1 month of the worsening of symptoms, and the vision improved from counting fingers to 20/400. Of note, this patient was diabetic and developed ocular neovascularization.

DISCUSSION

Although tPA is presumed to cross the venous vessel wall to reach the retrolaminar clot, this has not been established. Lack of a suitable animal model and the inability to image the small clot in the retrolaminar central vein, let alone see it dissolve in response to any treatment, hinders our ability to evaluate thrombolytic therapy irrespective of the mode of delivery. However, the histopathologic evidence for the development of CRVO and the successful reports of tPA use for submacular hemorrhage provide the rationale for the use of intravitreal tPA in CRVO.

Lahey and associates[14] were the first to report on intravitreal tPA injection for CRVO. They treated 23 CRVO eyes and showed doubling of the visual angle in 4 eyes. Although 1 eye developed a small vitreous hemorrhage, there were no major complications related to the treatment.

Glacet-Bernhard and colleagues[15] treated 15 CRVO eyes with intravitreal tPA. None of the eyes sustained serious complications related to the intravitreal tPA injection. At the end of follow-up, visual acuity “was improved

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TABLE I: STUDY RESULTS

CASE	AGE	SEX	PRETREATMENT VISION	VISION AT 6 MO	VISION CHANGE AT 6 MO	BASELINE MEDICAL CONDITIONS	BASELINE ANGIOGRAM
1	66	M	20/63	Counts fingers	-11	Hypertension	Perfused
2	59	F	Counts fingers	Counts fingers	0	Hypertension, Coumadin	Ischemic
3	72	M	20/125	20/32	6	Plavix	Perfused
4	61	F	20/32	20/20	2	Hypertension, glaucoma	Perfused
5	77	F	20/125	20/80	2	Hypertension, diabetes	Perfused
6	68	F	Counts fingers	20/50	12	Hypertension	Perfused
7	79	M	Hand motions	20/320	7	Hypertension	Ischemic
8	51	M	Counts fingers	20/400	3	Diabetes	Ischemic
9	57	F	Counts fingers	Light perception	-6	None	Ischemic

in 5 eyes (36%), unchanged in 5 eyes (36%), and worsened in 4 eyes (28%)." The investigators did not report change in lines of acuity, particularly at a set point in time after treatment. As in our series, none of the ischemic eyes showed improvement of visual acuity beyond 20/200; all of the eyes with dramatic improvement following tPA were nonischemic.

Although our series is small, the percentage of eyes gaining 3 or more lines vision at 6 months post-treatment (44%) parallels the improvement (42%) we saw with intravenous tPA. However, the nature of this report (small sample size, absence of randomized controls) precludes comparison between the efficacy of intravenous tPA and intravitreal tPA. Indeed, definitive recommendations regarding efficacy can be made only through a randomized controlled study. However, we were able to demonstrate the feasibility and relative safety of this approach. Together with the cases reported by Lahey and associates[14] and Glacet-Bernhard and colleagues,[15] a total of 47 eyes with CRVO have been reported to have undergone intravitreal tPA injection without any major complication. Although Hrach and coworkers[20] reported fundus pigmentary alterations in cats at a concentration of 50 μg/mL, we did not observe retinal pigment changes at this dose. The poor natural history of CRVO, the lack of a safe and effective treatment, the scientific rationale underlying thrombolytic treatment in CRVO, and the apparent relative safety and feasibility of intravitreal tPA injections strongly support further, more definitive investigations of its efficacy and safety in CRVO.

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DISCUSSION

DR ANDREW K. VINE. Despite extensive research concerning the risk factors for central retinal vein occlusion, we have no effective therapy for this condition which results in significant visual morbidity. In assessing possible innovative therapies, Dr Elman and colleagues have retrospectively reviewed 9 patients with central retinal vein occlusion who were treated with an intravitreal injection of tissue plasminogen activator (t-PA) 100 micrograms, followed by aspirin therapy. There is no mention whether the protocol was approved by an IRB. The authors state that 4 of the 9 patients showed an improvement in visual acuity of 3 or more lines by 6 months.

These results, however, are partially based on the authors assumptions that hand motions visual acuity is equivalent to 20/1600, and that counting fingers visual acuity is equivalent to 20/800. With these assumptions, the authors state that an improvement from hand motions to 20/320 is an improvement in 7 lines of visual acuity. Hand motions and count fingers visual acuities are poor measurements of visual acuity. The authors used EDTRS charts[1] which are designed to be used at 4 meters. If the patient is unable to read the largest letters, the patient can be moved to 2 meters or 1 meter from the chart. A visual acuity of 5/200 is a reproducible measurement of visual acuity, whereas hand motions or count fingers are not.

This study is the third uncontrolled pilot study[2,3] of intravitreally injected t-PA in eyes with recent onset central retinal vein occlusion. The similarities and differences of these 3 studies are listed in Table I. Follow-up visual acuities of the treated eyes are summarized in Table II. An improvement in visual acuity of 3 lines or more ranged from 28% to 44% in these 3 studies, but without a control group it is not possible to state whether the treatment was actually efficacious. In a small series[4] evaluating the natural course of central retinal vein occlusion, 40% of eyes with a non-ischemic central retinal vein occlusion had a visual improvement of 3 lines or more.

Previous studies with the rabbit model[5-7] have shown that topical t-PA results in reasonable levels in the aqueous, and that subconjunctival t-PA results in significant vitreous levels; but intravitreal t-PA did not diffuse through the intact neural retina in this model. If intravitreal t-PA can reach the central retinal vein and cause lysis of the presumed intraluminal thrombus, one would expect some rapid improvement in retinal circulation time post injection. In our series[3] from France, however, none of the eyes showed an improvement in retinal circulation time on the first day post injection. Fifty percent of eyes actually showed a decrease in retinal circulation time and 50% showed no change. Only at the end of follow-up was an improvement in retinal circulation time seen in 38% of eyes.

This study combined with the 2 previous investigations[2,3] support the conclusion that intravitreal t-PA is safe. Whether a controlled study to show the efficacy of this therapy should be undertaken is questionable. In our series[3] of 15 patients, only 1 patient with an underlying thrombotic disorder, showed a dramatic improvement in visual acuity the first day post injection. More aggressive fibrinolytic therapy suggests that intravitreal t-PA for central retinal vein occlusion will not be effective. Paques and co-investigators[8] have used selective cannulation of the ophthalmic artery to infuse Urokinase directly into the ophthalmic artery in patients with central retinal vein occlusion. Despite this aggressive approach, only 1 of 14 patients with classical central retinal vein occlusion showed a temporary improvement in visual acuity. If injection of fibrinolytic agents directly into the ophthalmic artery of eyes with central retinal vein occlusion is ineffective, then it is very unlikely that intravitreal t-PA will be an effective therapy.

The timing of t-PA therapy for central retinal vein occlusion may be critical. In our series,[3] the only patient who showed an immediate improvement in visual acuity was treated on the same day his symptoms developed. In Dr Elman's series, patients were treated within 1 month of the onset of symptoms. A previous case report[9] documented a recanalized thrombus in a central retinal vein which had developed 11 days after first symptoms appeared. With a recanalized thrombus, both intravitreal and intra-arterial t-PA would be ineffective. It is possible that the thrombus or occlusion is extensively developed when the patient has initial symptoms.

Many features of central retinal vein occlusion

TABLE I: INTRAVITREAL T-PA FOR CENTRAL RETINAL VEIN OCCLUSIONS

STUDY	LAHEY	GLACET-BERNARD	ELMAN
Number of eyes with CRVO*	23	15	9
t-PA mg	65-110	75-100	100
Additional treatment	ASA† or LMWH‡	LMWH‡	ASA

*central retinal vein occlusion
†aspirin
‡low molecular weight heparin

TABLE II: IMPROVEMENT IN VISUAL ACUITY BY 3 LINES POST INJECTION OF T-PA

STUDY	LAHEY	GLACET-BERNARD	ELMAN
VA ↑ 3 Lines	10 (43%)	4 (28%)	4 (44%)
VA ↓ 3 Lines	3 (13%)	4 (28%)	2 (22%)
Same VA	10 (43%)	6 (43%)	3 (33%)

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remain unknown. Although development of an intraluminal thrombus[10] is assumed to be the final or precipitating event, there are many aspects of central retinal vein occlusion which would not be amenable to fibrinolytic therapy. These features include vascular compression from the adjacent sclerotic artery which shares a common adventitia with the central retinal vein, and increasing phlebosclerosis with age.

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[Editor's note] DR. RICHARD P. MILLS asked why some of the successful examples of TPA treatment showed collateral vessels at the disc? He pointed out that if the clot in the central retinal vein were lysed by the treatment, there would be no continued stimulus for the development of collaterals.

DR MICHAEL J. ELMAN. I would like to thank Dr Vine for a very thought provoking discussion. Let me start by trying to answer Dr Mills' question and the answer is I don't know. First, we don't know definitively if the treatment even works. With respect to the issues that Dr Vine raised, equating a change in vision between hand motions and counting fingers to doubling of the visual angle was not my innovation. This approach was used in the Ischemic Optic Neuropathy Decompression Trial. The IONDT was a randomized controlled clinical trial evaluating optic nerve sheath decompression for the treatment of ischemic optic neuropathy. This trial underwent peer review by the NIH. As Vice Chairman of the IONDT, I can tell you that this aspect of the study design was never questioned. Considering a change in level of vision is comparable to doubling of the visual angle is an assumption. I agree that it would be preferable if we could measure all the visions on a visual acuity chart. If one were to design a trial, perhaps one would want to stratify the preenrollment population based on those who have visions on the chart versus those who don't. In fact I believe that was done in the analysis of the IONDT.

The natural history of CRVO is variable. In the CVOS only 6% of patients with 20/50 to 20/200 visual acuity at the start of the trial improved 3 or more lines without treatment.

Reproducible retinal circulation times have always been a very difficult thing for us to measure. We tried timed transits in the TICVO pilot study and were not successful. When we started giving t-PA intravenously we shared your feelings. We thought that t-PA was going to be Drano for the eye and that we would have to give a beeper to every photographer so that as soon as we administered this drug we would be able beep them to run and photograph the eye as the blood was going "whoosh" through the freshly opened central retinal vein. That isn't the way it works. And if you think of it there might be a good reason. When one does surgery on the eye, or any other part of the body, to correct an abnormality, function on the operated part doesn't go back to normal overnight, although our patients think it should. For example, if a patient undergoes orthopedic surgery on his knee he is not going to go back to running the next day. Healing takes time. Even if t-PA does work in CRVO, there is fluid accumulation in the macula, which takes time to improve. So I don't necessarily think that a change in visual acuity the next day or perhaps a change in circulation time would necessarily be critical but again it is an area of concern and needs to be investigated further. These methods are indirect measures of clot dissolution. Ideally we want to directly image the clot before and after treatment. In contrast to our cardiology colleagues, this remains impossible for CRVO.

With respect to other papers on thrombolytic therapy, I can only offer the data in our intravenous t-PA paper, published as my AOS thesis, which do not support this conclusion. Finally, timing of the infusion is important. There is information in the literature suggesting there is still substrate for the t-PA to act on at 2 weeks. Unfortunately to my knowledge, there are no reports in the literature of histopathology in CRVO at 1 month's duration. So if one were to design a trial I think I would do pre-randomized stratification for treatment divided between patients with symptoms less than 2 weeks duration and those between 2 and 4 weeks.

Thank you again for your attention.

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