Tissue Plasminogen Activator versus Aspirin in Central Retinal Vein Occlusion

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Abstract

Purpose: To compare the effect of tissue plasminogen activator (TPA) and aspirin in patients with central retinal vein occlusion.

Methods: A prospective interventional study was conducted on patients with central retinal vein occlusion of less than 28 days' duration. Patients in the TPA group received 100 μg intravitreal tissue plasminogen activator and the patients who declined intravitreal injection were considered as Aspirin group. Patients were followed up for 6 months.

Results: sixty five patients were enrolled, 19 in the TPA group and 46 in the Aspirin group. The mean 6-month change in visual acuity for TPA-treated patients was -0.29±0.42 (range: -1.4 to +0.5) while in the Aspirin group, it was 0.28±0.79 with a range of -1 to +2.5. TPA group had a significantly better visual improvement in comparison to Aspirin group (P< 0.0005).

Conclusion: Intravitreal tissue plasminogen activator can be injected safely and easily. Patients treated with intravitreal tissue plasminogen activator within 28 days of the onset of central retinal vein occlusion are more likely to improve visual acuity.

Keywords: Central Retinal Vein Occlusion, Tissue Plasminogen Activator, Visual Acuity, Neovascularization of Iris

Introduction
Central retinal vein occlusion (CRVO) is a common retinal vascular problem that frequently can devastate vision. Eyes with extensive capillary nonperfusion are at significant risk of neovascular complications. Prognosis is usually poor, especially in the ischemic type and visual acuity at baseline is a strong predictor of final vision. Histopathologic studies implicate thrombosis at the central retinal vein at the level of the lamina cribrosa retrolaminar optic nerve as the cause of CRVO.

At present no safe treatment exists promoting the recovery of lost vision. All of the investigational treatments may have serious complications and are, to varying degrees, controversial in regard to safety and/or efficacy. Several surgical approaches to modify the natural course of the disease have been proposed in recent years. These options include laser-induced chorioretinal venous anastomosis, the injection of tissue plasminogen activator into a retinal vein, optic nerve decompression, and vitrectomy for macular edema.

Fibrinolytic therapy aims at early restoration of blood flow. To limit the systemic side effects of treatment with thrombolytic agents, investigators have used other approaches to deliver the thrombolytic agent locally. Multiple studies introduced the use of intravitreal tissue plasminogen activator (TPA) for acute CRVO. Numerous investigators have confirmed its safety and suggested that it may have a beneficial role in the treatment of acute central retinal vein occlusion.

All of these studies reported their finding in a non-comparative fashion and concluded that the intravitreal TPA improves prognosis.

The purpose of the current study is to evaluate the success of intravitreal TPA in terms of visual acuity improvement and prevention of neovascularization.

Methods
This is a two prospective interventional case series on patients with CRVO referred to Farabi Eye Hospital. The study, following the tenets of Declaration of Helsinki, was approved by the Institutional Review Board.

Patients
From September 2003 to July 2005, 65 eyes of patients affected with CRVO fulfilled the inclusion and exclusion criteria and were included in the study. Patients were diagnosed with CRVO when they presented with vision loss, retinal hemorrhages in all four quadrants, and edema of the macula and optic nerve. Only patients with visual symptoms of 28 days or less were enrolled in the study.

Excluded from the study were patients with late onset CRVO (duration of symptoms of more than 4 weeks); patients with only a slight decrease in visual acuity (VA > 20/30); patients with CRVO already complicated with anterior or posterior neovascularization or already treated by laser photocoagulation; patients with other ocular disorders known to decrease visual acuity (such as uncontrolled glaucoma, cataract, age related macular degeneration, and diabetic retinopathy); pregnant women and children.

The risks and benefits of the intravitreal injection were fully explained to all patients and written informed consent was obtained. The patients who declined the injection were considered as the controls.

Therefore first group of our patients' undergone intravitreal TPA: The procedure was explained to the patients, and those who consented received a single intravitreal injection of TPA. 100 micrograms of sterile tissue plasminogen activator solution in 0.1 cc of balanced salt solution was stored at -70 deg C which has been shown to be stable. After topical anesthesia, instillation of povidone iodine solution, and an anterior chamber paracentesis of 0.1 cc, 100 ug of TPA was injected into the vitreous cavity using a 30 gauge needle placed 3 or 4 mm from the limbus in pseudophakic or phakic eyes, respectively.

After injection, each patient was placed on strict bed rest in the supine position for at least 4 hours. Patients were placed on topical corticosteroid and antibiotics for 1 week. Second group of patients (control group) who declined TPA injection were prescribed oral aspirin 80 mg for 6 months.

The patients underwent complete ophthalmic and medical examinations, as well as laboratory evaluation including clotting tests.
Complete ophthalmic examination included visual acuity measurement with ETDRS chart, intraocular pressure measurement, indirect ophthalmoscopy, gonioscopy, fundus fluorescein angiography, and fundus photography.

Main outcome measures
Patients in each group were further divided into ischemic and nonischemic subgroups based on their initial visual acuity, afferent pupillary defect, ophthalmoscopic findings, and fluorescein angiography. The patients were followed for a minimum of 6 months at 1 week, 1, 2, 3, 4, and 6 months by a complete ophthalmologic examination.

Best corrected VA at baseline and during follow-up was checked and for analysis, the denominators of the visual acuities were converted to their logarithm using the logMAR (logarithm of the minimum angle of resolution) method.

A minimum difference of -0.3 logMAR or +0.3 logMAR between the 6-month and the initial visual acuity, which is nearly equal to a change of 3 lines, respectively showed improvement and aggravation of the patient’s visual acuity. The values falling in between -0.3 to +0.3 were considered as not changed.

Statistical analysis
By “interval” we mean the time period from the onset of vein occlusion to the time of referral and the expression “month 6 postevent VA” refers to the visual acuity six months after the occurrence of vein occlusion. The Mann-Whitney U and the Wilcoxon ranked tests were used to compare the VA data of the two study groups and to compare baseline with month 6 postevent VA of the TPA group respectively. The x2 test was used to compare VA improvement between the two groups, and to compare the occurrence of neovascularization.

To evaluate the effect of (potential) confounders, the two groups were compared for age, sex, right/left, interval, and presentation VA with x2 and Mann-Whitney U tests. Multinomial logistic regression analysis was used to evaluate the association of the month 6 postevent VA with baseline VA. The statistical power was β=0.8 and the probability of first-degree error was α=0.05.

Results
Between September 2003 and July 2005, 65 consecutive patients with CRVO were enrolled in our study. 19 of the participants consented to TPA injection. The mean age of the patients (±SD) was 55.0±15.2 years, with a range of 20 to 87 years. There were 37 men and 28 women. The mean duration from the approximate onset of central retinal vein occlusion to injection was 16.3±8.4 days. Patients’ demographic are shown in Table 1. No statistically significant differences were found between groups regarding age, gender, the ratio of left to right eyes, or the interval between onset of symptoms and injection. But statistically significant differences were found between ratio of ischemic to nonischemic CRVO and baseline visual acuity. Table 1 summarizes the baseline characteristics of the 65 patients enrolled.

Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intravitreal TPA</th>
<th>Aspirin</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of eyes</td>
<td>19</td>
<td>46</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.6±12.0</td>
<td>56.4±16.2</td>
<td>0.258</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>9/10</td>
<td>28/18</td>
<td>0.41</td>
</tr>
<tr>
<td>Left/right</td>
<td>8/11</td>
<td>23/23</td>
<td>0.59</td>
</tr>
<tr>
<td>Interval† (days)</td>
<td>18.0±7.4</td>
<td>16.0±8.7</td>
<td>0.40</td>
</tr>
<tr>
<td>Ischemic/Non ischemic</td>
<td>17/2</td>
<td>27/19</td>
<td>0.020</td>
</tr>
<tr>
<td>Baseline VA (logMAR)§</td>
<td>1.75±0.84</td>
<td>1.30±0.78</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Tissue plasminogen activator
† Interval between presumed occurrence and intervention (days)
§ Logarithm of minimal angle of resolution

The means of logMAR month 6 postevent VA were equivalent to counting fingers at 2.5 m and 2 m for the TPA and Aspirin groups, respectively. When presentation VA was compared with the month 6 postevent VA, in a paired fashion for the TPA group improvement in VA was significant (P=0.007). In TPA group Eight patients (42.1%) had improved visual acuity (the 6-month change in logMARS ≤ -0.3), 1 (5.36%) had aggravated visual acuity (the 6-month change in logMAR≥ +0.3), and in 10
patients (52.6 %) the 6 month logMAR did not change significantly. In Aspirin group nine patients (19.6%) had improved vision, 16 patients (34.8%) showed decreased visual acuity, and in 21 (45.7%) it remained unchanged (Figure 1). The difference between two groups was significant (Chi-square test, P=0.027).

The mean 6-month change in logMAR (the difference between 6-month and initial logMAR) for TPA-treated patients was -0.29±0.42 (range: -1.4 to +0.5). In the aspirin group, the average 6-month change in logMAR was 0.28±0.79 with a range of -1 to +2.5. Therefore VA improvement (month 6 postevent VA minus presentation VA) was 0.57 logMAR units more in the TPA group (P=0.000; actually control subjects lost 0.28 logMAR and the TPA group achieved 0.29 logMAR units). But mean visual acuity in 1, 2, 3 and 6 months between two groups were not significant (Table 2).

Table 2. Comparison between intravitreal TPA* and aspirin groups in terms of visual acuity

<table>
<thead>
<tr>
<th>Visual acuity (logMAR)*</th>
<th>Intravitreal TPA † Mean (±SD)</th>
<th>Aspirin Mean (±SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.75±0.84</td>
<td>1.30±0.78</td>
<td>.044</td>
</tr>
<tr>
<td>1 month</td>
<td>1.53±0.92</td>
<td>1.41±0.78</td>
<td>0.59</td>
</tr>
<tr>
<td>2 month</td>
<td>1.46±0.93</td>
<td>1.55±0.88</td>
<td>0.73</td>
</tr>
<tr>
<td>3 months</td>
<td>1.46±0.93</td>
<td>1.60±0.94</td>
<td>0.59</td>
</tr>
<tr>
<td>6 months</td>
<td>1.45±0.93</td>
<td>1.58±0.99</td>
<td>0.12</td>
</tr>
<tr>
<td>Improvement in visual acuity</td>
<td>-0.29±0.42</td>
<td>.28±0.79</td>
<td>.000</td>
</tr>
</tbody>
</table>

* Logarithm of minimal angle of resolution
† Tissue plasminogen activator

Iris neovascularization developed in 5 of 19 (26.3%) in the TPA group, all 5 eyes were ischemic and iris neovascularization developed in 9 of 46 (19.6%) in the aspirin group. Six of 9 were in ischemic group. The difference between TPA and aspirin group was not significant (P= 0.71).

In multivariate analysis, presentation VA remained to be a significant covariate and we observed that final visual acuity was related to baseline visual acuity (b=0.71, P=0.000).

None of the eyes sustained any complications related to the injection, such as vitreous hemorrhage, choroidal hemorrhage, retinal detachment, or endophthalmitis.

Discussion

Systemic fibrinolytic therapy aimed at early restoration of blood flow appears to be a promising therapeutic approach in hemorrhagic retinopathy.

Hattenbach suggests that treatment with TPA and hemodilution has the potential to improve the visual prognosis in ischemic CRVO, but systemic fibrinolysis was associated with bleeding complication.13,14

In the other study TPA injected into the optic nerve of normal rabbit eyes and found it is a safe and simple procedure without apparent toxicity or damage to optic nerve or retina. Injection of TPA increased the incidence of the recanalization of the vessels in experimental retinal vein occlusion.15

Intravitreal administration of TPA, which avoids systemic complications of fibrinolytic therapy, had been used. The timing of TPA therapy for CRVO may be critical. In our study patients were treated within 1 month of onset of symptoms. Animal studies of venous thrombi have demonstrated that TPA is most effective on immature clots, since after 4 to 6 weeks they develop fibrin cross linking and become organized.16

Although TPA is presumed to cross the venous vessel wall to reach the retrolaminar clot, this has not been established. Laboratory studies have demonstrated that proteins...
similar in weight to TPA, when injected into the vitreous cavity can diffuse across the retina.\textsuperscript{17,18} Other experimental study also showed injection of TPA into the vitreous cavity can penetrate the retinal vessels of pigs. Vascular occlusion or breakdown of the blood retinal barrier does not seem to play a role in the ability of intravitreal TPA to enter the retinal vessels.\textsuperscript{19} But Kamei et al showed intravitreal t-PA did not diffuse through the intact neural retina in rabbit model.\textsuperscript{20}

There are multiple uncontrolled pilot studies of intravitreally injected t-PA in eyes with recent onset central retinal vein occlusion, but without a control group it is not possible to state whether the treatment was actually efficacious.

\textit{Lahey} et al reported intravitreal TPA for recent onset CRVO. They found 8 (34.7\%) of 23 of patients achieved more than 20/40 visual acuity at 3 months post injection and doubling of visual acuity in four eyes.\textsuperscript{6}

\textit{Ghazi} et al evaluated intravitreal TPA injection in CRVO patients presented within 3 days from the onset of symptoms. 75\% of patients had best-corrected visual acuity of 20/200 or worse at presentation. 55\% of these patients had final visual acuity that improved to 20/50 or better. The remaining patients did not have improvement or their vision continued to worsen. They suggest that patients with CRVO who have evidence of >10 disk areas of capillary nonperfusion at presentation have a poor prognosis despite early injection.\textsuperscript{7}

\textit{Glacet-Bernard} et al evaluated patients with recent onset CRVO (from 1–21 days' duration) were given 75–100 μg of TPA intravitreally associated with low dose low molecular weight heparin. At the end of follow up, visual acuity had improved to 20/30 or better in 36% of eyes, including two with complete recovery.\textsuperscript{8} Also \textit{Elman} et al showed 44\% of eyes gaining 3 or more lines vision at 6 months after intravitreal TPA injection.\textsuperscript{10}

In our study, 8 of 19 eyes (42\%) gained 3 lines (6-month change in logMAR < -0.3) in contrast to aspirin group for which the figure was 19\%. Follow up visual acuities of treated eyes in 4 studies are listed in table 3. An improvement in visual acuity of 3 lines or more ranged from 28\% to 44\% in these 4 studies.

Our study showed improvement in visual acuity in TPA-group even in ischemic CRVO. Also \textit{Elman} et al found 2 of 4 ischemic eyes showed significant improvement of 3 lines acuity but none of them improved beyond 20/400. This is in contrast to other studies that hypothesize that in ischemic CRVO despite the fibrinolytic effect of TPA and its potential for reestablishing outflow, enough damage has been caused to the capillary bed during the process that creates irreversible inflow problems. Although in ischemic CRVO, ischemic damage to the macular retinal ganglion cells quickly produce irreversible damage and it seems reestablishing retinal circulation with TPA would not regenerate destroyed ganglion cells and visual acuity but reestablishing retinal perfusion could save cells that have not yet reached the “point of no return”. It has been hypothesized that if the parafoveal and perifoveal areas remain nonischemic in an eye with an otherwise largely ischaemic CRVO, there may be some visual benefit.\textsuperscript{21}

\begin{table}[h]
\centering
\caption{Improvement in visual acuity by 3 lines post injection of TPA*}
\begin{tabular}{|l|l|l|l|l|l|}
\hline
STUDY & \textit{LAHEY} & \textit{GLACET-BERNARD} & \textit{ELMAN} & \multicolumn{2}{l|}{Our study} \\
\hline
& VA\textsuperscript{1} improved more than 3 lines & 10 (43\%) & 4 (28\%) & 4 (44\%) & 8 (42\%) & 9 (19\%) \\
\hline
& VA improved less than 3 lines & 3 (13\%) & 4 (28\%) & 2 (22\%) & 1 (5\%) & 16 (34\%) \\
\hline
& Same VA & 10 (43\%) & 6 (43\%) & 3 (33\%) & 10 (52\%) & 21 (45\%) \\
\hline
\end{tabular}
\footnotesize{* Tissue plasminogen activator} \\
\footnotesize{† Visual acuity}
\end{table}
With improvement in retinal perfusion, eyes may recover several lines of acuity as edema clears, yet the final acuity will depend on the extent of injury that was still reversible.

In statistical terms, some of the improvements and deteriorations of VA—respectively, in the TPA group and aspirin group could be attributed to the regression-towards mean phenomenon and this may invalidate the inference of the effect of the TPA. This phenomenon may explain part or all of the observation on the control cases—that is, the VA deterioration. But in the case of VA improvement in TPA group, studies on the natural course of ischemic CRVO have shown that only 10% of these cases gain or maintain a VA of 20/400 or better (in our study 37% of the TPA group achieved a VA of 20/400 or better). In our study, mean logMAR visual acuity at 6 months in aspirin group was 1.58±0.99, while mean logMAR visual acuity in TPA group was 1.45±0.93 without any significant difference between two group. This may be due to the late administration of TPA, i.e. later than the ischemic changes are reversible. Other possible explanation may be patient selection. It seemed that those who referred to us with good baseline visual acuity had less of a desire for intervention and declined TPA injection.

An important point in patient selection is severe retinal ischemia. Our data suggest that patients with TPA group had evidence of ischemic CRVO at presentation and had statistically significant differences between ratio of ischemic to nonischemic and baseline visual acuity between two groups. Central Vein Occlusion Study Group (COVS) showed retinal ischemia correlates with poor baseline visual acuity and has been documented to be an important negative predictor of final visual outcome. COVS found the most important risk factor predictive of iris neovascularization in CRVO is poor visual acuity. In our study initial visual acuity in TPA group was poorer than aspirin group. But because of intervention iris neovascularization was not different between two groups.

**Conclusion**

In conclusion, stricter study designs such as randomized controlled trials are needed to control the effects of potential confounders and to better estimate the true clinical efficacy and safety. Furthermore, the role of this modality should be placed in the context of other emerging approaches in the management of retinal vein occlusion, such as radial optic neurotomy, surgical induction of chorioretinal venous anastomosis which has shown preliminary success.

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**References**