

EXTENDED REPORT

Intracameral tissue plasminogen activator to prevent severe fibrinous effusion after congenital cataract surgery

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Background/aims: To evaluate the efficacy of intracameral recombinant tissue plasminogen activator (r-TPA) in prevention of fibrinous effusion after lensectomy, anterior vitrectomy, and posterior chamber intraocular lens (PCIOL) implantation in patients with congenital cataract.

Methods: The study was done as a double masked randomised clinical trial between April 2002 and November 2003 in Farabi Eye Hospital. 34 eyes of 26 patients with congenital cataract were included in the study and randomised into two groups (18 cases and 16 controls). Mean age was 8.1 years (3–14 years). Each eye underwent lensectomy and anterior vitrectomy with PCIOL implantation. At the end of surgery 20 µg r-TPA was injected intracamerally in the case group. The control group received only balanced salt solution. All patients received periocular, systemic, and topical steroids after surgery. Patients underwent follow up examinations for 3 months.

Results: The incidence of intraocular fibrin membrane formation was significantly lower in the case group on days 1, 3, 7, 14 ($p=0.02$, $p=0.01$, $p=0.01$, and $p=0.01$, respectively, χ^2 test), but there was no significant difference on days 30 and 90. The frequency of pigmented intraocular lens precipitates was significantly lower in the case group at the end of the third month ($p<0.001$, χ^2 test). No gross ocular side effects were noted after r-TPA injection.

Conclusion: It seems that prophylactic intracameral r-TPA is effective in prevention of fibrinous effusion at least in the first 2 weeks after cataract extraction in the paediatric age group and decreases the incidence of pigmented IOL precipitates.

Fibrinous effusion into the anterior chamber is a rare complication of uneventful cataract surgery. However, if it occurs, visual recovery is delayed and intensive topical or systemic anti-inflammatory treatment may be required. Although intracameral injection of recombinant tissue plasminogen activator (r-TPA) has been advocated for treatment as well as for prophylaxis in adults,^{1–5} the use of it is not a cost effective treatment for prophylaxis at present, and it probably should be used judiciously once the condition occurs. Also its preventive role in congenital cataract has not been well documented.

The pathogenesis of the postoperative fibrinous reaction is not clear but involves the breakdown of the blood-ocular barrier as a result of inflammation and dysfunction of the coagulation and fibrinolytic pathways.¹ While fibrinous uveitis occurs in less than 3% of the cases after normal cataract extraction and intraocular lens (IOL) implantation, fibrin exudation more frequently appears in paediatric age group.⁶ In children implantation of a posterior chamber intraocular lens (PCIOL) is a predisposing factor for an augmented postoperative intraocular inflammatory response. Placing it in the ciliary sulcus may be another risk factor.^{1 7} Fibrinous membrane formation after cataract surgery may cause many complications including displacement of the IOL, pupillary block glaucoma, posterior capsule opacification, compromise in structural and functional integrity of the cornea, trabecular meshwork, lens, uveal tissue, and side effects as a result of long term use of mydriatics and steroids.^{1 5} Moreover, following paediatric cataract extraction there is a reduction in visual acuity, which hinders the potential for improvement during this sensitive period; thus emphasising the need for early intervention.^{1 8} Mild fibrinous membranes may be treated successfully with topical non-steroid anti-inflammatory agents and cycloplegics. However, for moderate fibrinous membranes it may be necessary to add

topical or systemic corticosteroids to the drug regimen, and in very severe cases periocular corticosteroid injection may be needed.³ But in spite of an extended period of therapy the result may still not be promising.

In some studies dramatic fibrinolysis has been achieved in 95% of cases receiving 25 µg of r-TPA for moderate to severe fibrinous membrane formation.¹ Klais *et al* have noted the use of intracameral r-TPA for fibrinolysis of post-cataract pupillary fibrin membranes in children.⁸ A shorter intensive course of topical steroids is needed postoperatively in cases with fibrinous effusion after paediatric cataract surgery who received intracameral r-TPA for dissolution of the fibrin membrane.¹

The purpose of this study was to investigate whether prophylactic application of intracameral r-TPA following cataract extraction with IOL implantation could decrease the incidence of fibrinous effusion in patents with visually significant congenital cataract.

MATERIALS AND METHODS

A double masked randomised clinical trial was conducted to evaluate the efficacy of prophylactic intracameral r-TPA. A total of 34 eyes from 26 patients with congenital cataract were included in the study between April 2002 and November 2003. Eyes were randomised into two groups (18 cases and 16 controls) using the balanced blocked method. Inclusion criteria were visually significant congenital cataract and age between 3 years and 14 years. Central lens opacity >3 mm in cycloplegic retinoscopy or diffuse lens opacity obscuring retinal view in direct ophthalmoscopy; and in older children visual acuity $\leq 20/70$ are considered visually significant for cataract. Patients with underlying ocular

Abbreviations: IOL, intraocular lens; PCIOL, posterior chamber intraocular lens; r-TPA, recombinant tissue plasminogen activator

disorders (glaucoma, anterior, and posterior segment anomalies), underlying systemic disorders (diabetes, hypertension, and endocrine disorders) connective tissue disorders (juvenile rheumatoid arthritis), metabolic disorders (galactosaemia), previous intraocular surgery, and traumatic cataracts were excluded. Patients were included in the study after informed consent was obtained from the parents.

The same surgeon performed all the surgical procedures for the patients. General anaesthesia was used in all cases. After peritomy, a 5.5 mm scleral tunnel incision was made 2 mm posterior to limbus. Two stab incisions were created at 2 o'clock and 11 o'clock. The pupil was dilated preoperatively with topical cyclopentolate 0.5% and intraoperatively with diluted adrenaline (1:1 000 000). Anterior capsulotomy and lensectomy was done using a vitrectomy probe. The posterior capsule was completely removed and after anterior vitrectomy the anterior chamber was reinflated with Healon, the scleral tunnel incision was opened into the anterior chamber, and a one piece polymethylmethacrylate (PMMA) intraocular lens implanted into the ciliary sulcus. Residual viscoelastic was removed using the irrigation aspiration cannula, and the wound was closed with interrupted 10–0 nylon sutures. At the end of the procedure, 20 µg/0.1 ml r-TPA were injected into the anterior chamber of patients in the case group using a 27 gauge needle via paracentesis site. In the control group 0.1 ml balanced salt solution only was injected via the paracentesis site. The surgeon was not aware of the content. All patients received subconjunctival betamethasone (4 mg) and gentamicin (20 mg) and sub-Tenon Depomedrol (20 mg). The eye was covered with a shield. For the first week after cataract surgery all patients received betamethasone 0.1% eye drops 2 hourly, chloramphenicol 0.5% eye drops 4 hourly, and homatropine 2% eye drops three times per day and oral prednisolone (1 mg/kg), tapered gradually after 1 week.

r-TPA was prepared in the Sinadaru pharmaceutical company by reconstitution of 20 mg of lyophilised TPA in 10 ml of sterile water according to the manufacturer's recommendations. All preparations took place under sterile hood. The reconstituted r-TPA was diluted 1:10 in sterile balanced salt solution that was further divided into multiple aliquots of 0.1 ml (20 µg) of r-TPA in insulin syringes (each syringe for one patient). The syringes were then stored at -70°C in an ultralow freezing device. Before use the syringes were thawed to room temperature.

On days 1, 3, 7, 14, 30, and 90 after surgery slit lamp examinations including evaluation of corneal oedema and anterior chamber reaction were done for all patients. Applanation tonometry was also performed using the TonoPen (Mentor, Norwell, MA, USA). All follow up visits were done by another ophthalmologist who was unaware of cases receiving intracameral r-TPA. Classification criteria for

anterior chamber reaction,⁹ hyphaema,⁹ and corneal oedema¹⁰ are listed in table 1. Fibrin formation was defined as several fibrin strands or more (compact fibrin aggregates, fibrin membranes, or clots).

SPSS software (version 11.5) was used for data entry and analysis. $\alpha < 0.05$ was considered as the level of significance. The χ^2 test was used to compare the groups regarding qualitative variables such as sex, anterior chamber reaction, fibrin formation, and hyphaema. The Student's *t* test was used to compare the quantitative variables such as the age and postoperative IOP.

RESULTS

There were 34 eyes of 26 patients (16 males and 10 females) with congenital cataract who underwent cataract extraction and PCIOL implantation in the specified period. Mean age of the patients in the total dataset was 8.1 (SD 3.4) years with a minimum of 3 years and maximum of 14 years. According to our randomisation, 18 eyes received r-TPA injection (52.9%) and 16 eyes (47.1%) had balanced salt solution injection. There was no significant difference (Student's *t* test, $p = 0.17$) in mean age of 7.9 (3.4) years for the case group compared with the mean age of 8.5 (3.8) years for the control patients. There was no significant difference (χ^2 test, $p = 0.26$) in sex between case group (nine male, five female) and control patients (seven male, five female).

Results of comparing anterior chamber (AC) reaction, fibrin formation, hyphaema, corneal oedema, posterior synechiae, and pigmented IOL precipitates between the two groups are listed in detail in table 2.

In summary, no patients in the case group developed fibrin membrane formation. The incidence of intraocular fibrin membrane formation was significantly lower in the case group on days 1, 3, 7, 14 ($p = 0.02$, $p = 0.01$, $p = 0.01$, and $p = 0.01$ respectively, χ^2 test); but there was no significant difference on days 30 and 90. This was also true for $\geq 2+$ AC reaction. Indeed, on day 90 all patients in the two groups had $\leq 1+$ AC reaction.

Three months after surgery three patients in the control group, but no one in case group had posterior synechiae ($p = 0.05$, χ^2 test). At the end of the third month, 14 patients (87.5%) in the control group had multiple pigmented IOL precipitates and in two cases (12.5%) IOLs were clear. In the case group 15 patients had clear IOLs (83.3%) and three patients (16.7%) had pigmented IOL precipitates ($p < 0.001$, χ^2 test). Finally, there was no significant difference in postoperative IOP on days 1, 3, 7, 14, 30, and 90 ($p = 0.32$, $p = 0.17$, $p = 0.10$ and $p = 0.28$, $p = 0.28$, and $p = 0.28$ respectively, Student's *t* test) (fig 1).

DISCUSSION

Plasminogen activators (PAs) are serine proteases that cleave plasminogen to form plasmin; thus they have a key role in the regulation of proteolysis, especially fibrinolysis. TPA (tissue plasminogen activator) is secreted by the vascular endothelial cells as well as the corneal epithelium and endothelium and trabecular meshwork.¹¹ A significant decrease of TPA activity is found in the first days following cataract surgery and iIOL implantation.¹² Fluctuations in TPA concentration in the aqueous humour following cataract surgery associated with additional risk factors that aggravate breakdown of the blood-aqueous barrier, may increase the risk of severe fibrinous membrane formation.¹³

Streptokinase and urokinase have been used previously intraocularly but they were associated with large inflammatory responses and corneal toxicity.¹⁴ Low molecular weight has also been added to irrigation to prevent postoperative fibrin formation.¹⁵ r-TPA has not been seen to be damaging to human corneal endothelium^{14 16} with no change in corneal

Table 1 Classification criteria used for anterior chamber cellular reaction,⁹ hyphaema,⁹ and corneal oedema¹⁰

Anterior chamber cellular reaction and hyphaema*

- 0: no cell
- Trace: <5 cell
- 1+: 5–10 cells
- 2+: 10–20 cells
- 3+: 20–30 cells
- 4+: cells too numerous to count

Corneal oedema

- 1+: folds in descemet membrane
- 2+: stromal oedema in a ground glass appearance
- 3+: microcystic epithelial oedema or subepithelial bullae

*The intensity of cellular reaction in the anterior chamber is graded according to the number of inflammatory cells seen in a 1×3 mm high powered beam at full intensity at a 45°–60° angle.

Table 2 Results of 3 months follow up examinations in two groups

Days after surgery	Cases (n = 18)	Controls (n = 16)	p Value*
Anterior chamber reaction ($\geq 2+$)			
1	3 (16.7%)	15 (93.8%)	<0.001
3	4 (22.2%)	13 (81.2%)	0.001
7	1 (5.6%)	8 (50%)	0.003
14	0 (0%)	8 (50%)	0.001
30	0 (0%)	1 (6.2%)	NS
90	0 (0%)	0 (0%)	NS
Fibrin formation			
1	0 (0%)	4 (25%)	0.024
3	0 (0%)	5 (31.3%)	0.01
7	0 (0%)	5 (31.3%)	0.01
14	0 (0%)	5 (31.3%)	0.01
30	0 (0%)	1 (6.2%)	NS
90	0 (0%)	0 (0%)	NS
Pigmented IOL precipitates			
90	3 (16.7%)	14 (87.5%)	<0.001
Posterior synechiae			
90	0 (0%)	3 (18.7%)	NS
Hyphaema $\geq 2+$			
1	9 (50%)	3 (18.7%)	NS
3	5 (28%)	2 (12.5%)	NS
7	3 (16.7%)	1 (6.2%)	NS
14	1 (5.6%)	0 (0%)	NS
30	1 (5.6%)	0 (0%)	NS
90	0 (0%)	0 (0%)	NS
Corneal oedema $\geq 2+$			
1	3 (16.7%)	2 (12.5%)	NS
3	1 (5.6%)	1 (6.2%)	NS
7	0 (0%)	1 (6.2%)	NS
14	0 (0%)	0 (0%)	NS
30	0 (0%)	0 (0%)	NS
90	0 (0%)	0 (0%)	NS
Intraocular pressure†			
1	11.2 (1.1)	12.2 (0.8)	NS
3	12.1 (0.6)	13.0 (0.9)	NS
7	14.2 (1.2)	13.4 (1.1)	NS
14	16.1 (1.1)	14.8 (1.0)	NS
30	16.0 (1.2)	15.0 (1.0)	NS
90	16.2 (1.2)	15.1 (1.3)	NS

NS, no significant statistical difference.

* χ^2 test.

†Mean (SD).

endothelial size or morphology even with doses as high as 200 μg .⁵ It is a fibrinolytic serine protease that is genetically cloned and obtained by expression of recombinant DNA.^{1 11} Its fibrinolytic activity is based on the conversion of plasminogen into plasmin, which promotes fibrin degradation. The plasma half life of intravenous r-TPA is approximately 7 minutes and with the low concentrations used for intraocular fibrinolysis the risk of systemic plasminogen activation is low.¹⁷

r-TPA has been used in cases of fibrinous effusion in adults after cataract surgery,⁴⁻⁶ vitrectomy,¹⁸ penetrating keratoplasty,¹⁴ glaucoma surgery,¹⁹ and traumatic hyphaema.²⁰ Moon *et al* used 25 μg r-TPA in 52 patients to treat moderate

to severe fibrinous membrane with 90% complete fibrinolysis and demonstrated no change in intraocular pressure, endothelial cell density, size and morphology; but they reported hyphaema in four eyes and AC clouding in three eyes.⁵ Mehta and Adams¹ used r-TPA to treat severe postcataract fibrinous membrane in paediatric groups, safely and effectively with no complications at a dose of 25 μg . Rehfeldt *et al* used r-TPA for prophylactic purposes in adults at a dose of 10 $\mu\text{g}/0.1$ ml. They found that 75% of their cases had no fibrin reactions in AC but 5.4% of them showed hyphaema and 3.5% developed transient corneal clouding.² They recommended a prospective controlled study to evaluate this issue.

In this study which to our knowledge is the first randomised controlled study done using r-TPA as a prophylactic measure in paediatric cataract surgery, we found a significant difference in the rate of AC reaction and fibrin formation between the two groups at least in the first 2 weeks after surgery; but after 1 month the difference was not significant.

These results show that prophylactic intracameral r-TPA is effective in prevention of fibrinous reaction at least in the first 2 weeks after cataract extraction and PCIOL implantation in paediatric age groups. Our data are consistent with Rehfeldt and Hoh's² study in adults, but our study is prospective and controlled. Also we found that intracameral r-TPA reduced the incidence of pigmented IOL precipitates at the end of the third month ($p < 0.001$, χ^2 test). To our knowledge up to now there has been no report on reducing

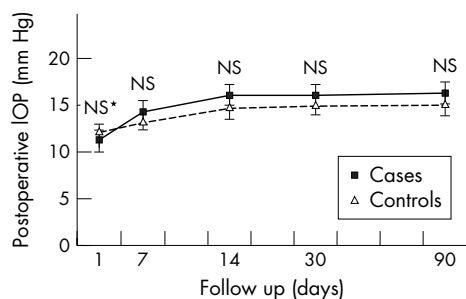


Figure 1 Comparison of postoperative intraocular pressure (IOP) (mean (SD)) between two groups (Student's *t* test). *NS, no significant statistical difference.

such IOL precipitates in the literature. In our study frequency of posterior synechiae to the IOLs was reduced by the r-TPA injection, but the difference between the two groups did not reach the level of statistical significance. This is also compatible with the study of Heiligenhaus *et al* in 1998.⁶

Our study showed no significant difference in incidence of hyphaema, IOP rise or corneal oedema between the groups during the 3 month follow up, although in some uncontrolled studies there has been reports of increased incidence of these complications in patients receiving intracameral r-TPA.²⁻¹³ Lack of significant hyphaema, intraocular pressure rise, and corneal oedema in our cases could be because of the smaller sample size in our study. Age discrepancy and inclusion of second eyes in the study also could have some effects on the rate of fibrinous formation in our patients, as fibrinous formation is more common in younger children and second eyes. In this study we did not perform endothelial cell count, so we could not claim that there was no endothelial toxicity. Finally, we had no major complications of r-TPA injection in the 3 months of follow up.

In summary, fibrinous membrane formation after cataract surgery may cause many complications including displacement of the intraocular lens, pupillary block glaucoma, decreased visual acuity, and side effects caused by long term use of mydriatics and steroids.¹⁻⁵ Particularly following paediatric cataract extraction, fibrinous membrane may cause a reduction in visual acuity and hinder the potential for improvement in visual development during this sensitive period, thus emphasising the need for early intervention.¹⁻⁸ Prophylactic intracameral r-TPA can improve the visual potential of the patient by reducing the incidence of fibrinous reaction and can help in the efficient treatment of amblyopia by providing a clear visual axis in this critical period.

In conclusion, 20 µg/0.1 ml r-TPA may be safely used for prophylaxis of fibrin formation in paediatric cataract extraction and it is recommended to be used at least in those patients who are at increased risk of severe postoperative fibrin formation. We suggest conducting a prospective study with larger sample size, with a more limited age range and longer term follow up.

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Ethical approval: The review board and ethics committee of Eye Research Center of Tehran University of Medical Sciences approved the trial.

Informed consent: Written informed consent was obtained from all the parents after complete explanation.

REFERENCES

- 1 Mehta JS, Adams GG. Recombinant tissue plasminogen activator following pediatric cataract surgery. *Br J Ophthalmol* 2000;**84**:983-6.
- 2 Rehfeldt K, Hoh H. Therapeutic and prophylactic application of TPA (recombinant tissue plasminogen activator) into the anterior chamber of the eye. *Ophthalmologie*. 1999;**96**: 587-93 (abstract).
- 3 Miyake K. The significance of inflammatory reactions following cataract extraction and intraocular lens implantation. *J Cataract Refract Surg* 1996;**22**:759-63.
- 4 Wedrich A, Menapace R, Ries E, *et al*. The use of recombinant tissue plasminogen activator for intracameral fibrinolysis following cataract surgery. *Int Ophthalmol* 1995;**18**:277-80.
- 5 Moon J, Chung S, Myong Y, *et al*. Treatment of postcataract fibrinous membranes with tissue plasminogen activator. *Ophthalmology* 1992;**99**:1256-9.
- 6 Heiligenhaus A, Steinmetz B, Lapuente R, *et al*. Recombinant tissue plasminogen in cases with fibrin formation after cataract surgery. *Br J Ophthalmol* 1998;**82**:810-15.
- 7 Koch DD, Kohlen T. Retrospective comparison of techniques to prevent secondary cataract formation after posterior chamber intraocular lens implantation in infants and children. *J Cataract Refract Surg* 1997;**23**:657-63.
- 8 Klais CM, Hattenbach LO, Steinkamp GWK, *et al*. Intraocular recombinant tissue plasminogen activator fibrinolysis of fibrin formation after cataract surgery in children. *J Cataract Refract Surg* 1999;**25**:357-61.
- 9 Liesegang TJ, Deursch T, Gilbert M. Clinical approach to uveitis. In: *Basic and clinical science course: intraocular inflammation and uveitis*. San Francisco: American Academy of Ophthalmology, 2003:103.
- 10 Miller CA, Krachmer JH. Endothelial dystrophies. In: Kaufman HE, Barron BA, McDonald MB. *The cornea*. Boston: Butterworth-Heinemann, 1998:455-6.
- 11 Tripathi RC, Park JK, Tripathi BJ, *et al*. Tissue plasminogen activator in human aqueous humor and its possible therapeutic significance. *Am J Ophthalmol* 1988;**106**:719-22.
- 12 Yoshitomi F, Utsumi E, Hayashi M, *et al*. Postoperative fluctuation of tissue plasminogen activator (t-PA) in aqueous humor of pseudophakos. *J Cataract Refract Surg* 1991;**18**:252-64.
- 13 Wedrich A, Menapace R, Ries E, *et al*. Intracameral tissue plasminogen activator to treat severe fibrinous effusion after cataract surgery. *J Cataract Refract Surg* 1997;**23**:873-7.
- 14 Synder RW, Lambrou FH, Williams GA. Intraocular fibrinolysis with recombinant human tissue plasminogen activator; experimental treatment in rabbit model. *Arch Ophthalmol* 1987;**105**:1277-80.
- 15 Iverson DA, Katsura H, Hartzler MK, *et al*. Inhibition of intraocular fibrin formation following infusion of low-molecular-weight heparin during vitrectomy. *Arch Ophthalmol* 1990;**109**:405-9.
- 16 McDermott ML, Edelhauser HF, Hyndiuk RA, *et al*. Tissue plasminogen activator and corneal endothelium. *Am J Ophthalmol* 1989;**108**:91-2.
- 17 Gerding PA, Hamor RE, Ramsey DT, *et al*. Evaluation of topically administered tissue plasminogen activator for intraocular fibrinolysis in dogs. *Am J Vet Res* 1994;**55**:1368-70, (abstract).
- 18 Jaffe GJ, Lewis H, Han DP, *et al*. Treatment of postvitrectomy fibrin popillary block with tissue plasminogen activator. *Am J Ophthalmol* 1989;**108**:170-5.
- 19 Tripathi RC, Tripathi BJ, Park JK, *et al*. Intracameral tissue plasminogen activator for resolution of fibrin clots after glaucoma filtering procedures. *Am J Ophthalmol* 1991;**111**:247-8.
- 20 Laatikainen L, Mattila J. The use of tissue plasminogen activator in post-traumatic hyphema. *Graefes Arch Clin Exp Ophthalmol* 1996;**234**:67-8.



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