·Clinical Research·

Recombinant tissue plasminogen activator for treatment of fibrinous membranes after cataract surgery

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Abstract

• AIM: To investigate the efficacy of recombinant tissue plasminogen activator (TPA) for treatment of fibrinous membranes following cataract surgery.

• METHODS: 25μ g of TPA was injected into the anterior chamber of 15 pseudophakic eyes with moderate to severe fibrinous membranes that developed after cataract surgery. Simultaneously, topical corticosteroid and cycloplegic therapy was continued. Routine follow-up included slit-lamp examination and intraocular pressure measurement.

• RESULTS: Injection of the solution of tissue plasminogen activator into anterior chamber of 15 eyes resulted in complete dissolution of the fibrinous membranes in 9 (60.0%) eyes after 2 hours, and 11 (73.3%) eyes within 1 day. In 3 eyes, within a few days after injection, fibrinous membrane recurred. Increased anterior chamber reaction (P=0.54) and corneal edema (P=0.083) were seen after 24 hours. No evidence of toxicity was observed as measured by slit-lamp biomicroscopy and intraocular pressure. Finally, expectable stable result was obtained in all of the eyes.

• CONCLUSION: Safety and high efficacy of TPA in the treatment of fibrinous membranes after cataract surgery are confirmed.

• KEYWORDS: recombinant tissue plasminogen activator; fibrinous membrane; cataract surgery

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INTRODUCTION

Fibrous effusion into the anterior chamber is a rare complication of uneventful cataract surgery in normal eyes (less than 3%)[1], however in eyes with concomitant disease such as diabetes, uveitis, pseudoexfoliation, glaucoma, or pediatric age group the prevalence may increase from 4%[2] to 54%[3-5]. If it occurs visual recovery is delayed and intensive topical or systemic anti-inflammatory treatment is required. This insoluble fibrin may eventually lead to synechiae, loss of pupillary function, membrane formation on the intraocular lens, IOL dislocation, or secondary glaucoma. Posterior capsule opacification, found in 15%-50% of the patients after cataract extraction, may also result from postoperative fibrinous reaction [6]. Introduction of a potent fibrinolytic substance for the treatment of postsurgical fibrin formation therefore seems reasonable. Recombinant tissue plasminogen activator (TPA) is a highly potent fibrinolytic protein [7-9]. Its fibrinolytic activity is clot specific, which significantly decreases the risk of hemorrhages[10]. In several clinical trials intracameral TPA injections of 25μg or less have been shown to lyse postcataract intracameral fibrin membranes[11-18].

This prospective study was undertaken to investigate the efficacy of anterior chamber injections of 25μg TPA for resolution of moderate to severe fibrin formation following extracapsular cataract extraction (ECCE) or phacoemulsification with posterior chamber intraocular lens implantation (PC-IOL) in order to determine its effects on secondary complications such as synechiae and its tolerability.

PATIENTS AND METHODS

Patients Developing moderate to severe anterior chamber fibrin after ECCE or phacoemulsification with PC-IOL between March 2003 and December 2006 that did not resolve after about one week medical therapy were included in this study. ECCE or phacoemulsification techniques were performed. Betamethasone, 4mg, was injected subcon-

junctivally at the end of the surgery. Age of the patients was 20-85 years. The inclusion criteria: intracameral fibrin membranes or clots after ECCE or phacoemulsification with PC-IOL that has not been resolved after one week conventional therapy with betamethasone drop every 1-3 hours, homatropine drop every 8 hours, and tablet prednisolone 1mg/kg; and able to participate for the entire follow-up period. Exclusion criteria: Known hypersensitivity to active ingredients or excipients of the study medication; uncertain compliance; Known coagulopathy; Intraoperative posterior capsule rupture; and traumatic cataract. A detailed review of systems and eye examinations was performed when the patients were recruited to this study, which was carried out in accordance with the Declaration of Helsinki concerning medical research in humans. Patients were included in this study after obtaining informed consent.

Methods The study was designed as a prospective study. Patients with fibrin reaction after cataract surgery, for the first week received betamethasone eye drops 2 hourly, chloramphenicol eye drops 4 hourly, and homatropine eye drops 8 hourly to reduce the postoperative inflammatory response. Patients with severe fibrinous reaction also received oral prednisolone 1mg/kg. Patients with moderate or severe postsurgical fibrinous membranes or clots after 1 week medical therapy were assigned to the study. The TPA was prepared in Faculty of Pharmacy, Tehran University of Medical Science, by reconstitution of 20mg of lyophilised tissue plasminogen activator in 20mL of sterile water according to the manufacturer's recommendations. All preparation was under a sterile hood. The reconstituted TPA was diluted 1∶4 in sterile balanced salt solution which was then divided into multiple aliquots of 1mL (250μg) of TPA. The syringes were then stored at -70℃ in an ultralow freezer and before use the syringes were thawed to room temperature.

The patients received a single intraocular injection of 25μg TPA under topical anesthesia; 0.1μL of the solution containing 25μg TPA were injected into the anterior chamber under an operation microscope. Before injection 0.1 ml of the aqueous was taken for culture.

Before injection, 2 hours after injection, on days 1, 3, 7, 30, and 90, applanation tonometry, and slit-lamp examinations were performed. The eyelids, the conjunctiva, the wound area, cornea, anterior chamber, iris, and IOL were evaluated. The findings were graded on scales and were documented in detailed standardized protocols. The presence of intraocular fibrin was graded as slight (several fibrin strands), moderate (compact fibrin aggregates that vitreous can be seen beyond it), or severe (fibrin membranes or clots that vitreous can not be seen beyond it). Classification criteria for anterior chamber reaction were as follows; 0: no cell, Trace: <5 cells, 1+: 5-10 cells, 2+: 10-20 cells, 3+: 20-30 cells, 4+: cells too numerous to count, and 5+: gross hyphaema. Corneal oedema was classified as; 1+: folds in descemet membrane, 2+: stromal edema in a ground glass appearance, 3+: microcystic epithelial edema or subepithelial bulla[15]. The intensity of cellular reaction in the anterior chamber was graded according to the number of inflammatory cells seen in a 0.2 mm high powered beam at full intensity at a 45°-60° angle.

The primary efficacy variable was the rate of fibrinolysis in the anterior chamber, on the IOL surface, or on the other intracameral structures. The secondary efficacy variables were the development of synechiae, cellular reaction in the anterior chamber, hyphaema, IOP change, corneal edema. Any adverse events were reported, including physical signs, and diseases that occurred or worsened during the study period.

Statistical Analysis Performed by χ^2 test. The statistical analysis of the secondary variables such as the age and postoperative IOP was done with Student's *t* test; the frequencies were evaluated by means of a χ^2 test.

RESULTS

There were 15 eyes of 15 patients (7 males and 8 females) which enrolled in this study. Mean age of the patients in the total dataset was 68 years with a minimum of 21 years and maximum of 81 years. Mean time between fibrin formation after cataract surgery and our injection was 9.27 days (7-25 days). Eleven patients had undergone phacoemulsification and 4 ECCE. Three patients had pseudoexfoliation, 5 patients had mature cataract before surgery. None of the patients had uveitis before surgery. Two patients had diabetes mellitus. Results of comparing fibrin dissolution and reformation, anterior chamber (AC) reaction, corneal edema, posterior synechiae, and IOP before and after treatment are listed in detail in Table 1.

Fibrin The time for complete dissolution of fibrin varied between the patients. Nine patients (60%) showed complete dissolution by 2 hour. Eleven (73.3%) patients had complete dissolution by the following day, and 4 patients (26.7%) had only mild fibrin. All patients received betamethasone 2 hourly, chloramphenicol eye drops 4 hourly, homatropine

Table 1 Pre- and postoperative finding after TPA injection in patients with fibrin formation after cataract surgery (Values are %)

	Before treatment	After treatment					
		2h	1d	3d	7d	30d	90d
Presence of fibrin							
None	—	60.0	73.3	80.0	86.7	100.0	100.0
Mild	—	26.7	26.7	—	—	—	—
Moderate	40.0	13.3	—	20.0	13.3	—	—
Severe	60.0	—	—	—	—	—	—
AC reaction							
None	20.0	—				100	100
1+	20.0		20.0				
2+	26.7		40.0				
3+	33.3		33.3				
4+	—		6.7				
Corneal edema							
None	33.3		26.7			100	100
1+	13.3		13.3				
2+	53.3		53.3				
3+	—		6.7				
Posterior synechiae	26.7	26.7	20.0	13.3	13.3		
IOP rise	—	—	—	—	—	—	—

eye drops 8 hourly postinjection for at least one week until reviewed in clinic where the intensive steroid regimen was reduced with cessation of the other drops.

Three days after treatment, 12 patients (80.0%) had not any fibrin, but 3 patients had moderate fibrin, which was due to reformation. In summary, 3 patients developed fibrin membrane reformation in the 3rd day after TPA injection (20.0%) that in these patients medical treatment continued. In all of these patients degree of fibrin formation was lower than before injection and in all of them fibrin gradually resolved with medical treatment.

Anterior Chamber (AC) Reaction Six patients had increased AC reaction 24 hours after injection (P=0.54). It seemed that TPA injection caused to increased AC reaction that may be due to intervention and lysis of fibrin.

Corneal Edema Transient corneal edema was seen in 3 patients 24 hours after injection (P=0.083) that were resolved after 3 days. It seems to be due to increase in manipulation or increase in cellular reaction.

Posterior Synechiae (PS) Before procedure 4 patients had PS that in 3 patients after TPA injection and application of cycloplegic for 2 weeks was removed. In the last one, in was resolved after one month. Three months after surgery none of the patients had posterior synechiae or multiple pigmented IOL precipitates.

Intraocular Pressure (IOP) There was no significant difference in postoperative IOP on 2 hours after injection and days 1, 7, 30, and 90 (P=0.274, P=0.220 and P=0.855, P=0.779, and P=1.000 respectively, Student's t-test). Although mean IOP had no significant difference, one of our patients had IOP rise from 14mmHg to 22mmHg that after 2 days and without any medication was decreased to 14mmHg.

Other Complications Hyphaema was not observed in any case in this study. Corneal complications, wound healing problems, or disturbances in the IOP were not found in any of the patients. All of the other study variables listed in Table 1.

DISCUSSION

The pathogenesis of the postoperative fibrin response is unclear but it involves the breakdown of the blood-ocular barrier by inflammation and dysfunction of the coagulation and fibrinolytic pathways[19]. Mild fibrinous membranes may be treated successfully with topical corticosteroids, nonsteroidal anti-inflammatory agents, and cycloplegics. However, for moderate to severe fibrinous membranes conventional treatment may need to be extended for several weeks and still may be unsuccessful. The duration of treatment may be associated with many complications and also it may be difficult to administer such intensive regimens to young children.

TPA is secreted by the vascular endothelial cells as well as the corneal epithelium/endothelium and trabecular meshwork[20]. A significant decrease of TPA activity is found in the first days following cataract surgery and intraocular lens implantation [21]. Fluctuations in the TPA concentration in the aqueous humor following cataract surgery accompanied by additional risk factors that enhance the breakdown of the blood-aqueous barrier may increase the risk of severe fibrinous membrane formation[13].

TPA is a fibrinolytic serine protease that its fibrinolytic activity is based on the conversion of plasminogen into plasmin, which promotes fibrin degradation. TPA requires fibrin binding which enhances its affinity for plasminogen so that plasminogen activation is confined to the surface fibrin clot; hence, it is clot specific and is not associated with systemic fibrinolysis unlike streptokinase or urokinase. The plasma half life of intravenous TPA is approximately 7 minutes [22]. With the low concentrations used for intraocular fibrinolysis the risk of systemic plasminogen activation is low [23] . Streptokinase and urokinase have been previously used intraocularly but they were associated with large inflammatory responses and corneal toxicity[22].

TPA has been used in cases of fibrinous effusion in adults

after vitrectomy [24], penetrating keratoplasty [22], glaucoma surgery [25], traumatic hyphaema [26], and in patients undergoing surgical removal of choroidal neovascular membranes with age related macular degeneration [27]. Following adult cataract surgery complete fibrinolysis has been achieved in 95% of cases receiving 25μg of TPA for moderate to severe fibrinous membrane formation [13]. The mean time for effect was 3.3 hours[5]. Moon *et al*[11] reported complete fibrinolysis of moderate to severe fibrinous membranes after cataract surgery in 90% of 52 eyes also using 25μg of TPA but the maximum effect was observed 1 hour after injection. However, in a larger study 10μg TPA successfully accelerated fibrinolysis in 93% of adults by 2 weeks following cataract surgery [28]. In the other reported study, Wedrich *et al* [13] used 25μg TPA and achieved complete dissolution in 90% of cases within 24 hours. In our cases the time for complete fibrinolysis was longer than the adult series but similar to the series of Klais *et al* [29]. In our study after 2 hours fibronolisis was seen on only 60.0% of cases, after 24 hours this rate reached 73.3%, and after 3 days to 80.0%.

There are some reports of the application of TPA that has decreased rate of posterior capsule fibrosis [18]. There is compelling evidence that proliferation, migration, and methaplasia of the lens epithelial cells that causes posterior capsular opacification, are related to post-operative disruption of the blood-aqueous barrier and are associated with exudation of fibrinogen and fibrin [30-35]. TPA has not been found to be damaging to the human corneal endothelium [22,36]. No changes in corneal endothelium cell size or morphology even with doses as high as 200μg have been seen [11]. Retinal toxicity increases with intravitreal doses between 50-100μg in animal models[37].

The main complications of TPA use in adults postcataract surgery are anterior chamber hemorrhage, increase in IOP, and persistent posterior synechiae[38]. The risk of hemorrhage may be reduced significantly if the TPA is given after the third day after the cataract surgery and some have advised waiting 1 week [38]. All of our patients received TPA after a minimum time of 7 days and no hemorrhage was observed. A temporary increase in IOP up to 30mmHg has been noted in some studies after TPA injection but the pressure returned to normal in all the cases by 3-4 days [38] without antiglaucoma treatment as we saw in one of our patients. The pressure increase may be due to transient blockage of the trabecular meshwork after fibrinolysis of thick membranes[13]. Acute band keratopathy has been described in adults who underwent intracameral injection of TPA and were receiving topical drops containing a phosphate based drug[23,39].

In this study we found that TPA is effective in treatment of fibrinous reaction in nearly 80.0% of patients after cataract extraction and PCIOL implantation. Our data are consistent with previous studies. In 3 patients we had fibrin reformation that were cleared after 2 weeks. In our study frequency of posterior synechiae to the IOLs was reduced by the TPA injection. Our study showed no significant increase in incidence of hyphaema, and IOP rise 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 TPA[38,40]. Lack of significant hyphaema and intraocular pressure rise in our cases could be due to the smaller sample size in our study. In this study we did not perform endothelial cell count, so we could not claim that there was no endothelial toxicity. In our patients TPA injection caused to increase AC cellular reaction in 6 patients. This seems to be due to intervention and interring to AC. We can conclude that after injection of TPA, anti-inflammatory drugs should be continued and may be needed to increase their dosage. In 3 patients corneal edema was increased that was transient. It may be due to increase in inflammation in AC that will resolve during 1-2 days. Finally, we had no major complications of 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. Although anterior chamber injections of TPA in postcataract patients already complicated by fibrin formation might induce additional inflammation, however it is an effective and safe procedure in treatment of AC fibrin in such cases. In conclusion, 25μg/0.1mL TPA may be safely used for treatment of fibrin formation in cataract extraction and it is recommended to be used at least in those patients who have severe postoperative fibrin formation.

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