Original Article

Effectiveness of Intracameral Tissue Plasminogen (r-tPA) Activator in Resolution of Fibrinous Reaction in Refractory Toxic Anterior Segment Syndrome (TASS)

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Bilal Khan[1], Adnan Ahmad[2], Javed Rasul[3]
[1]Khyber Teaching Hospital, Peshawar, [2]Nowshera Medical College, [3]Pak international Medical College

ABSTRACT

Purpose: To evaluate the effectiveness of tissue plasminogen activator (r-tPA) in resistant toxic anterior segment syndrome (TASS) after Phacoemulsification.

Study Design: Quasi experimental.

Place and Duration of Study: Khyber Teaching Hospital, Peshawar from August 2021 to August 2023.

Methods: Forty-six patients (46 eyes) with an anterior chamber fibrin reaction after cataract surgery were treated with intra-cameral injection of t-PA (30µg/0.1cc) following failure to respond to conventional treatment with intensive topical and subconjunctival steroids. Outcome measures were best corrected visual acuity (BCVA), clearance/recurrence of the fibrin reaction and complications.

Results: Intra-cameral t-PA was injected2 to 6 weeks post Phacoemulsification in TASS cases. Mean post-operative injection time was 18.5 ± 10.2 days. After 1st day post injection, we observed total abolition of fibrinous exudate in 36(78.2%) cases and subtotal resolution in 10 (21.7%) cases. After 6 weeks the TASS was completely settled in 43(93.4%)cases. Mean BCVA improved from 0.59 ± 0.40 log MAR pre-injection to 0.38 ± 0.40 log MAR at 6th week post-injection (p=0.07). There was no statistically significant difference in BCVA and rate of fibrinolysis between the two groups after post r-tPA injections. Intra-cameral r-tPA was not associated with adverse effects like raised IOP or endophthalmitis.

Conclusion: Intra-cameral t-PA injection (30µg/0.1cc)appears to be a safe and effective treatment option for resolving anterior chamber fibrin reaction refractory to conventional steroid therapy following cataract surgery.

Key words: Tissue plasminogen activator, Fibrin, Toxic Anterior Segment Syndrome, Phacoemulsification.

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Correspondence: Adnan Ahmad
Nowshera Medical College, Nowshera
Email: dradnanahmad82@gmail.com

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INTRODUCTION

Toxic anterior segment syndrome (TASS) is a non-infective fibrinous reaction in the anterior chamber of an after cataract surgeries and to lesser extent after other anterior chamber procedures. It develops in acute manner, but sometimes it has late onset.[1]Its incidence is reported to be 0.18% to 0.75% in different studies.[2,3] The prominent finding includes corneal edema resulting from toxic insult of inflammatory mediators circulating in the anterior segment. Marked disruption of the blood–aqueous barrier leads to formation of an exudative membrane as well as hypopyon in 80% cases. One of the differentiating features between TASS and infective endophthalmitis is absence of vitritis in the former but meticulous observation is required as the consequences may be hazardous if

misdiagnosed.[4] TASS is mainly treated with intensive topical steroids i.e. dexamethasone or prednisolone acetate/phosphate. Careful monitoring and follow up is required especially during the 1st post-operative week to make sure that inflammatory reaction is resolving and anterior segment changes are reverting to normal with steroids. Any worsening raises the concern of potential endophthalmitis and prompt therapy in the form of intravitreal antibiotics should be instituted.[5,6]Meticulous attention should be paid to the inflammatory processes going on in the anterior segment as well as IOP checkup should be done at regular intervals as both the inflammatory processes and steroids contribute to the development of glaucoma.

In steroid resistant TASS, different treatment options have been tried to resolve the inflammatory reaction, which includes anterior chamber wash, Nd:YAG laser membranotomy and intra-cameral injection of tissue plasminogen activator(t-PA).[7,8]The use of t-PA, (a protease activated by fibrin) catalyzes the conversion of plasminogen into plasmin leading to fibrinolysis and hence resolving the fibrinous inflammatory reactions.[9,10]

The objective of current study is to evaluate the effectiveness of intra-cameral t-PA in the treatment of resistant TASS in post Phacoemulsification cases.

METHODS

A quasi experimental study was done from August 2021, to August, 2023 at department of Khyber Teaching Hospital, Peshawar. The sample size was calculated by using WHO sample size calculator using the equation 1.1. With confidence interval of 95% and anticipated population proportion as well as absolute precision taken as 0.05%, the sample size was 46.Ethical approval was obtained from the institutional ethical review board prior to study with IERB # 3478/R&D/IERB/KMC. We recruited 46 consecutive patients with an inflammatory fibrinous reaction in the anterior chamber (after excluding Endophthalmitis meticulously by both clinically and by specific investigations). Patients who underwent Phacoemulsification with posterior chamber intraocular lens (PCIOL) implantation and resistant to conventional therapy of intensive topical and sub-conjunctival steroids for TASS were included. We conducted the study according to the tenets of declaration of Helsinki and guidelines of good clinical practice. In all cases topical dexamethasone phosphate 0.1% eye drops were given 1 hourly, Moxifloxacin 0.5%, 4 hourly along with cyclopentolate 1% eye drops three times a day for 1 week. If no improvement was observed with the above therapy, a single injection of sub-conjunctival steroids (Dexamethasone 4mg) was given, if still there was suboptimal response, an intra-cameral injection of 30µg/0.1ccr-tPA was administered. The r-tPA preparation (Actilyse, Boehringer Ingelheim Limited, UK) was diluted under sterile conditions to a concentration of 30µg/0.1cc, distributed into insulin syringes and stored at −70°C in ultra-freezing freezer in blood bank. Prior to administration, the prefilled syringes were de-frosted at room temperature. Injections were given in the operating theatre.

Before r-tPA injection, topical proparacaine 1% and 5% povidone iodine drops were administered and the eyelids were opened with an eyelid speculum. Aqueous was drained (0.1cc) from the anterior chamber, and 0.1cc of r-tPA was injected intra-camerally using a 30-gauge needle through one of the side ports formed during Phacoemulsification. Post injection, topical Dexamethasone 0.1% drops were started in QID regimen for 1 week. The steroids were tapered down over 6 weeks. Baseline values had been documented prior to treatment. Patients were assessed for a fibrinous reaction or complications at 1st day, 1st, 4th and 6th week following r-tPA injection using slit-lamp bio-microscope. Intraocular pressure (IOP) was measured by applanation tonometer and best-corrected visual acuity BCVA was documented by using a standard Snellen chart and then converted into logMAR for statistical analysis. Signs observed at each follow up visit was compared with baseline values and with the prior examination findings.

Statistical analysis was done by using the SPSS version 26.0 (IBM Corp. USA). The qualitative variables like age, side of the eye, gender and resolution of fibrin were expressed in frequencies and percentages. The quantitative variables like BCVA and IOP were expressed as mean and standard deviation. The analysis between pre and post injection at different intervals were done by using the statistical analysis of repeated measures for fibrin resolution, BCVA and IOP for statistical significance. The significance was set at < 0.05.

RESULTS

Out of total 46 participants, 22 were men and 24 women with a mean age of 62 ± 08 years. The right

Table 1: *Outcome of intra-cameral r-tPA in 46 patients with TASS.*

Variables	Pre-injection r-tPA	1 day post r-tPA	p-value
Fibrin in AC, n (%)	46 (100%)	10 (21.7%)	<0.05
BCVA (log MAR) (n=46)	0.59 ± 0.40	0.61 ± 0.42	0.66
IOP (mmHg), mean ± SD	14.5±1.8	13.6±2.6	0.42
Variables	**Pre-injection r-tPA**	**7th day post r-tPA**	**P value**
Fibrin in AC, n (%)	40 (100%)	9 (23.7%)	<0.05
BCVA (logMAR) (n=46)	0.59 ± 0.40	0.46 ± 0.40	0.12
IOP (mmHg), mean±SD	12.8±3.2	13.7±3.2	0.31
Variables	**Pre-r-tPA injection**	**4th week post r-tPA**	**p-value**
Fibrin in AC, n (%)	46 (100%)	5(10.9%)	<0.05
BCVA (log MAR) (n=46)	0.59 ± 0.40	0.42 ± 0.28	0.08
IOP (mmHg), mean±SD	13.2±1.8	13.0±.4	0.32
Variables	**Pre-r-tPA injection**	**6th week post r-tPA**	**p-value**
Fibrin in AC, n (%)	46 (100%)	3 (6.5%)	<0.05
BCVA (log MAR) (n=46)	0.59 ± 0.40	0.38 ± 0.40	0.07
IOP (mmHg), mean±SD	12.8±3.2	13.9±2.8	0.19

AC, anterior chamber; BCVA, best-corrected visual acuity, IOP, intraocular pressure, r-tPA, recombinant tissue plasminogen activator; TASS, Toxic anterior segment syndrome.

Table 2: Outcome of r-tPA in 46 patients with TASS by time of intervention post-phacoemulsification.

Variables	Early injection of r-tPA 2-3weeks (N= 20)	Late injection of r-tPA 4-6weeks (N= 26)	p-value
Fibrin in AC, n (%)			
1st day	4 (20%)	6 (23.07%)	0.88
1st week	4 (20%)	5 (19.23%)	0.92
4th week	2 (10%)	3 (11.53%)	0.98
6th week	1 (5%)	2 (7.69%)	0.90
BCVA (log MAR), mean±SD			
Baseline	0.58 ± 0.38	0.59 ± 0.20	0.96
1st day	0.66 ± 0.45	0.58 ± 0.62	0.18
1st week	0.48 ± 0.34	0.40 ± 0.52	0.54
4th week	0.40 ± 0.28	0.39 ± 0.26	0.76
6th week	0.39 ± 0.20	0.37 ± 0.22	0.72
IOP (mm Hg), mean±SD			
Baseline	13.0±2.4	12.8±2.8	0.80
1st day	12.3±3.0	12.0±3.2	0.76
1st week	14.3±3.3	13.5±3.2	0.32
4th week	14.5±4.1	13.6±2.7	0.28
6th week	13.9±3.6	13.7±3.2	0.78

AC, anterior chamber; BCVA, best corrected visual acuity; IOP, intraocular pressure; r-tPA, recombinant tissue plasminogen activator; TASS, Toxic anterior segment syndrome.

eye was involved in 20 subjects while left eye in 26 patients. Thirty-two participants (69.5%) were given sub-conjunctival steroids before intra-cameral t-PA, at a mean of 12.2 ± 5.5 days post-operative. Intra-cameral t-PA was given at a mean of 18.5 ± 10.2 days post-operative (range 2–6 weeks). Mean follow-up interval after r-tPA injections was 28 ± 20 days (range 2 to 12 weeks).

The efficacy of intra-cameral r-tPA treatment is shown in Table 1.

For group wise comparison between the BCVA at baseline and post-injection at day 1, day4 and week 6 refer to Table 2. IOP remained within normal range after r-tPA injections in all cases.

DISCUSSION

Any intra-ocular surgery leads to disruption of blood aqueous barrier due to tissue manipulation resulting in exudation of plasma constituents and leukocytes along with inflammatory mediators i.e. prostaglandins which

appear as flare and cells. The post-operative fibrinous reaction is basically the result of intra-cameral conversion of fibrinogen to fibrin which is catalyzed by thrombin.[11,12] The fibrin/fibrinogen, along with other chemokine recruit the inflammatory cells along with platelets which produce leukotrienes. All these lead to increased capillary permeability and exudation of plasma constituents into the extracellular spaces with increased protein content and this inflammatory cascade ultimately results in fibrinous reaction in AC.[13] Post-operative inflammatory reaction in AC ranges from 1.8-7.6%.[14] In one of the study it was observed that the level of endogenous t-PA was sufficiently reduced in aqueous for the 1st few days after cataract surgery, suggesting that the fibrinous reaction was attributed to decreased intrinsic levels of t-PA.[15,16] The replenishment of the normal levels of t-PA takes about 4 to 12 weeks along with normalization of the blood barriers inside the AC for restoration of the normal aqueous composition post cataract surgery with PC IOL.[17]

TASS, or Toxic Anterior Segment Syndrome, is essentially a sterile inflammatory response characterized by the formation of post-operative inflammatory membranes in the anterior chamber (AC) of the eye. The severity of TASS can vary depending on its underlying cause and the promptness of treatment. Prolonged resolution of TASS can result in complications such as iris atrophy, leading to irregularities in pupil shape, increased intraocular pressure (IOP) caused by blockage of the trabecular meshwork by inflammatory cells or membrane formation in the angle recess, and physical damage to the trabecular meshwork due to the presence of various toxins and inflammatory mediators.[10] Moreover TASS can cause chronic complications like bullous keratopathy, chronic macular edema, anterior capsular contraction, posterior capsule opacification and IOL tilting due to capsular bag distortion. Other than that it can cause reduction in vision due to changes in the AC morphology, glare/haze, chronic secondary glaucoma which can be both of open type or closed angle.[19]Various treatment modalities used for the refractory fibrinous membrane formation post cataract surgery i.e. argon/Nd:YAG laser or surgical removal by AC wash all carry risk of flare up of inflammatory process in the already compromised eyes.[20]

In an animal study, conducted by Snyder et al showed that r-tPA was effective in resolution of fibrin and was not associated with any side effects.[8]After these studies r-tPA was started in humans for fibrinolysis after cataract surgery, in doses ranging from 3–30µg/0.1ccshowing efficacy yet no adverse reactions.[19]

In our trial, complete resolution of fibrinous reaction was achieved in 78.2% of the patients within 24hours of r-tPA injection. We observed neither a case of endophthalmitis nor raised IOP after injection throughout the period of follow up. As we did not conduct post injection specular microscopy, so effect on endothelial cell count or morphology was not analyzed. At the end of 6th week, 93.4% of our patients achieved fibrinolysis with r-tPA. Factor 12 mediates the cross linkage of fibrin making it resistant to lysis. This mechanism explains the delay in eight of our patients and partial resolution in two patients.

Analysis of BCVA revealed a trend towards improvement by excluding those with pre-existing eye diseases. Mean BCVA improved from 0.59 ± 0.40 log MAR pre-injection to 0.38 ± 0.40 log MAR at 6th week post-injection. Besides high rate of fibrinolysis on day 1st there was a lag in visual improvement commencing on day 7th and 6th week post injection. Initial decrease in BCVA can be attributed to the presence of extensive inflammatory reaction in AC, which obviously took time towards resolution after injection.

In the current study, intra-cameral r-tPA was used only in refractory cases. Thus, the 1st injection was given at 2nd week post cataract surgery while the mean interval post-operative was 18.5 ± 10.2 days. Statistically insignificant difference was noted between earlier versus later interventions.

The study outlined certain limitations that could affect the generalizability and interpretation of its findings. The study sample size is relatively small, with only 46 patients included which may not adequately represent the broader population, and there could be inherent biases in patient selection, potentially affecting the study's external validity. The follow-up period of 6 weeks post-injection might not be sufficient to capture longer-term outcomes or potential complications associated with intra-cameral t-PA injection. The absence of a control group receiving alternative or no intervention makes it challenging to ascertain the true effectiveness of intra-cameral t-PA injection. Factors such as variations in surgical techniques, patient demographics, and

underlying ocular conditions could influence treatment outcomes and safety profiles.

Addressing these limitations through larger, multicenter studies with longer follow-up periods and robust control groups could enhance the reliability and applicability of the study's findings in clinical practice.

CONCLUSION

Our research revealed that the administration of 30µg/0.1cc of r-tPA significantly improved resistant fibrinous reactions following cataract extraction. Intra-cameral administration was correlated with rapid resolution of fibrinous reactions, thus mitigating complications such as increased intraocular pressure (IOP), synchiae formation, and pupillary abnormalities.

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Authors Designation and Contribution

Bilal Khan; Assistant Professor: *Concepts, Design, Data acquisition, Manuscript preparation, Manuscript review.*

Adnan Ahmad; Associate Professor: *Design, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review.*

Javed Rasul; Assistant Professor: *Literature search, Data acquisition, Data analysis, Statistical analysis.*