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Research Article

INTRAVITREAL AUTOLOGOUS PLASMIN VS. TRIAMCINOLONE ACETONIDE FOR DIABETIC MACULAR EDEMA: A COMPARATIVE STUDY

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ABSTRACT

Purpose: The study aims to compare the efficacy and safety of intravitreal autologous plasmin (IAP) injections with triamcinolone acetonide (TA) injections in the treatment of diffuse diabetic macular edema (DME). The research evaluates improvements in central macular thickness (CMT), best-corrected visual acuity (BCVA), and intraocular pressure (IOP) over a six-month follow-up period. Methods: A prospective, comparative study was conducted at Swamy Vivekananda Institute of Medical Sciences, Tiruchengode, Tamil Nadu, India, and Indira Medical College and Hospitals, Chennai, Tamil Nadu, India, involving 100 patients with bilateral DME. Participants were randomly assigned to receive either intravitreal 4 mg TA injections or IAP injections, prepared using autologous blood-derived plasmin. Ophthalmic evaluations, including OCT, fluorescein angiography, Goldmann applanation tonometry, and BCVA assessment, were performed at baseline, 1 month, 3 months, and 6 months post-injection. Statistical analysis was conducted using SPSS software, with Wilcoxon rank-sum tests applied for comparisons. A p-value ≤ 0.05 was considered statistically significant. Results: Both treatment groups demonstrated a significant reduction in CMT ($P<0.05$) and improvement in BCVA ($P<0.05$) at 1 month post-injection, followed by a gradual decline in efficacy over six months. The IAP group showed a more sustained reduction in CMT ($P<0.05$) at six months compared to the TA group, indicating a longer-lasting therapeutic effect. BCVA improvements were similar between the groups initially but showed greater preservation in the IAP group at six months. IOP was significantly elevated in the TA group at 3 and 6 months ($P<0.05$), whereas no significant changes in IOP were observed in the IAP group. Conclusion: Both intravitreal TA and IAP injections were effective in reducing CMT and improving BCVA in patients with diffuse DME. However, IAP provided a more sustained reduction in macular thickness and was associated with fewer adverse effects on IOP. The findings suggest that IAP may be a safer alternative to TA, particularly for patients at risk of steroid-induced IOP elevation. Further long-term studies are needed to evaluate the durability of these effects and the potential need for repeat injections.

Keywords:- Diabetic macular edema, intravitreal autologous plasmin, triamcinolone acetonide, central macular thickness.

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INTRODUCTION

The rising prevalence of diabetes has become a global health challenge. By 2030, the number of individuals diagnosed with diabetes is projected to double, significantly increasing the burden of diabetes-related complications. One of the primary microvascular complications, diabetic retinopathy (DR), accounts for

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approximately 12% of blindness cases among individuals aged 20 to 64 years [1]. Among diabetic individuals over 40 years old, the prevalence of retinopathy is estimated to be 40%, with 8.2% experiencing vision-threatening retinopathy [2].

The pathogenesis of diabetic retinopathy involves multiple cellular pathways, primarily triggered by chronic hyperglycemia, which leads to various metabolic changes in the retina and ultimately causes microvascular damage [3]. In addition to non-proliferative leakage and ischemia-induced neovascularization, vascular permeability and subsequent leakage contribute significantly to disease progression. Four major biochemical alterations associated with hyperglycaemia-induced DR include:

1. Increased polyol pathway flux
2. Elevated formation of advanced glycation end-products (AGEs)
3. Activation of protein kinase C isoforms
4. Increased hexosamine pathway flux [4].

These pathways contribute to oxidative stress, inflammation, vascular occlusion, and enhanced permeability, ultimately leading to cardiovascular dysfunction [5].

The plasminogen activation system plays a crucial role in the disease mechanism by facilitating the conversion of plasminogen to plasmin via tissue plasminogen activators (tPA) and urokinase-plasminogen activators (uPA) [6]. Plasmin influences angiogenesis indirectly by activating extracellular matrix metalloproteinases (MMPs) and directly through the degradation of matrix molecules. The breakdown of the extracellular matrix generates degradation products that promote endothelial cell migration and neovascularization [7].

In cases without posterior vitreous detachment (PVD), the vitreous cortex remains adhered to the internal limiting membrane of the retina, which is thought to contribute to macular edema and visual impairment in diabetic eyes. Clinical studies indicate that surgical vitrectomy can improve visual acuity and reduce diabetic macular edema (DME) in cases of proliferative diabetic retinopathy (PDR) and DME [8].

To reduce surgical complications, pharmacological vitreolysis is utilized to induce posterior vitreous detachment. This process involves enzymatic liquefaction of the vitreous gel, which aids in reducing vitreous traction and retinal detachment risks. Studies have shown that intravitreal ovine hyaluronidase injection is effective in treating vitreous hemorrhage [9].

In a comparative prospective study, intravitreal autologous plasmin injections were evaluated against triamcinolone acetonide (TA) therapy for the treatment of diabetic macular edema. This study aimed to determine the efficacy of plasmin injections in reducing DME and improving visual function [10].

METHODS AND PATIENTS

This study was conducted at Swamy Vivekananda Institute of Medical Sciences, Tiruchengode, Tamil Nadu, India, and Indira Medical College and Hospitals, Chennai, Tamil Nadu, India, starting in October 2024. A total of 100 patients diagnosed with bilateral diabetic diffuse macular edema (DME) were included in the study at the Eye Subspecialty Center. The diagnosis of diffuse macular edema was confirmed using biomicroscopy and fluorescein angiography, focusing on macular thickening. The minimum central macular thickness (CMT) for inclusion was set at 360 μm, whereas the normal value is typically 200 μm [12].

Patients with uncontrolled diabetes, defined as a glycosylated hemoglobin (HbA1c) level above 9.5%, were excluded from the study. Additionally, individuals with hypertension or chronic kidney disease were not eligible. Patients with a history of ocular hypertension, glaucoma, or retinal ischemia, as indicated by fluorescein angiography, were also excluded. Moreover, those who had experienced posterior vitreous detachment (PVD) within the last six months, confirmed through microscopy, 90D lenses, or optical coherence tomography (OCT), were not considered for participation.

The study followed ethical guidelines outlined in the Declaration of Helsinki, ensuring that all participants provided written informed consent before their inclusion. Each patient underwent a comprehensive ophthalmological examination, which included slit lamp biomicroscopy, Goldmann applanation tonometry for intraocular pressure (IOP), fundus photography, fluorescein angiography, indirect ophthalmoscopy, and optical coherence tomography (OCT). The best-corrected visual acuity (BCVA) was assessed at baseline and during follow-up examinations.

A randomized allocation was used to divide participants into two groups: one receiving intravitreal 4 mg Triamcinolone Acetonide (TA) injections and the other receiving intravitreal autologous plasmin (IAP) injections.

Preparation of Autologous Plasmin

Autologous plasmin was prepared immediately before injection. Blood samples were collected from a peripheral vein and subjected to centrifugation for 15 minutes. The separated plasma was transferred into a vial containing streptokinase and incubated at 37°C for 15 minutes. Following incubation, the vial was shaken vigorously for five minutes to allow proper mixing of streptokinase with the plasma. A second incubation at 37°C for 15 minutes was then performed. The resulting solution was filtered using a 0.22 μm Millipore filter to ensure sterility before being prepared for intravitreal injection [13].

Injection Procedure

Before the injection, topical anesthesia was administered three times, and povidone-iodine solution was applied to disinfect the eye. The conjunctiva was washed, and anterior chamber paracentesis was performed to prevent posterior reflux during the intravitreal injection.

For the IAP group, a combination of Triamcinolone Acetonide (4 mg/0.1 mL) and autologous plasmin solution was injected intravitreally at a depth of 0.5 mm or 4 mm from the limbus. After the injection, an absorbing sponge was placed over the injection site to prevent reflux.

Post-treatment, patients were prescribed a five-day regimen of dexamethasone eye drops and ciprofloxacin antibiotic drops to reduce inflammation and prevent infection. Regardless of the initial response, plasmin was injected as a standalone treatment in affected eyes.

Statistical Analysis

The data collected were presented in terms of numerical values, percentages, percentage ranges, and ratios. To compare differences between the groups, the Wilcoxon rank-sum test (Z-test) was used for unrelated data, and SPSS software was employed for statistical analysis. A p-value of ≤ 0.05 was considered statistically significant in determining the effectiveness of intravitreal autologous plasmin injections compared to triamcinolone acetonide therapy in reducing diabetic macular edema and improving visual acuity.

RESULTS

Study participants included 100 people with an average age of 66.4 years (range 45 to 79), 18 males and 32 females. The mean diabetes patient had glucose-sylated hemoglobin level of 6.8 x 1.2 mmHg (range, 3.9%–9%) and in the range of 9-19 years, the average diabetes duration was 142.4 years. Comorbidities associated with 34 patients included dyslipidemia in 20, hypertension in eight, and cardiomyopathy in six. One-third of the patients had right eye affections, while 38 had left eye affections. Pseudophakic patients constituted 12 of the 92 patients, whereas phakic patients constituted 88 of the patients. As far as enrollment data are concerned, the two study groups did not differ significantly (Table 1).

CMT thickness decreased significantly ($P<0.05$) following treatment with TA and plasmin compared with baseline thickness. CMT decreased significantly ($P<0.05$) after one month and then declined thereafter until six months after injection, but still remained significantly thinner than baseline ($P<0.05$).

Table 1: Patient enrollment number

	TA group	**IAP group**	**Total**
Years of age (in years)	65.4 ± 8.5 (45–77)	67.4 ± 7 (49–79)	66.4 ± 7.8 (45–79)
Sex			
Male	16 (16%)	20 (20%)	36 (36%)
Female	34 (34%)	30 (30%)	64 (64%)
Data on diabetes			
diabetes mellitus duration	15.4 ± 3.6	14.7 ± 3.4	15 ± 3.5
Hemoglobin with glycosylation	7.7 ± 2.4	8 ± 2.2	7.9 ± 2.3
Comorbidities associated with the disease			
Nil	36 (36%)	30 (30%)	66 (66%)
Deficiency of cholesterol	8 (8%)	12 (12%)	20 (20%)
High blood pressure	4 (4%)	4 (4%)	8 (8%)
Cardiovascular	2 (2%)	2 (2%)	6 (6%)
Examining the local area			
Side			
Right	32 (32%)	30 (30%)	62 (62%)
Left	18 (18%)	20 (20%)	38 (38%)
Lens			
Phakic	42 (42%)	46 (46%)	88 (88%)
Pseudophakic	8 (8%)	4 (4%)	12 (12%)
Treatments in the past			
Bevacizumab	8 (8%)	10 (10%)	18 (18%)
Bevacizumab + triamcinolone acetonide	14 (14%)	10 (10%)	24 (24%)
photocoagulation + triamcinolone acetonide	18 (18%)	22 (22%)	40 (40%)

photocoagulation + triamcinolone acetonide + bevacizumab	10 (10%)	8 (8%)	18 (18%)

With TA, macula thickness increased There were significant differences (P<0.05) in macular thickness at 6 months from 1, 3 and 6 months, while there were significant differences in macular thickness at 3 months (P<0.05) from 3 months with 1 month, suggesting significant deterioration (P<0.05). Comparing the follow-up measurements at 3 and 6 months with those at 1 month and to each other, the Plasmin showed less deterioration. TA and plasmin were both elevated at one and three months had nonsignificant differences in CMT (P<0.05); however, at 6 months, the difference was significant (P<0.05) in favor of plasmin.

Both groups did not show any significant differences in BCVA improvement following intravitreal therapy, irrespective of the medication used. After 1 month after injection, significant improvements were

apparent (P<0.05) and then began to fade thereafter until nonsignificant gains (P<0.05) were observed at 6 months after injection. In the TA group, the mean BCVA significantly degraded at 6 months compared to 3 months, but the difference was not significant (P<0.05) in the IAP group despite the degraded BCVA (Table 2).
The IAP group's IOP was significantly lower than the TA group's at 1 month after intravitreal injection, regardless of medication used. While IOP was significantly higher than baseline in the TA group at 3 and 6 months after injection, it was non-significantly lower in IAP group compared to baseline IOP at 3 and 6 months after injection. A significant difference was found between the TA group and the IAP group in terms of mean IOP estimated at 3 and 6 months (Table 2).

DISCUSSION

A significant improvement in CMT and BCVA was observed following intravitreal therapy, regardless of the medication used, indicating the benefit of this therapeutic modality for treating diffuse diabetic macular edema (DDME). According to the findings, intravitreal TA injections are effective in improving retinal sensitivity and fixation properties in eyes that have macular edema due to central retinal vein obstruction. Following vitrectomy with internal limiting membrane peeling and intravitreal TA, intravitreal TA resulted in a rapid reduction in DDME. Within a short time period after surgery, A study [14] reported reduced DDME following intravitreal TA. In many cases, reinjection is necessary to maintain these promising results. TA intravitreal injections need to be administered for only a short period of time, as indicated in previous studies and in the current study.

An intravitreal injection of autologous plasmin enzyme, called APE, was analyzed as a treatment for refractory DDME in a study [15,16]. Injections of low-dose intravitreal APE significantly improved DDME that was resistant to vitrectomy. Intravitreal APE injections have been shown to improve vision in cases that do not respond to conventional laser photocoagulation, improve vision in the short term, and persist over time when treating macular thickening caused by DDME. This condition may be treated safely and effectively with IAP as an alternative to vitrectomy.

IAP significantly reduced CMT at 6 months compared with TA, which indicated a more sustained effect of IAP and could be attributed to a difference in the mechanism of action. The extent of improvement was greater with IAP compared to TA as manifested by the significantly lower CMT estimated at 6 months. By stabilizing the blood-retinal barrier and downregulating vascular endothelial growth factor production, triamcinolone acts as a drug that is anti-inflammatory and anti-edematous. The reduction of vascular permeability and edema was achieved by this vascular permeability factor [17]. A-oxidative stress and proinflammatory cytokines are released, aggravating retinal hypoxia, triggering edema and activating the inflammatory cascade. The short-lived effect of intravitreal TA may be due to the fact that once the suppressive effect of the corticosteroid has worn off, the condition recurs.

Table 2: Baseline and postinjection data

	Baseline	**1 month**	**3 months**	**6 months**
Central mascular thickness (□m)				
Triamcinolone acetonide	540.5 ± 86.3	303 ± 43.7*	320.4 ± 51*, †	338± 58.4*, †, #
Intravitreal autologous plasmin	543.6 ± 91.3	305.3 ± 47.9*	317 ± 45.3*	323 ± 58.4*, ‡
Best-corrected visual acuity (logMAR)				
Triamcinolone acetonide	0.413 ± 0.10	0.25 ± 0.13*	0.313 ± 0.130*, †	0.387±0.094*, †, ‡
Intravitreal autologous	0.403 ± 0.096	0.249 ± 0.117*	0.290 ± 0.109*, †	0.347 ± 0.12†

plasmin				
Intraocular pressure (mmHg)				
Triamcinolone acetonide	16.9 ± 2.9*	18.9 ± 2.9*	18.3 ± 2.8*,†	17.9 ± 3*,†
Intravitreal autologous plasmin	16.8 ±2.8	17 ± 2.8*,#	16.8 ± 2.9†,#	16.5 ± 3†,#

In addition to improving visual and vascular outcomes with dexamethasone intravitreal implants, a study [18] demonstrated safety and efficacy with vitrectomized eyes with diabetic macular edema. An intravitreal plasmin injection's proteolytic activity causes Immediately after injection, the drug inhibits rapid recurrence while reducing retinal hypoxia and preventing posterior retinal detachment. The drug produces pronounced and sustained effects for six months after injection. Proteolytic activities of intravitreal plasmin injections result in posterior retinal detachments and retinal hypoxia. It has been demonstrated by researcher [19] that pharmacologic vitreolysis can reduce blight, increase oxygen supply to the retina, and cleave the vitreoretinal junction. As a result, retinal hypoxia may be significantly slowed by an overexpressed vasoactive substance such as vascular endothelial growth factor, which is known to interfere with biochemical pathways.

IOP levels in the IAP group were found to be nonsignificant at three and six months after injection compared to their baseline levels, whereas their IOP levels in the TA group remained significantly higher throughout the follow-up period compared to their baseline levels. An unwanted side effect of intravitreal TA is elevated IOP. TA intravitreal injections are often associated with a significant increase in intravitreal IOP, typically within two months of injection, according to study [20]; Approximately one-third of patients who do not experience an elevated IOP after an initial injection will not experience a pressure rise after another one, and need topical glaucoma therapy to control the pressure. In spite of these effects, selected refractory cases should be treated with caution. The effects may last a short time and may cause side effects. Selective laser trabeculoplasty can prevent the elevation of IOP following intravitreal TA injections, as reported as a prophylactic measure. A baseline IOP of $21 mmHg is considered, selective laser trabeculoplasty before intravitreal TA injection may prevent IOP elevation.

CONCLUSION

It may be concluded that with intravitreal injection of TA without elevating IOP, CMT was significantly reduced as well as BCVA was improved. These effects lasted for longer periods and were safer than vitreolysis with IAP injection. For a longer follow-up period, larger scale studies are therefore needed to determine the maximum duration of action and the need for repeated injections.

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