



INVASIVE AUTOLOGOUS PLASMIN TREATMENT FOR DIFFUSE DIABETIC MACULAR EDEMA: A PROMISING APPROACH

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Abstract:

In one study, IAP injections and triamcinolone acetonide injections are being compared for Diabetic macular edema in diffuse form. 66.4% of the population is older than 64 and 14.4% of the population has diabetes for 14 years or more were measured for the 100 diabetic patients in this study. There were 36 males and 64 females. Two groups of patients were randomly assigned to receive 4 mg TA or 0.2 mL Autologous plasmin freshly prepared after undergoing a full ophthalmologic examination and a full ophthalmologic examination. CMT, BCVA, and IOP were measured at 1, 3, and 6 months to determine the outcome of the study. There was no significant difference between the two groups in the reduction of CMT thickness after TA and plasmin treatment, as both decreased it significantly when compared to baseline thickness. At 6 months after injection, CMT peaked again but remained lower than baseline after 1 month after injection. Plasmin showed less improvement than 1-month measurement and each other. As compared to the BCVA in the IAP group at baseline and at 1 and 3 months, the BCVA in the TA group considerably declined after 6 months. One month after injection versus one month after injection, both groups had lower IOP at 3 and 6 months, although the TA group had a significantly higher IOP, whereas the IAP group did not have a significantly lower IOP. A significant difference was noted between IAP and TA groups in terms of Three- and six-month estimates of IOP. In summary, IAP injections decreased CMT and improved BCVA more effectively than intravitreal injections of TA, and this was safer and longer lasting than intravitreal injections of TA.

Keywords: Acute diabetic macular oedema, autologous plasmin, triamcinolone, and intravitreal injection

Introduction

A significant increase in diabetics worldwide has made diabetes a global problem. In 2030, the number of diabetics is expected to double, causing a dramatic increase in complications related to diabetes. A microvascular complication of diabetes, diabetic retinopathy, is responsible for approximately 12% of blindness cases among working-age populations (20-64). The prevalence of retinopathy among diabetics aged over 40 years is estimated to be 40%, with 8.2% of these people

suffering from Retinopathy that threatens vision. [2–3] Diabetic retinopathy pathogenesis involves multiple cellular pathways, mostly through hyperglycemia, which leads to various metabolic changes in the retina that can result in microvascular damage [4-6]. In addition to diabetic retinopathy caused by nonproliferative leakage and ischemia-induced neovascularization, vascular leakage has been shown to cause the disease also result in microvascular damage. Four main biochemical alterations are associated with hyperglycemia-induced diabetic retinopathy. (i) There is an increase in the flux of polyols. (ii). Glycation end-products are formed at a higher rate. (iii). Protease C isoforms are activated. and (iv). The flux of hexosamine was Increasing. Moreover, these pathways result in increased oxidative stress, inflammation, and vascular occlusion as well as increased permeability and vascular occlusion, and cardiovascular dysfunction [4].

By activating tissue plasminogens and converting proteinases, tissue plasminogen activators and urokinase-plasminogen activators promote the production of plasmin in the local community. The effect of plasmin on angiogenesis is indirectly via the activation of extracellular matrix metalloproteinases and directly through its degradation of matrix molecules. During this process, extracellular matrix degradation products are produced, which are chemotactic and permit endothelial cell degradation. [7–9] Vitreous cortex adhering to inner retina's limiting lamina is common when there is no posterior vitreous detachment. It is thought that the vitrectomy junction plays a role This agent has been linked to reduced macular edema and improved visual acuity in diabetic eyes, including proliferative diabetic retinopathy and diabetic macular edema [10]. Drugs are used to induce retinal detachment and reduce surgical complications associated with vitrectomy by causing a posterior vitreous detachment. It is a phenomenon known as 'pharmacological vitreolysis' that induces a posterior vitreous detachment by liquefying vitreous gel with enzymes. Vitreous hemorrhage was effectively treated with intravitreal ovine hyaluronidase injection. [11] We compared intravitreal autologous plasmin injections with triamcinolone acetonide (TA) Diabetic macular edema can be reduced by this therapy in this prospective comparative study.

Methods and patients

In 100 patients with bilateral diabetic diffuse macular edema were included in the present study at the Eye Subspecialty Center. Biomicroscopy and fluorescein angiography were used to define diffuse macular edema in the macular region. A radius of 0.360 mm (normally 200 μm) was the It comprises the minimum thickness of the central macular trough (CMT). [12]

An unacceptable limit for inclusion is 9.5% glycosylated hemoglobin, for patients with uncontrolled diabetes. Hypertensive patients or those with chronic kidney disease were excluded from the study. A history of ocular hypertension, glaucoma, fluorescein angiography showing evidence of ischemia is not required. Prior posterior vitreous detachments should not have occurred in the last six months, either by microscopy, 90 D lenses, or optical coherence tomography.

Following the International Association of Medical Associations Declaration of Helsinki, every patient provided a written, fully informed consent. The full range of ophthalmological in addition to a slit lamp examination, applanation tonometry, Fundus photography, fluorescein angiography, and indirect ophthalmoscopy, each patient was also screened with fluorescein angiography. There were no cases of vitreous detachment cases in this study, optical coherence tomography and biomicroscopy are utilized. To determine the best-corrected visual acuity (BCVA) during follow-up, we used Goldmann applanation tonometry to measure baseline IOP. A total of two groups of A random assignment was done to divide the participants into groups of TA and IAP and to administer home-prepared IAP and intravitreal 4 mg TA injections.

Preparation of homologous plasmin

Injections were made immediately after plasmin was prepared. After 15 minutes of centrifugation, blood samples were collected. after being drawn from a peripheral vein. We transferred the results into a vial containing streptokinase following a 15-minute incubation at 37°C with streptokinase. A five-minute vigorous shake of the vial follows, the diluted streptokinase was combined with plasma. A second 15-minute incubation at 37°C was performed on the solution resulting from this first

incubation. Following sterilization with a 0.22 mm Millipore filter, the solution was ready for injection. [13]

How injections are performed

Three times, topical anaesthesia was used in conjunction with povidone solution, then conjunctiva washing was performed and anterior chamber paracentesis was performed, to prevent posterior reflux on injecting intravitreal. In the IAP group, Triamcinolone 4 mg/0.1 mL in autologous plasmin solution gold were injected intravitreally into 0.5 or 4 mm of the limbus, respectively. The injection point was covered with an absorbing sponge to prevent reflux. It was prescribed to Five days' worth of dexamethasone eye drops should be applied consecutively while taking the antibiotic ciprofloxacin. Independent of the initial response, plasmin was injected into the eye alone.

Analyses of statistics

A number of numbers, percentages, percentage ranges, and ratios were used to express the data collected. In unrelated data, Wilcoxon rank-sum tests (Z-tests) were used to compare results. We used the SPSS software for our Analysis of statistics. A P value of 0.05 was considered statistically significant.

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 ± 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 month	6 month
Central macular thickness (μm)				
Triamcinolone acetate	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 acetate	0.413 ± 0.10	0.25 ± 0.13*	0.313 ± 0.130*,†	0.387±0.094*,†,‡
Intravitreal autologous plasmin	0.403 ± 0.096	0.249 ± 0.117*	0.290 ± 0.109*,†	0.347 ± 0.12†
Intraocular pressure (mmHg)				
Triamcinolone acetate	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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