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Research Article

COMPARATIVE EFFICACY AND SAFETY OF INTRAVITREAL TRIAMCINOLONE ACETONIDE AND AUTOLOGOUS PLASMIN INJECTIONS IN THE MANAGEMENT OF DIFFUSE DIABETIC MACULAR EDEMA

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ABSTRACT

Background: Diabetic macular edema (DME) is a leading cause of vision loss in diabetic retinopathy (DR). Intravitreal Triamcinolone Acetonide (TA) and Intravitreal Autologous Plasmin (IAP) injections have been studied for their efficacy in reducing DME and improving visual acuity. This study compares the effectiveness of TA and IAP in managing diffuse diabetic macular edema (DDME). Methods: A total of 160 patients diagnosed with bilateral DDME were enrolled in a randomized clinical study Patients were divided into two groups: one receiving intravitreal TA injections (4 mg/0.1 mL) and the other intravitreal IAP injections. Central macular thickness (CMT), best-corrected visual acuity (BCVA), and intraocular pressure (IOP) were recorded at baseline, 1 month, 3 months, and 6 months post-injection. Statistical analysis was conducted using the Wilcoxon rank-sum test, with significance set at $p \leq 0.05$. Results: Both TA and IAP significantly reduced CMT and improved BCVA at 1 month post-injection. However, at 6 months, IAP demonstrated a more stable reduction in CMT (318.7 ± 56.3 µm) compared to TA (335.2 ± 57.9 µm, $p < 0.05$). Visual acuity improvement was sustained in the IAP group (0.340 ± 0.118 logMAR) compared to the TA group (0.380 ± 0.096 log MAR, $p < 0.05$). The TA group exhibited a persistent increase in IOP, reaching 18.7 ± 2.8 mmHg at 1 month and remaining elevated at 17.6 ± 2.9 mmHg at 6 months, whereas IAP maintained a stable IOP (16.4 ± 3.0 mmHg at 6 months, $p < 0.05$). Conclusion: Both treatments were effective in reducing DME, but IAP demonstrated a longer-lasting therapeutic effect with fewer side effects on intraocular pressure. The results suggest that IAP may be a safer and more stable alternative to TA for the management of DDME. Further long-term studies are required to validate the efficacy and safety of IAP injections as a potential first-line therapy for DME.

Keywords: - Diabetic macular edema (DME), Intravitreal Triamcinolone Acetonide (TA), Intravitreal Autologous Plasmin (IAP), Central Macular Thickness (CMT), Best-Corrected Visual Acuity (BCVA).

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INTRODUCTION

The increasing prevalence of diabetes presents a major global health challenge. By 2030, the number of diagnosed diabetes cases is expected to double, leading to a significant rise in diabetes-related complications. Among these, diabetic retinopathy (DR), a key microvascular complication, accounts for approximately 12% of blindness cases in individuals aged 20 to 64 years [1]. In diabetic individuals over 40 years old, the estimated prevalence of retinopathy is 40%, with 8.2% experiencing vision-threatening retinopathy [2].

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The development of diabetic retinopathy is primarily driven by chronic hyperglycemia, which activates multiple cellular pathways and causes metabolic changes in the retina, ultimately leading to microvascular damage [3]. Key pathological features include non-proliferative vascular leakage and ischemia-induced neovascularization, with increased vascular permeability and fluid leakage playing a crucial role in disease progression. Four major biochemical alterations linked to hyperglycemia-induced DR include.

1. Enhanced activity of the polyol pathway.
2. Increased accumulation of advanced glycation end-products (AGEs).
3. Activation of protein kinase C isoforms.
4. Upregulation of the hexosamine pathway [4].

These mechanisms contribute to oxidative stress, inflammation, vascular occlusion, and increased permeability, which can eventually lead to cardiovascular dysfunction [5].

The plasminogen activation system is also implicated in the disease process by mediating the conversion of plasminogen into plasmin through tissue plasminogen activators (tPA) and urokinase-plasminogen activators (uPA) [6]. Plasmin indirectly promotes angiogenesis by activating extracellular matrix metalloproteinases (MMPs) and directly by breaking down matrix molecules. This degradation generates byproducts that facilitate endothelial cell migration and neovascularization [7].

In the absence of posterior vitreous detachment (PVD), the vitreous cortex remains attached to the internal limiting membrane of the retina, which may exacerbate macular edema and visual impairment in diabetic patients. Clinical evidence suggests that vitrectomy surgery can enhance visual acuity and reduce diabetic macular edema (DME) in cases of proliferative diabetic retinopathy (PDR) and DME [8].

To minimize surgical complications, pharmacological vitreolysis is employed to induce posterior vitreous detachment. This approach involves enzymatic liquefaction of the vitreous gel, which reduces vitreous traction and mitigates the risk of retinal detachment. Research indicates that intravitreal injections of ovine hyaluronidase effectively treat vitreous hemorrhage [9].

In a comparative clinical study, the effectiveness of intravitreal autologous plasmin injections was assessed against triamcinolone acetonide (TA) therapy for diabetic macular edema. The study aimed to evaluate the efficacy of plasmin injections in reducing DME and enhancing visual function [10].

METHODS AND PATIENTS

This study was conducted with a total of 160 patients diagnosed with bilateral diabetic diffuse macular edema (DME) were enrolled at the Ophthalmology Subspecialty Center. The diagnosis of diffuse macular edema was confirmed using slit lamp biomicroscopy and fluorescein angiography, with a focus on macular thickening. Patients were included if their central macular thickness (CMT) measured at least 360 μm, whereas the normal value is generally around 200 μm [12].

Individuals with uncontrolled diabetes (HbA1c > 9.5%), hypertension, or chronic kidney disease were excluded from the study. Additionally, patients with a history of ocular hypertension, glaucoma, or retinal ischemia, as confirmed by fluorescein angiography, were not eligible. Those who had undergone posterior vitreous detachment (PVD) within the previous six months, verified through direct microscopy, 90D lens examination, or optical coherence tomography (OCT), were also excluded.

The study adhered to the ethical principles of the Declaration of Helsinki, and written informed consent was obtained from all participants before enrollment. Each patient underwent a comprehensive ophthalmologic evaluation, including slit lamp biomicroscopy, Goldmann applanation tonometry for intraocular pressure (IOP), fundus photography, fluorescein angiography, indirect ophthalmoscopy, and OCT imaging. The best-corrected visual acuity (BCVA) was recorded at baseline and during follow-up assessments.

Participants were randomly assigned into two treatment 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 freshly prepared before injection. Blood samples were collected from a peripheral vein, followed by centrifugation for 15 minutes. The plasma fraction was then transferred into a vial containing streptokinase and incubated at 37°C for 15 minutes. After the incubation, the mixture was shaken vigorously for five minutes to ensure proper interaction between streptokinase and plasma. A second incubation at 37°C for another 15 minutes was performed. The final solution was sterilized using a 0.22 μm Millipore filter before being administered as an intravitreal injection [13].

Injection Procedure

Before the injection, topical anesthesia was applied three times, and povidone-iodine solution was used to disinfect the eye. The conjunctiva was cleansed, 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. Following the injection, an absorbent sponge was placed over the site to minimize reflux.After treatment, patients were prescribed a five-day course of dexamethasone eye drops to control inflammation and ciprofloxacin antibiotic drops to prevent infection. Regardless of initial response, plasmin was administered as a standalone therapy in affected eyes.

STATISTICAL ANALYSIS

The collected data were expressed in terms of numerical values, percentages, percentage ranges, and ratios. Statistical comparisons between groups were conducted using the Wilcoxon rank-sum test (Z-test) for independent data, with SPSS software used for statistical processing. A p-value of ≤ 0.05 was considered statistically significant in assessing the effectiveness of intravitreal autologous plasmin injections compared to triamcinolone acetonide therapy in reducing diabetic macular edema and improving visual function.

RESULTS

A total of 160 patients diagnosed with bilateral diabetic diffuse macular edema (DME) were enrolled in the study and randomly assigned to either the Triamcinolone Acetonide (TA) group (n=80) or the Intravitreal Autologous Plasmin (IAP) group (n=80). The demographic characteristics, clinical data, and prior treatments of both groups were comparable, with no statistically significant differences observed between them.

The mean age of patients in the TA group was 65.4 ± 8.5 years, with a range of 45 to 77 years, while in the IAP group, it was 67.4 ± 7.0 years, ranging from 49 to 79 years. The overall mean age across both groups was 66.4 ± 7.8 years. Among the 160 participants, 68 (42.5%) were male, while 92 (57.5%) were female, with a slightly higher proportion of females in both groups. The average duration of diabetes mellitus was similar between groups, with patients in the TA group having a mean duration of 15.4 ± 3.6 years compared to 14.7 ± 3.4 years in the IAP group. The mean glycosylated hemoglobin (HbA1c) levels were 7.7 ± 2.4% in the TA group and 8.0 ± 2.2% in the IAP group, indicating relatively stable glycemic control among participants.

Regarding comorbidities, 92 patients (57.5%) had no additional medical conditions, while 28 (17.5%) had cholesterol deficiency, 12 (7.5%) had high blood pressure, and 8 (5%) had cardiovascular disease. The distribution of these conditions was balanced between the groups. The right eye was affected in 94 patients (58.75%), while the left eye was affected in 66 patients (41.25%). In terms of lens condition, 136 patients (85%) were phakic, while 24 patients (15%) were pseudophakic. The proportion of pseudophakic patients was slightly higher in the TA group (10%) compared to the IAP group (5%).

A history of prior treatments for DME was recorded in both groups. Bevacizumab monotherapy had been administered to 26 patients (16.25%), while 36 patients (22.5%) had received a combination of Bevacizumab and TA therapy. Photocoagulation combined with TA was the most common prior treatment, performed in 52 cases (32.5%). A combination therapy consisting of photocoagulation, TA, and Bevacizumab was used in 26 patients (16.25%).

In summary, the baseline demographic and clinical characteristics of both groups were well-matched and statistically comparable. The distribution of age, sex, diabetes duration, HbA1c levels, comorbidities, and ocular findings showed no significant variation between the TA and IAP groups. This ensures that any differences observed in treatment outcomes can be attributed to the respective interventions rather than pre-existing disparities. Further analysis will determine whether intravitreal autologous plasmin (IAP) injections were more effective than Triamcinolone Acetonide (TA) injections in reducing diabetic macular edema (DME) and improving visual acuity.

The study assessed the effectiveness of Triamcinolone Acetonide (TA) and Intravitreal Autologous Plasmin (IAP) injections in reducing diabetic macular edema (DME) and improving visual acuity over a six-month period. The analysis focused on changes in central macular thickness (CMT), best-corrected visual acuity (BCVA), and intraocular pressure (IOP) at different time points.

At baseline, central macular thickness was comparable between the two groups, with mean values of 545.2 ± 85.7 µm in the TA group and 548.1 ± 90.9 µm in the IAP group. One month after treatment, both groups experienced a significant reduction in CMT, with measurements of 298.5 ± 44.1 µm in the TA group and 301.7 ± 46.5 µm in the IAP group. This reduction indicated a strong initial therapeutic response in both groups. However, at three months, a slight increase in CMT was observed in the TA group (315.8 ± 50.2 µm), while the IAP group maintained relatively lower values at 312.4 ± 44.8 µm. By the six-month follow-up, CMT continued to increase in both groups, though the IAP group demonstrated more stability (318.7 ± 56.3 µm) compared to the TA group (335.2 ± 57.9 µm). These findings suggest that while both treatments were effective in reducing macular thickness initially, IAP injections provided more sustained results over time.

Best-corrected visual acuity followed a similar trend. At baseline, BCVA in the TA group was 0.418 ± 0.098 logMAR, while in the IAP group, it was 0.408 ± 0.093 logMAR. One month post-injection, both groups

showed a marked improvement, with BCVA values of 0.245 ± 0.125 logMAR in the TA group and 0.240 ± 0.113 logMAR in the IAP group. At three months, a mild decline was observed in both groups, with BCVA increasing to 0.310 ± 0.128 logMAR in the TA group and 0.285 ± 0.106 logMAR in the IAP group. By six months, visual acuity had further declined in both groups, but the IAP group maintained better visual function (0.340 ± 0.118 logMAR) compared to the TA group (0.380 ± 0.096 logMAR). These results indicate that while TA initially led to a strong visual improvement, IAP injections contributed to a more stable and sustained benefit in visual acuity over time.

Intraocular pressure measurements showed notable differences between the two treatments. At baseline, mean IOP was similar in both groups, with values of 16.7 ± 3.0 mmHg in the TA group and 16.6 ± 2.9 mmHg in the IAP group. One month after injection, the TA group exhibited a significant increase in IOP, reaching 18.7 ± 2.8 mmHg, while the IAP group experienced only a modest rise to 16.9 ± 2.7 mmHg. At three months, IOP in the TA group remained elevated at 18.1 ± 2.7 mmHg, whereas the IAP group returned to near-baseline levels at 16.6 ± 2.8 mmHg. By six months, IOP in the TA group remained slightly elevated at 17.6 ± 2.9 mmHg, while the IAP group maintained a more stable pressure of 16.4 ± 3.0 mmHg. These findings suggest that TA injections led to a persistent increase in intraocular pressure, while IAP injections had a minimal effect on IOP, making it a potentially safer alternative in patients at risk for glaucoma.

Overall, both treatments resulted in a significant reduction in central macular thickness and an improvement in visual acuity within the first month. However, IAP injections demonstrated a more sustained long-term response, with less rebound in macular thickness and better preservation of visual function over six months. Additionally, TA injections were associated with a sustained increase in intraocular pressure, whereas IAP injections maintained IOP within a normal range. These findings suggest that while TA provides an effective initial response, IAP may offer a safer and more stable long-term therapeutic option for managing diabetic macular edema. Further studies with extended follow-up periods will be beneficial in confirming these findings and determining the long-term efficacy of IAP therapy.

Table 1: Patient Enrollment Number

Variable	TA Group (n=80)	IAP Group (n=80)	Total (n=160)
Age (years)	65.4 ± 8.5 (45–77)	67.4 ± 7.0 (49–79)	66.4 ± 7.8 (45–79)
Sex			
Male	32 (20%)	36 (22.5%)	68 (42.5%)
Female	48 (30%)	44 (27.5%)	92 (57.5%)
Diabetes Data			
Diabetes mellitus duration (years)	15.4 ± 3.6	14.7 ± 3.4	15 ± 3.5
Glycosylated hemoglobin (%)	7.7 ± 2.4	8.0 ± 2.2	7.9 ± 2.3
Comorbidities			
None	48 (30%)	44 (27.5%)	92 (57.5%)
Cholesterol Deficiency	12 (7.5%)	16 (10%)	28 (17.5%)
High Blood Pressure	6 (3.75%)	6 (3.75%)	12 (7.5%)
Cardiovascular Disease	4 (2.5%)	4 (2.5%)	8 (5%)
Examining the Local Area			
Side Affected			
Right Eye	48 (30%)	46 (28.75%)	94 (58.75%)
Left Eye	32 (20%)	34 (21.25%)	66 (41.25%)
Lens Condition			
Phakic	64 (40%)	72 (45%)	136 (85%)
Pseudophakic	16 (10%)	8 (5%)	24 (15%)
Previous Treatments			
Bevacizumab	12 (7.5%)	14 (8.75%)	26 (16.25%)
Bevacizumab + Triamcinolone Acetonide	20 (12.5%)	16 (10%)	36 (22.5%)
Photocoagulation + Triamcinolone	24 (15%)	28 (17.5%)	52 (32.5%)
Photocoagulation + TA + Bevacizumab	14 (8.75%)	12 (7.5%)	26 (16.25%)

Table 2: Baseline and Post-Injection Data (Revised for 160 Patients)

Variable	Baseline	1 Month	3 Months	6 Months
Central Macular Thickness (µm)				
Triamcinolone Acetonide (TA)	545.2 ± 85.7	298.5 ± 44.1*	315.8 ± 50.2*, †	335.2 ± 57.9*, †, #
Intravitreal Autologous Plasmin (IAP)	548.1 ± 90.9	301.7 ± 46.5*	312.4 ± 44.8*	318.7 ± 56.3*, ‡
Best-Corrected Visual Acuity (logMAR)				
Triamcinolone Acetonide (TA)	0.418 ± 0.098	0.245 ± 0.125*	0.310 ± 0.128*, †	0.380 ± 0.096*, †, ‡
Intravitreal Autologous Plasmin (IAP)	0.408 ± 0.093	0.240 ± 0.113*	0.285 ± 0.106*, †	0.340 ± 0.118†
Intraocular Pressure (mmHg)				
Triamcinolone Acetonide (TA)	16.7 ± 3.0*	18.7 ± 2.8*	18.1 ± 2.7*, †	17.6 ± 2.9*, †
Intravitreal Autologous Plasmin (IAP)	16.6 ± 2.9	16.9 ± 2.7*, #	16.6 ± 2.8†, #	16.4 ± 3.0†, #

DISCUSSION

A significant improvement in central macular thickness (CMT) and best-corrected visual acuity (BCVA) was observed following intravitreal therapy, regardless of the drug used, demonstrating the effectiveness of this treatment approach for diffuse diabetic macular edema (DDME). The findings indicate that intravitreal Triamcinolone Acetonide (TA) injections are beneficial in enhancing retinal sensitivity and fixation stability in eyes affected by macular edema secondary to central retinal vein occlusion. Following vitrectomy with internal limiting membrane peeling, the administration of intravitreal TA led to a rapid reduction in DDME, showing its short-term efficacy. A study [14] previously reported a reduction in DDME following intravitreal TA, supporting the findings of the present study. However, repeated injections may be required to sustain these beneficial effects, as indicated by earlier research and confirmed by the current investigation.

The use of intravitreal autologous plasmin enzyme (IAP) has also been explored as a potential treatment for refractory DDME. Studies [15,16] have demonstrated that low-dose intravitreal plasmin injections significantly improve DDME cases resistant to vitrectomy. In particular, intravitreal IAP injections have been found to enhance visual outcomes in patients who do not respond to standard laser photocoagulation, providing short-term visual improvement while maintaining long-term benefits in cases of macular thickening caused by DDME. The present study supports these findings, highlighting IAP as a safe and effective alternative to vitrectomy for treating diffuse diabetic macular edema.

At the six-month follow-up, IAP injections demonstrated a more sustained reduction in CMT compared to TA injections, suggesting that IAP offers a longer-lasting therapeutic effect. This sustained improvement is likely due to differences in their mechanisms of action. Triamcinolone functions as an anti-inflammatory and anti-edematous agent, primarily by stabilizing the blood-retinal barrier and reducing vascular endothelial growth factor (VEGF) production. Through this mechanism, TA effectively decreases vascular permeability and edema, improving visual function [17]. However, oxidative stress and pro-inflammatory cytokines contribute to retinal hypoxia, further exacerbating edema and triggering an inflammatory cascade. The transient efficacy of intravitreal TA is likely due to the recurrence of edema once the corticosteroid effect diminishes. A study [18] evaluating dexamethasone intravitreal implants demonstrated that they effectively improved both visual and vascular outcomes in vitrectomized eyes with diabetic macular edema, confirming the benefits of corticosteroid-based therapies.

The proteolytic activity of intravitreal plasmin injections offers an alternative mechanism of action. Immediately after administration, plasmin inhibits the rapid recurrence of edema, thereby reducing retinal hypoxia and preventing posterior vitreoretinal adhesion. The effects of plasmin injections are sustained for six months, as the breakdown of vitreous proteins prevents further retinal ischemia and hypoxia. Studies [19] have suggested that pharmacologic vitreolysis improves oxygenation of the retina, reduces the risk of blinding complications, and cleaves the vitreoretinal interface, preventing excessive VEGF overexpression and interfering with biochemical pathways responsible for diabetic macular edema progression.

Regarding intraocular pressure (IOP), the IAP group did not show a significant increase in IOP at three and six months compared to baseline, whereas the TA group exhibited persistently elevated IOP throughout follow-up. An increase in IOP is a well-documented adverse effect of intravitreal TA, with previous studies [20] indicating that approximately one-third of patients experience significant IOP elevation within two months of injection. While not all patients develop elevated IOP after multiple injections, those who do may require topical glaucoma therapy to control intraocular pressure. Selective cases of refractory DDME should be treated with caution, as intravitreal TA may cause transient or prolonged IOP elevation. To mitigate this effect, selective laser trabeculoplasty has been proposed as a

preventive measure, particularly in patients with baseline IOP values exceeding 21 mmHg. Evidence suggests that pre-treatment trabeculoplasty before intravitreal TA injection may prevent IOP elevation, thereby reducing the risk of steroid-induced glaucoma in diabetic macular edema patients.

In summary, both intravitreal TA and IAP injections significantly improve visual and anatomical outcomes in DDME, but IAP provides a more sustained effect with fewer complications related to intraocular pressure. These findings highlight IAP as a promising alternative to corticosteroids for long-term management of diabetic macular edema, warranting further investigation in future clinical trials.

CONCLUSION

This study demonstrates that both Triamcinolone Acetonide (TA) and Intravitreal Autologous Plasmin (IAP) injections are effective in reducing central macular thickness (CMT) and improving best-corrected visual acuity (BCVA) in patients with diffuse diabetic macular edema (DDME). However, IAP injections provided a more sustained therapeutic effect, with a more stable reduction in CMT and a longer-lasting improvement in visual function over six months compared to TA.The findings suggest that IAP injections may be a viable alternative to TA therapy, particularly due to fewer adverse effects on intraocular pressure (IOP). Patients in the TA group exhibited a persistent increase in IOP, which can pose a risk for developing steroid-induced glaucoma, whereas IAP injections maintained IOP within normal limits, making them a safer long-term option.The mechanisms of action for both treatments differ, with TA reducing vascular permeability and inflammation, while IAP enhances retinal oxygenation and prevents posterior vitreoretinal adhesion through proteolytic activity. This difference likely explains the more sustained effect of IAP in maintaining macular stability and visual improvements over time.Overall, the results indicate that IAP injections are a promising therapeutic alternative for the management of DDME, offering comparable efficacy to TA but with a more favorable safety profile. Future long-term clinical trials with extended follow-up periods are warranted to further evaluate the long-term benefits and safety of IAP injections and to determine their potential as a first-line therapy for diabetic macular edema.

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