

Outcomes of Intravitreal Triamcinolone Acetonide Injection in Patients With Diabetic Macular Edema

Diyabetik Maküla Ödemi Olan Hastalarda İntravitreal Triamsinolon Asetonid Enjeksiyonu Sonuçları

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ABSTRACT

Objective: To evaluate the effectiveness of intravitreal triamcinolone acetonide injection (IVTA) in chronic diabetic macular edema (DME) and to assess complications of treatment.

Material and Method: 4 mg/0.1ml triamcinolone acetonide was injected into the intravitreal cavity of 34 eyes of 20 patients. 7 male and 13 female patients; with diabetic retinopathy that unresponsive to laser photocoagulation were enrolled. The visual acuity, intraocular pressure (IOP) and macular edema were compared in pretreatment and posttreatment 1st week, 1st, 3rd, and 5th months.

Results: Median duration of follow-up was 5.05±0.76 months (4-6 months). The macular edema was significantly improved (27/34 eyes (79.4%); 30/34 eyes (88.2%), and 27/34 eyes (79.4%) at the 1st, 3rd, and 5th months; respectively). Visual acuity improved 13/34 eyes (38.2 %) at the 1st week, 23/34 eyes (67.6%) in the 1st month, 23/34 (67.6%) in the 3rd month, and 24/34 (70.5%) in the 5th month. Except cataract formation in 2 eyes, none of other patient experienced a complication related to IVTA injection. In addition, none of the patients had IOP above 21 mmHg.

Conclusion: IVTA is a safe and effective therapeutic method for chronic diabetic macular edema unresponsive to prior laser photocoagulation. However, further studies with longer follow-up and larger number of patients are required to assess the long-term efficacy and to determine the criterias for retreatment.

Key Words: Diabetic macular edema, triamcinolone acetonide, intravitreal

ÖZET

Amaç: Kronik diyabetik maküler ödemde (DME) intravitreal triamsinolon asetonid enjeksiyonunun (İVTA) etkinliğini ve tedavinin komplikasyonlarını değerlendirmek.

Gereç ve Yöntem: Yirmi hastanın 34 gözünün intravitreal kavitesine 4 mg/0.1 ml triamsinolon asetonid enjekte edildi. Lazer fotokoagülasyona yanıt vermeyen 7 erkek ve 13 kadın diyabetik retinopatili hasta kaydedildi. Tedavi öncesi ve tedavi sonrası 1. hafta, 1. ay, 3. ay ve 5. aylarda görme keskinliği, göziçi basıncı (GİB) ve maküla ödemleri karşılaştırıldı.

Bulgular: Ortalama takip süresi 5.05±0.76 ay (4-6 ay)'dı. Maküla ödemi (birinci, üçüncü ve beşinci aylarda sırasıyla 27/34 gözde (%79.4), 30/34 gözde (%88.2) ve 27/34 gözde (%79.4) iyileşti. Görme keskinliği birinci haftada 13/34 gözde (%38.2), birinci ayda 23/34 gözde (%67.6), üçüncü ayda 23/34 (%67.6) ve beşinci ayda 24/34 (%70.5) arttı. İki gözdeki katarakt oluşumu hariç diğer hiçbir hastada IVTA enjeksiyonu ile ilgili bir komplikasyon görülmedi. Ayrıca hiçbir hastada GİB 21 mmHg'nin üstüne çıkmadı.

Sonuç: İVTA, daha önceki lazer fotokoagülasyonuna yanıt vermeyen kronik diyabetik maküler ödem için güvenli ve etkili bir tedavi yöntemidir. Fakat uzun süreli etkinliğin değerlendirilmesi ve yeniden tedavi kriterlerinin belirlenmesi için daha uzun süreli takip ve daha fazla hastalarla daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Diyabetik maküla ödemi, triamsinolon asetonid, intravitreal

Introduction

Diabetes mellitus (DM), with increasing incidence across worldwide, is the most frequent cause of end stage renal disease, nontraumatic amputation

of lower extremities and adulthood blindness. Due to progression in the treatment of DM, surveillance of patients improved and frequency of retinopathy increased. Macular edema; diminishing visual acuity significantly in diabetic

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individuals, can be detected in any stage of DM and may lead to irreversible, progressive and severe visual loss. Fundus fluorescein angiography (FFA) and Optic coherence tomography (OCT) are effective diagnostic procedures in the detection of macular edema (1). Etiology of diabetic macular edema (DME) is usually idiopathic however; posterior hyaloid growth factors are accused as triggering pathogenetic mechanisms (2).

Panretinal laser photocoagulation (PRP) for proliferative retinopathy and, grid and focal laser photocoagulation for macular edema are usual therapeutic approachments (3). Diffuse DME may persist and visual acuity may worsen in some patients that unresponsive to grid laser photocoagulation (4). In addition, irreversible destruction in the retinal tissue subsequent to expansion of laser scars is a serious disadvantage of procedure (5). Triamcinolone acetonide; a corticosteroid derived agent, inhibits phospholipase A2 and thus diminishes the production of leukotrienes and prostaglandins. These pathways are the major pathogenetic mechanisms of diabetic retinopathy. It was previously reported that intravitreal triamcinolone acetonide injection (IVTA) is extremely effective in the treatment of diffuse DME that unresponsive to laser photocoagulation (5,6).

We aimed to evaluate the affectivity of IVTA injection in terms of improvement in visual acuity and regression in macular thickening in chronic DME that unresponsive to laser photocoagulation and to assess complications of treatment.

Material and Methods

Thirty four eyes of 20 patients with chronic DME unresponsive to laser photocoagulation were evaluated in Ophthalmology Department of Medical School, Dicle University between February 2005 and October 2005. PRP and grid and/or focal laser photocoagulation were performed in 23 and 11 eyes, respectively. Macular ischemia was observed in 4 eyes prior to IVTA. Patients were followed up for at least 4 months to observe efficacy of photocoagulation. Chronic macular edema was persisting for 9.60 ± 1.31 months (8-13 months) prior to IVTA. Patients with glaucoma, ocular hypertension, that experienced vitreoretinal surgery or uveitis were excluded. None of our patients were receiving systemic or topical steroid, nonsteroid antiinflammatory and acetazolamide. I have been approved of my thesis work at the medical faculty of Dicle University. Patients were informed and written approval was

obtained. The study adhered to the tenets of the Declaration of Helsinki.

Goldmann's 3 mirror contact lens, FFA and color fundus photographs were used to establish the presence of DME. Topcon TRC.50X retinal camera was used to perform FFA. Visual acuity was evaluated with Snellen chart. Anterior segment and fundus examination were performed with biomicroscope. Tonometry was used to assess the intraocular pressure (IOP) in 1st week, 1st, 3rd and 5th month and FFA was reinstituted at the 5th month.

4 mg/0.1ml triamcinolone acetonide (Kenacort A; 40 mg/ml, Bristol-Myers Squibb Co, Princeton, NJ) injected intravitreally. 4mg/0.1 ml triamcinolone acetonide was injected slowly to mid posterior vitreal cavity across upper nasal quadrant by 27 gauge sharp needle. Distance of injectional area from limbus were 3.5 mm in aphakic patients and 3.0 mm in pseudophakic patients. Antibiotics were administered 6 times a day for 10 days.

Functional improvement was described as an increase in visual acuity for more than 1 line or 1 meter increase in finger counting distance. Anatomic success was defined as recovery of macular edema in fundus examination, observation of foveola and improvement of macular edema, disappearance of fluorescein leak and decrease or recovery of hard exudates determined by FFA. Decreased visual acuity was determined as decline for more than 1 line or 1 meter in finger counting distance. Improvement of best corrected visual acuity (BCVA) and reduction in macular thickness were primary outcomes and changes in IOP and presence of complications were secondary outcomes.

Statistical analysis was performed by using SPSS 13 version (SPSS Inc. Chicago, Illinois, USA). Wilcoxon, Friedman's test, and Analysis of Variation were used to determine mean variations. A "P" value of less than 0.05 was considered to be statistically significant.

Results

Thirty four eyes (19 right and 15 left eyes) of 7 male and 13 female were included. The mean age was 60.35 ± 5.79 years (44-72 years), mean duration of follow-up was 5.05 ± 0.76 months (4-6 months) and mean duration of DM was 12.30 ± 4.44 years.

At the 1st week of posttreatment period, augmentation in visual acuity (Table 1) and minimal improvement in macular edema were observed in 13 eyes (38.2%). Visual acuity was constant in 19 eyes (55.8%) and worsen for 1 line in 2 eyes (5.8%) according to the Snellen chart.

Augmentation in visual acuity (Table 1) and minimal improvement in macular edema were observed in 23 eyes (67.6%). Visual acuity was constant in 10 eyes (29.4%). 4 patients (11.7%) had ischemic macular edema and, 6 patients (17.6%) had persistent macular edema. Visual acuity had worsened for 1 line in 1 eye (2.9%) and macular edema had persisted. At the 3rd month, improvement in visual acuity was preserved in 23 eyes (67.6%) (Table 1) and 3 additional eyes experienced improvement in macular edema and visual acuity. Decrease in visual acuity for 1 line and persistent macular edema was observed in 1 eye (2.9%). Edema was persisting in 4 patients with ischemic macular edema. At the 5th month, 24 eyes (70.5%) had improved visual acuity (Table 1). Visual acuity decreased in 4 eyes (11.7%) with persistent macular edema and 2 eyes (5.8%) with cataract development. It was constant in 4 eyes (11.7%) with ischemic macular edema. Macular edema was persisting in 3 of 4 eyes (8.8%) with ischemic maculopathy and premacular membrane. Visual acuity was better at the 5th month compared to those before IVTA (0.27 ± 0.22 and 0.19 ± 0.17 , respectively; $p=0.002$).

FFA was reinstated to patient with decreased visual acuity in the 3rd month. Fluorescein leak was detected in lower and temporal side of macula and additional argon laser photocoagulation performed. None of our individuals; including this patient, underwent to additional IVTA. Improvement in visual acuity was surviving in 1st and 3rd months, however it was remained stable in 5th month (Table 1). At the 5th month FFA was performed to 5 eyes with neovascularization and chronic macular edema. Fluorescein leak disappeared (focal-diffuse leak) and neovascularization decreased or disappeared.

Table 1. Visual acuity of patients (n:34) according to Snellen chart in pretreatment and posttreatment period

	Pretreatment Period	5th month
Pe(+) Pr(+) Am	2	-
CF	7	6
1/10 – 3/10	20	21
4/10 – 6/10	5	3
7/10 – 10/10	-	4

Pe: Perception; **Pr:** Projection; **Am:** Arm movement visible (only); **CF:** Counting fingers.

Improvement of macular edema was observed in 27 eyes (79.4%) in 1st month, 30 eyes (88.2%) in

3rd month and 27 eyes (79.4%) in the 5th month. 3 eyes had repetitive macular edema.

Mean IOP was 13.1 ± 1.6 mmHg (8-17 mmHg) in the pretreatment period. Subsequent to IVTA, it was 16.2 ± 2.4 mmHg (8-20 mmHg) in the 1st week, 16.5 ± 2.4 mmHg (8-20 mmHg) in the 1st month, 15.1 ± 2.2 mmHg (10-20 mmHg) in the 3rd month and 13.9 ± 1.8 mmHg (10-14 mmHg) in the 5th month. Variations in IOP from pretreatment period to posttreatment 1st week, 1st month and 3rd month were statistically significant ($p < 0.001$) (Table 2, Graphic 1). Statistical difference between IOP of pre and post IVTA period did not remain stable in the 5th month ($p > 0.05$). Mean increase in IOP were 22% in 1st week, 24.2% in 1st month, 14.4% in 3rd month. Mean decrease in IOP was 3.4% in the 5th month. None of our patient experienced IOP higher than 21 mmHg and received antiglaucomatous treatment. IOP of entire patients returned to normal range in the 5th month (Table 2, Graphic 1).

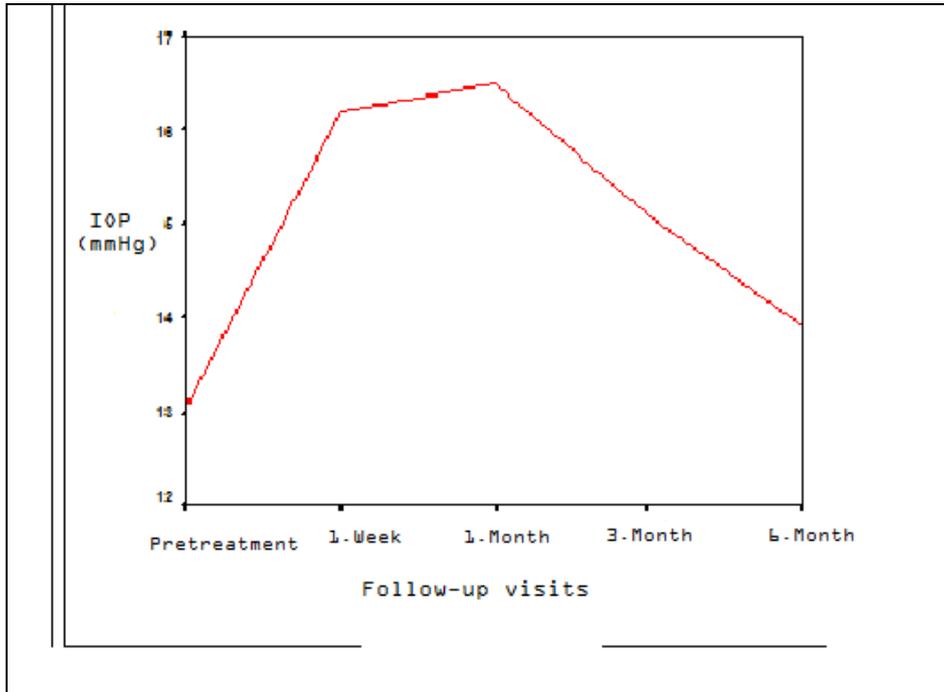
Nuclear, cortical and posterior subcapsular lens opacities were classified according to LOCS III (Lens opacities classification system). Cataract formation was observed in 2 eyes (5.8%) in the 5th month. In the 1st week subsequent to treatment, entire patients complained of blurred vision and disappeared ultimately. No complication like retinal tear, retinal detachment, intravitreal hemorrhage and endophthalmitis was observed.

Discussion

Controversial in the treatment of proliferative diabetic retinopathy still exists (7). Laser photocoagulation is extremely effective in the treatment of focal macular edema however results of the procedure is poorer in diffuse macular

Table 2. Mean IOP of patients in pretreatment period and posttreatment 1st week, 1st, 3rd, and 5th months

	Mean IOP (mmHg)	SD
Pretreatment	13.20 mmHg	1.59
Posttreatment 1st week	16.17 mmHg	2.51
Posttreatment 1st month	16.50 mmHg	2.50
Posttreatment 3rd month	15.11 mmHg	2.21
Posttreatment 5th month	13.79 mmHg	1.75

Graphic 1. Variations of mean IOP (mmHg) of patients at 1st week, 1st, 3rd, and 5th months.

edema (8). Outcomes of IVTA is better in unresponsive patients to laser photocoagulation and significantly decreases the proportion of macular edema (5,6,9). Recent reports indicated the reduction of macular thickness and improvement of visual acuity by IVTA procedure (5,10). Injection have some certain complications such as vitreous hemorrhage, retinal detachment, endophthalmitis and glaucoma or cataract development due to steroid administration (11,12). IVTA significantly minimize the risk of macular edema and vision loss (13). IVTA is an effective choice to improve visual acuity in DME refractory to laser photocoagulation (14). IVTA is also effective in earlier stages of cystoid macular edema and earlier response to IVTA may predict long-term outcome (9). In contrast, some authors stated that IVTA is superior to laser therapy only in regard to reduce central macular thickness (7,14,15).

Negi et al. (16) administered 4 mg triamcinolone acetonide into vitreal cavity of 24 eyes with DME refractory to laser photocoagulation. Visual acuity improved by 83%, 76% and 55% at 1st, 3rd and 6th month; respectively. Two independent studies carried out a study in 15 and 18 eyes with DME, respectively refractory to laser photocoagulation and observed significant improvement in visual acuity and reduction in macular thickness at 1st and 3rd months.

We observed improvement in visual acuity by 38.2%, 67.6%, 67.6% and 70.5% at 1st week, 1st, 3rd and 5th months; respectively. Similar to previous reports, improvement in visual acuity did not remain stable at 5th month. Improvements in macular edema were by 79.4%, 88.2%, and 79.4% at 1st, 3rd and 5th months; respectively.

In a study from Turkey, IOP was higher than 21 mmHg in 5 of 31 eyes with DME that underwent to IVTA injection. Increase in IOP was 33.5%, 26.4%, 23.2% and 17% at 1st, 2nd, 3rd and 5th months, respectively. Elevations of IOP were easily manageable with medical treatment (17).

The mean IOP was 13.1 ± 1.6 mmHg (8-17 mmHg) prior to IVTA in our study. Subsequent to treatment, the mean IOP were 16.2 ± 2.4 mmHg (8-20 mmHg), 16.5 ± 2.4 mmHg (8-20 mmHg), 15.1 ± 2.2 mmHg (10-20 mmHg) and 13.9 ± 1.8 mmHg (10-14 mmHg) at 1st week, 1st, 3rd and 5th months; respectively. Increase in mean IOP were 22%, 24.2%, and 14.4% at 1st week, 1st and 3rd months; respectively. At the 5th month, the mean IOP was less than baseline measurement. The difference between mean IOP values at 1st week, 1st and 3rd was statistically significant ($p < 0.001$). None of our patients experienced IOP level higher than 21 mmHg and required medical treatment.

A patient with diffuse DME refractory to grid laser photocoagulation and neovascularization in optic nerve underwent to injection of 4 mg triamcinolone acetonide. Visual acuity improved and macular thickness reduced significantly at 6th month and fluorescein leak in macula and optic nerve recovered as it was confirmed by FFA (18). We examined recovery of fluorescein leak and decrease of neovascularization in 5 eyes with neovascularization and chronic macular edema by both angiographic examination and color fundus photographs

Endophthalmitis and cataract formation are uncommon complications of IVTA in diabetic patients due to immunosuppressive nature of disease. Fifteen of 27 patients with DME required cataract surgery in 3 years period subsequent to IVTA (19). In two independent studies, the rate of cataract formation after 4 mg IVTA injection were 4.1% and 7% at 6th month (20,21). In our study, the rate of cataract formation was 5.8% at 5th month. Due to adequate sterility conditions, no other surgical complication was observed.

Ucgun et al. (22) performed subtenon injection of triamcinolone acetonide (40 mg) to a patient with ischemic macular edema due to retinal vein occlusion. Macular edema was resorbed however, no improvement in visual acuity was determined. We observed resorption in only 1 of 4 eyes with ischemic macular edema. To our opinion, it is related to lower dose of triamcinolone acetonide in our study (4 mg vs. 40 mg). Visual acuity remained unchanged in all of 4 eyes.

Some recent reports compared outcomes of IVTA and intravitreal bevacizumab (IVB) in diabetic macular edema. Improvement in BCVA was significantly higher in IVTA group than IVB group. Improvement in visual acuity remained stable much longer in IVTA than IVB group. That is probably related to the fact that bevacizumab is a anti-VEGF (vascular endothelial growth factor) agent and the pathogenesis of diabetic macular edema was not only depend on VEGF production but also related with other inflammatory mediators. Triamcinolone acetonide acts by inhibiting overproduction of VEGF and other mediators of inflammation such as prostaglandins and interleukins (23). Forte et al. (3) evaluated patients with DME that underwent to IVB or IVTA plus macular grid laser. At the 1st and 3rd months, visual acuity and foveal thickness improved significantly in both groups. At the 6th and 12th months, visual outcome and reduction in foveal thickness were better in IVB group.

To prevent accumulation of triamcinolone acetonide and development of transient blurred vision, some authors suggest to inject triamcinolone acetonide to inferior temporal quadrant (24). We performed injection to upper nasal quadrant. Injection from upper nasal and temporal quadrant has an advantage of easier management of retinal tear; if occurs, and also lower risk of endophthalmitis. Entire patients experienced blurred vision that was recovered spontaneously. Takata et al (9) compared the affectivity of intravitreal injection and subtenon infusion of triamcinolone. BCVA was significantly improved in IVTA group. Reductions in central macular thickness were significantly higher in IVTA group. Changes in mean IOP were similar in both groups.

Improvement in visual acuity and macular edema after IVTA were 70.5% and 79.4%, respectively in 34 eyes of patients with chronic DME refractory to laser photocoagulation. Except 2 eyes with cataract formation, no other complication like elevated IOP requiring antiglaucomatous treatment, vitreal hemorrhage, retinal tear or detachment and endophthalmitis was observed. Our study confirms the data that filtered triamcinolone acetonide represents a safe and effective choice in a short term by eliminating benzyl alcohol and carboxymethyl cellulose particles (25). Duration of diabetes mellitus and age as well as glycemic control significantly affects the outcomes of treatment in patients with chronic DME that unresponsive to laser photocoagulation. Large scaled studies with long-term follow-up are essential to determine appropriate dose and duration of triamcinolone acetonide treatment.

Statement of conflict of interest; There are no conflicts of interest.

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