Comparison of the Efficacy Between an Intravitreal and a Posterior Subtenon Injection of Triamcinolone Acetonide for the Treatment of Diffuse Diabetic Macular Edema

Diffüz Diyabetik Makula Ödemi Tedavisinde Triamsinolon Asetonidin İntravitreal ve Posterior Subtenon Enjeksiyonlarının Etkinliğinin Karşılaştırılması

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Abstract

Objective: To compare the efficacy of an intravitreal injection to a posterior subtenon injection of triamcinolone acetonide for the treatment of diffuse diabetic macular edema.

Materials and Methods: Sixty patients with diabetes mellitus presenting with diffuse diabetic macular edema were recruited for the study. In each patient, one eye received a 4.0 mg (0.1 mL) intravitreal (IVT) injection of TA and the other eye was treated with a 40 mg (1.0 mL) posterior subtenon (PST) injection of triamcinolone acetonide (TA). We measured the visual acuity, the intraocular pressure (IOP) and the thickness of the macula using optical coherence tomography (OCT) before treatment and at one, three, and six months after treatment.

Results: Eyes treated with PST showed 1-3 lines of improvement in Snellen’s acuity from their pre-injection baseline visual status. The eyes in the IVT group showed 1-3 lines of improvement in Snellen’s acuity in 80% of the treated eyes, but 20% of the treated eyes did not display any change at the end of six months. The difference in acuity between an IVT injection and a PST injection at six months post-treatment was statistically significant (p<0.05). The macular thickness of the eyes treated with an IVT injection was significantly reduced after one (222.7±13.4 μm, p<0.001) and three months (228.1±10.6 μm, p<0.001) of treatment. The eyes treated with a PST injection displayed a slow response and a significant improvement in macular thickness that was observed only after three months (231.3±10.9 μm; p<0.001). The difference between the eyes treated with an IVT injection (385.2±11.3 μm) and those treated with a PST injection (235.4±8.7 μm) was significantly different six months after treatment (p<0.001). The IOP of the eyes treated with an IVT injection was significantly increased after one (17.7±1.1 mm/Hg; p<0.020), three (18.2±1.2 mm/Hg; p<0.003) and six months (18.1±1.320 mm/Hg; p<0.007) when compared to the baseline value (16.1±1.4 mm/Hg). The eyes treated with a PST injection displayed no significant increase in IOP after one (16.4±1.2 mm/Hg; p>0.450), three (16.3±1.1 mm/Hg; p<0.630) and six months (16.2±1.1 mm/Hg; p<0.720) when compared to the baseline value (16.2±1.3 mm/Hg).

Conclusion: A PST injection is equally effective and safer than an IVT injection for the treatment of diffuse DME.

Key Words: Diabetes mellitus, diabetic macular edema, optical coherence tomography, triamcinolone acetonide
**Introduction**

Macular edema is the main cause of visual impairment in diabetic patients [1]. Based on the observations of the Early Treatment Diabetic Retinopathy Study (ETDRS), diabetic macular edema (DME) has been classified as clinically significant if it is well-defined. Specific clinical features are associated with retinal thickening at or within 1 disc diameter of the center of the macula or with definitive hard exudates in this region. For this subgroup that experiences hard exudates in this region of patients, focal laser photocoagulation has been demonstrated to be an effective treatment [2]. However, the paucity of clinically significant gains in visual acuity after laser therapy as well as the recrudescence or persistence of DME after appropriate laser treatment, particularly in eyes presenting a diffuse macular edema[2, 3], has led investigators to seek alternative treatments for the management of DME.

Among the alternative treatments currently under investigation for DME, the administration of triamcinolone acetonide (TA), either by an intravitreal (IVT) injection [4-11] or by a posterior subtenon (PST) injection, [12, 13] has demonstrated promising results for the management of refractory or primary diffuse DME.

Intravitreal triamcinolone injections are, however, associated with many ocular complications (i.e., the elevation of intraocular pressure, endophthalmitis, intraocular hemorrhages and detachment of the retina) [5-7, 9]. A posterior subtenon injection of steroids appears to offer a good alternative for the treatment of diabetic macular edema [10, 11]. This approach is less invasive than an intravitreal injection and may deliver equivalent therapeutic quantities of TA to the macula.

The purpose of this study was to compare the efficacy between an intravitreal (IVT) injection and a posterior subtenon (PST) injection of TA for the treatment of diffuse diabetic macular edema (DME).

**Materials and Methods**

The local ethical committee of our hospital approved this study. Sixty patients (120 eyes) with diabetes mellitus with diffuse diabetic macular edema were included in this study. Twenty patients were males and forty were females, with an age range of 61 to 74 years (mean 68.3 years). Written informed consent was taken from all the patients before the commencement of the study after explaining the procedures and the aims of the study. Patients with a past history of uveitis, ocular trauma (accidental or surgical), laser photocoagulation to the retina (Focal/Grid/Scatter) or glaucoma were excluded from this study.

All the patients participating in our study underwent a thorough clinical ophthalmic examination before treatment. The best corrected visual acuity was assessed using Snellen’s chart. Anterior and posterior segment examination was performed using an ophthalmic slit-lamp and a +90 D indirect fundus viewing lens. Intraocular pressure (IOP) was recorded using a Goldman applanation tonometer. Macular edema was defined by macular thickening that was revealed with biomicroscopy using a +90 D lens.

Macular thickness was quantified by optical coherence tomography (OCT).

In each patient, using a computer generated method, one eye was randomly assigned to receive an intravitreal (IVT) injection of TA. One week after the IVT treatment of the first eye and after excluding the appearance of complications (i.e., raised IOP, vitreous hemorrhage and endophthalmitis), the other eye was treated with a posterior subtenon (PST) injection of TA. To avoid a post-operative rise in IOP, the patients undergoing an IVT injection were prescribed a systemic treatment with 250 mg of acetazolamide, twice daily, for two days before the injection.

For the IVT injection, the patient was placed in a supine position, and then, we administered a surface anesthesia with topical 0.5% proparacaine eye drops (Alcaine) followed by preparing the area with 5% povidone iodine. A volume of 0.1 ml (4 mg/0.1 mL) preservative-free TA (Kenacort, Bristol-Myers Squibb) was injected through the inferotemporal pars-plana (4.0 mm posterior to the limbus) using a 30-gauge needle. Indirect ophthalmoscopy was used to confirm the correct intravitreal localization of the suspension. After the injection, topical 0.5% moxifloxacin eye drops (Vigamox) were prescribed for three days.

For the PST injection, the patient was placed in a supine position, and the conjunctiva and the Tenon's capsule were penetrated with the bevel of the needle facing the globe. The needle was advanced toward the macular area, taking care to maintain contact between the bevel of the needle and the sclera until the hub was firmly pressed against the conjunctiva. The corticosteroid was then slowly injected. After the injection, topical 0.5% moxifloxacin (Vigamox) eye drops were prescribed to the patients.

Subsequently, visual acuity and IOP were measured clinically, and the macular thickness was quantified with the help of OCT at one, three and six months after treatment.

The data were analyzed with SPSS (Version 11) software. A chi-square test was used to test the statistical significance. The results were considered statistically significant at a p-value of <0.05.
Results

The comparative improvement in Snellen’s acuity from baseline in terms of the number of lines in both groups at the end of six months following the TA injection is given in Table-II. The majority of eyes in both groups showed significant improvement in Snellen’s acuity up to 3-lines (50% in the PST group versus 40% in the IVT group), although the difference was not significant. The benefit of 2-lines of acuity was observed in an equal number of eyes (20%) in both groups, and 1-line improvement was observed in 30% of the PST group and 20% of the IVT group, which was not significant (Graph 1 and 2). In the PST group, every eye showed some benefit resulting from the injection in terms of a visual acuity improvement compared to the IVT group, in which twelve patients (20%) failed to show an improvement in visual acuity of even 1-line (Table 1, Graph 3). This result was statistically significant (p<0.05). The eyes treated with IVT showed rapid improvement in visual acuity in the first month compared to the PST group but then showed a significant worsening of visual acuity with the passage of time. However, eyes treated with PST displayed a gradual response but maintained a visual acuity improvement over time (Graphs 1, 2 and 3). The late worsening of visual acuity in the IVT group and the gradual but sustained improvement in the PST group was correlated with changes in the macular thickness values on OCT in both groups.

The macular thickness values before TA injection and after one, three and six months post-injection are shown in Table-II. In the IVT TA group, thickness values were significantly reduced both after one month (222.7±13.4 μm; p<0.001) and after three months (228±10.6 μm; p<0.01) when compared to the baseline values (386.3±12.4 μm). The eyes treated with PST injections displayed significant improvements in macular thickness one month (220.1±15.1 μm; p<0.001) and three months (231.3±10.9 μm; p<0.001) after treatment when compared to the baseline values (384.1±18.9 μm). Similarly, the difference in the macular thickness of the eyes treated with IVT (385.2±11.3 μm) and those treated with PST (235.4±8.7 μm) became significant six months after treatment (p<0.001). Figure 1 illustrates the changes in the macular thickness values on OCT in the PST injection group.

The mean intraocular pressure (IOP) before triamcinolone acetonide injection and after one, three and six months following treatment are shown in Table-IV. The IOP of the eyes treated with an IVT injection was significantly increased after one month (17.7±1.1 mm/Hg; p<0.020), three months (18.2±1.2 mm/Hg; p<0.003) and six months (18.1±1.320 mm/Hg; p<0.007) when compared to the baseline value (16.1±1.4 mm/Hg), but glaucoma medication was not needed to control this rise in IOP. The eyes treated with a PST injection displayed no significant increase in the IOP after one (16.4±1.2 mm/Hg; p<0.450), three (16.3±1.1 mm/Hg; p<0.630) or six months (16.2±1.1 mm/Hg; p<0.720) when compared to the baseline value (16.2±1.3 mm/Hg). The difference of IOP between eyes treated with an IVT injection and those treated with a PST injection became significant after three (p<0.026) and six (p<0.030) months (Graph 4 and 5).

Discussion

Macular edema is the main cause of the loss of visual acuity in diabetic patients [13, 14]. It may occur at any stage of the retinal disorder and is the most common cause of sight reductions in these subjects. In the edema, the blood-retinal barrier is damaged by an alteration in the tight junctions between the retinal capillary endothelial cells and the pigmented epithelial cells (RPE), with the consequent leakage of water and electrolytes into the retinal tissue [3,15-17].

As has been observed in numerous studies, including the Early Treatment Diabetic Retinopathy Study (ETDRS), macular photocoagulation treatment is effective in the treatment of clinically significant macular edema [2, 3, 18]. Thus, the laser photocoagulation for diabetic macular edema(DME), although successful in preventing a further visual loss in 50% of patients, is unable to cause substantial gains in the visual acuity that has already been lost [2, 4]. Moreover, laser photocoagulation is not very effective in eyes with a diffuse macular edema [19, 20].

The extent of the restoration of the hemato-retinal barrier function following laser treatment has been debated, as many studies indicate an increase in the edema following laser photocoagulation [20-22], most likely as a result of the release of pro-inflammatory molecules. Indeed, the initial clinical pattern of diabetic retinopathy with vasodilatation increased blood flow, tissue edema and vascular permeability and presents the characteristics of chronic inflammation. This hypothesis has been supported by recent studies, which have highlighted the appearance of leukostasis in diabetes with the adhesion of activated molecules to the endothelium and with an increased production of prostacyclin, vascular endothelial growth factor (VEGF) and macrophagic cellular component [23-26]. Further support for the hypothesis that inflammation is one of the causes of the onset of diabetic retinopathy has been provided by experimental studies in animals that demonstrate that hyperglycemia not only cause an increase in the production of cyclooxygenase-II (COX-II), through the activation of protein-kinase (PK-C) [27, 28], but also in prostaglandin synthetase (PG-IS) [29], which is a specific enzyme in the synthesis of prostaglandin PGI2 [30].

Furthermore, recent studies have confirmed the important role of COX-II and the prostanooids in the onset of renal
damage in patients with impaired glycemic control. The reduction in prostacyclin levels only occurs in the advanced stage of diabetic microangiopathy. This has been confirmed not only by the reduction in the blood PGI-II levels but also by the reduction in the PGE values observed at a vitreous level during proliferative diabetic retinopathy [31]. All these experimental and clinical data confirm the involvement of pro-inflammatory molecules, which also cause a subclinical increase in the aqueous humor cells in the early stages of diabetic retinopathy [32].

Recent studies have shown that intravitreal (IVT) injections of triamcinolone acetonide (TA) have a positive effect on the forms of diabetic macular edema that are refractory to retinal laser treatment [5, 7]. The use of corticosteroids for the treatment of retinal edema is linked to their capacity to inhibit the initial arachidonic acid cascade, which leads to a down-regulation of cytokines and attenuates the tearing of the hemato-retinal barrier [7, 15, 33].

The use of IVT TA is not, however, without risks [6, 12]. The main complications are endophthalmitis, vitreous hemorrhage, detachment of the retina [5-7, 9] and, possibly, IOP increases in a percentage of cases ranging from 20% to 80% [6, 7, 34, 35]. Finally, the intravitreal administration of corticosteroids is only effective for a few months [36], which means that it is necessary to repeat the injections at three-month intervals to maintain the stability of the retinal macula.

The posterior subtenon (PST) TA administration has already been used in the treatment of cystoid macular edema (CME) and intermediate uveitis [10, 11]. This administration route is not considered to be ideal to obtain a therapeutic dose of corticosteroids at the level of the retina [37], although this opinion can be contested on the basis of clinical results and ultrasound investigations that demonstrate that a proper administration of the injection enables the deposition of appreciable amounts of the drug in the macular area [38-40].

The posterior subtenon (PST) approach is clearly less invasive than the intravitreal (IVT) approach [39], although, again, this commonly used method is not free from potential complications, such as the accidental injection directly into the choroidal or retinal circulation, perforation of the globe, occlusion of the central retinal artery and cataract formation [39]. Other complications are blepharoptosis, orbital fat atrophy, strabismus and conjunctival necrosis [39, 41]. IOP is not increased by this approach, with the exception of steroid responder patients.

This study was performed to compare the two injection routes, IVT and PST, in terms of their efficacy, ease of administration and resulting complications, such as an increase in IOP after the injection.

Our study demonstrates that three months after the intravitreal injection of TA and the subtenon injection of TA there is a statistically significant improvement in visual acuity and an equally significant reduction in retinal thickness. Six months after IVT injection, the patients presented a recurrence of macular edema with the loss of visual acuity, whereas six months after PST injection, retinal thickness and visual acuity remained stable. After one, three and six months, we observed a statistically significant rise in IOP in the eyes treated with an IVT injection, whereas in the PST injection group, no statistically significant variations in IOP were found. None of the patients developed cataracts or needed anti-glaucoma drugs during the entire follow-up period.
There were some inherent limitations in our study: the small sample size, a limited follow-up period and the non-randomized nature of the trial. Large prospective, randomized, multi-centered clinical trials are necessary to establish the long-term efficacy and safety of the PST approach for TA injections in patients presenting with a diffuse diabetic macular edema.

In conclusion the changes in visual acuity and central macular thickness observed after treatment suggest that the PST injection technique is as effective as the IVT injection technique in patients with a diffuse diabetic macular edema. Therefore, the posterior subtenon approach is an easy, safe and valid alternative to the intravitreal approach of steroid administration for patients presenting with a diffuse diabetic macular edema.

Conflict of interest statement: The authors declare that they have no conflict of interest to the publication of this article.

References