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Posterior sub-tenon triamcinolone for refractory diabetic macular edema: A randomized clinical trial

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PURPOSE. *To evaluate the effect of posterior sub-tenon triamcinolone acetonide (TA) injection on clinical, angiographic, and optical coherence tomographic (OCT) parameters in refractory diabetic macular edema (DME).*

METHODS. *In a double-masked placebo-controlled clinical trial, 64 eyes were randomly assigned to two groups. The treatment group (32 eyes) received 40 mg posterior sub-tenon injection of TA and the placebo group (32 eyes) received subconjunctival injection of a placebo. The injections were repeated after 2 months in both groups. Complete ophthalmologic examination, fluorescein angiography, and OCT were performed before intervention and after 4 months. Quantitative measurement of angiographic variables such as the amount of hard exudates (HE), size of foveal avascular zone (FAZ), and leakage severity was performed by computer, using Photoshop software.*

RESULTS. *Initial best-corrected visual acuity (VA) was 0.93±0.39 logMAR in the placebo group and 0.75±0.38 logMAR in the treatment group. At 4 months, corrected VA was 0.88±0.48 logMAR in the controls versus 0.71±0.42 logMAR in the cases. Mean central macular thickness measured by OCT before and 4 months after injection was 392 and 377 microns in the treatment group and 388 and 357 microns in the placebo group, respectively. No statistically significant difference was detected between the two groups. The difference was also not significant in HE, FAZ, and leakage in the angiograms.*

CONCLUSIONS. *Two injections of posterior sub-tenon TA had no therapeutic effect on refractory DME. (Eur J Ophthalmol 2005; 15: 746-50)*

KEY WORDS. *Diabetes, Macular edema, Sub-tenon injection, Triamcinolone, Optical coherence tomography*

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INTRODUCTION

Macular edema is one of the leading causes of vision loss in patients with diabetes mellitus (1). Approximately 29% of patients having diabetes for more than 20 years will exhibit macular edema, with over 50% experiencing a loss of two or more lines of vision after 2 years of follow-up (2, 3). The Early Treatment Diabetic Retinopathy Study (ETDRS) (4) demonstrated a significant benefit of focal laser photocoagulation for clinically significant macular edema. It showed a therapeutic benefit in reducing the risk of moderate visual loss by 50%. However, more than 10% of the eyes will still lose a significant amount of vision after 3 years.

The failure of laser photocoagulation in a substantial subgroup of patients has prompted interest in other treatment methods, including surgical (5, 6) and recently medical therapy with corticosteroid drugs.

It has been shown that intravitreal triamcinolone acetonide (TA) has therapeutic effect on refractory diabetic

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macular edema (DME) (7). However, its administration needs sterile condition and catastrophic complications such as endophthalmitis, retinal detachment, and vitreous hemorrhage could occur (8, 9). On the other hand, subtenon injection of TA delivers a large amount of drug to the posterior segment of the eye via transscleral absorption (10, 11), and has been widely used as a treatment of cystoid macular edema secondary to uveitis (12) or intraocular surgery (13). Therefore, we used posterior subtenon route for injections. The purpose of this study was to evaluate the benefit of posterior sub-tenon TA injection for the treatment of refractory DME.

METHODS

A double-blind, randomized clinical trial was conducted on 78 eyes of 47 diabetic individuals referred to Emam Hossein Medical Center between March 2002 and June 2003. All cases with clinically significant macular edema (according to EDTRS criteria) were included in the study if they met at least one of the following criteria: macular ischemia, visual acuity (VA) ≤ 8804; 20/200, diffuse macular edema, hard exudates (HE) in the center of the macula, and lack of response to previous laser photocoagulations, the last one more than 3 months previously.

Monocularity, history of deep vitrectomy, glaucoma, or ocular hypertension, significant media opacity, and VA ≥ 20/50 were the exclusion criteria. The study protocol and its probable safety and efficacy were explained to all patients before obtaining the informed consent.

All participants were asked about the time of decreased vision, diabetes duration, history of systemic hypertension, smoking, macular photocoagulation (MPC), and panretinal photocoagulation (PRP). Corrected VA, presence and extent of neovascularization of iris (NVI), lens status, lens opacity in phakic eyes, intraocular pressure (IOP), and severity of retinopathy were recorded on data sheets. Fluorescein angiography and optical coherence tomography (OCT) were also performed.

Then the eyes were randomly assigned to control and case groups. In bilateral cases, each eye entered one of the study groups. In the treatment group, posterior subtenon injection was performed by using the technique of Smith and Nozik (14). The patient was asked to look in the inferonasal direction with the eye to be injected. Then 40 mg TA (Kenalog) was administered through a 5/8 inch, 26-gauge needle attached to a 3 mL syringe. With its bevel toward the globe, the needle was passed through the bulbar conjunctiva into the superotemporal fornix, and then advanced posteriorly while maintaining the needle tip adjacent to the globe. The needle was moved from side to side in a sweeping motion as it was advanced, to avoid inadvertent perforation of the globe. It was progressed until the hub was adjacent to the entry point in the conjunctiva, and then the drug was injected. In the controls, 0.1 cc lidocaine 2% was injected subconjunctivally as a placebo. The interventions were repeated after 2 months. One ophthalmologist did all the injections.

Ophthalmologic examinations were performed after 2 and 4 months for both groups, but cases had two extra examinations at 1 and 4 weeks. At each time, all participants were asked about VA changes. OCT and angiography were repeated after 4 months. Corrected VA was recorded in logMAR notations. The severity of NVI and retinopathy were expressed in clock hour and EDTRS scaling, respectively. Lens opacity was graded from 0 to 4+ for each of three different categories: nuclear sclerosis, posterior subcapsular opacities, and cortical cataract.

OCT mapping was performed using commercially available equipment (Zeiss, Dublin, CA) called OCT-2. Retinal thickness was evaluated in the foveal, perifoveal, and parafoveal regions and macular volume in the 3.5- and 6-mm circles centered on the fovea. Quantitative measurements of the amount of HE, size of foveal avascular zone (FAZ), and leakage severity were performed by computer using Photoshop 7.0 software.

The patients were unaware of the type of injections. All refractions were done by an optometrist who was masked to groups. One ophthalmologist performed all other examinations and injections. Therefore, the research was not double blinded in terms of IOP, lens opacity, and retinopathy changes. However, because the main outcomes were VA, OCT findings, and angiogram variations, the study could be considered as a double-masked randomized placebo-controlled clinical trial. This trial was approved by the review board/ethics committee of the Ophthalmic Research Center of the university.

For statistical analysis, chi-square test was used for fixed factors and Student's t and paired t test for covariates.

RESULTS

Of the 78 enrolled eyes, one was excluded due to vitreous hemorrhage and 13 cases did not complete the 4-

month follow-up. Therefore, statistical evaluation was performed on 64 eyes (32 in each group) of 38 patients. Only 1 out of 38 patients had insulin dependent diabetes mellitus. Ten men (26%) and 28 women (74%) with a mean age of 60.1 years (range: 26 to 81 years) participated in the study.

The mean frequency of the background or confounding factors (age, sex, diabetes duration and management, mean duration of deceased vision, history of systemic hypertension, and lens status) and some other preinjection variables including severity of retinopathy, presence of vitreous hemorrhage, lens opacity, and IOP were similar in both groups, which indicated an acceptable randomization.

The difference in IOP changes between the two groups was not statistically significant. Ocular hypertension (more than 21 mmHg) occurred only in two eyes of the cases (6%). It developed after 2 weeks in one and after 4 weeks in the other; both were controlled with topical medication. There was no significant cataract progression in any of the eyes. A sub-tenon injection-related complication was chemosis, which occurred in only two eyes.

Subjective visual changes at 2 and 4 months were similar in both groups. Mean corrected VA recorded in logMAR notations were compared before (month 0) and 2 and 4 months after intervention among groups. Although the mean initial VA was lower in controls (0.18 logMAR higher) than in cases, this relation persisted through the study and hence, no statistically significant difference was noticed at each compared time.

Statistical analyses of OCT findings were performed on five different variables: CMT, mean thickness in parafoveal and perifoveal rings, and macular volumes in two foveal-centered circles with diameters of 3.5 and 6 mm. As shown in Table I, statistical comparison of each variable could not find any meaningful difference between groups. Mean CMT before and 4 months after injection was 392 and 377 microns in the treatment group, and 388 and 375 microns in the placebo group, respectively.

There was also no statistically significant difference in the amount of HE, FAZ size, and leakage severity between the two groups (Tab. II).

TABLE I - OPTICAL COHERENCE TOMOGRAPHY FINDINGS BEFORE AND AFTER INTERVENTION IN EACH GROUP

		Month 0		Month 4	
		Mean	p value	Mean	p value
CMT,	Controls	388	0.907	357	0.627
µm	Cases	392		377	
Parafoveal	Controls	387	0.974	350	0.496
Thickness, µm	Cases	388		378	
Perifoveal	Controls	381	0.758	335	0.226
Thickness, µm	Cases	371		386	
Volume 3.5,*	Controls	3.64	0.857	3.26	0.478
mm^3	Cases	3.70		3.53	
Volume 6,†	Controls	10.92	0.798	14.45	0.444
mm^3	Cases	10.68		10.57	

*Macular volume in the central 3.5 mm circle
†Macular volume in the central 6 mm circle
CMT = Central macular thickness

TABLE II - THE AMOUNT OF HARD EXUDATE (HE), FOVEAL AVASCULAR ZONE (FAZ) SIZE, AND LEAKAGE SEVERITY IN EACH GROUP AT TWO COMPARED TIMES

	Unit	Groups	Number	Month 0	Month 4
HE	Pixel	Control	19	2,611	2,850
		Case	17	2,595	2,439
Leakage	Luminosity	Control	15	143	134
		Case	18	150	138
FAZ	Pixel	Control	8	14,539	17,079
		Case	10	15,719	18,573

DISCUSSION

Our study suggests that two posterior sub-tenon injections of TA have no effect on the treatment of refractory DME, and to our knowledge, this was the first double-masked randomized clinical trial with large sample size in this field.

Potential complications of posterior sub-tenon injection of corticosteroid include inadvertent injection into the choroidal or retinal circulation (15, 16), globe perforation (17, 18), cataract and glaucoma blepharoptosis, propto-

sis, orbital fat atrophy (19), delayed hypersensitivity reactions, strabismus, conjunctival hemorrhage, chemosis, and infection (20). Only two of these side effects (ocular hypertension and chemosis) occurred in our cases and fortunately, none of the major complications developed.

Posterior sub-tenon injections of corticosteroid appear to be less likely than anterior sub-tenon ones to produce glaucoma (21). Considering it as a safe procedure, Mueller et al (22) believe that posterior sub-tenon injection of corticosteroids does not induce a clinically significant IOP rise, which is compatible with our study. Helm and Holland, however, showed a higher than expected incidence of increased IOP after injection in intermediate uveitis (12). They supposed that increased IOP might be a function of both the disease and the use of topical or oral corticosteroids.

Our study showed that despite multiple injections, cataract progression did not occur, which was probably due to short-term follow up.

Estafanos and Kaiser found that multiple sub-tenon corticosteroid injections in DME with cystic changes could result in significant visual gain whether given alone or in conjunction with focal laser therapy (23). This was a retrospective study with no control group, which evaluated only the VA changes. In a clinical trial, Verma et al showed a significant improvement in corrected VA and contrast sensitivity with posterior sub-tenon injection combined with grid laser photocoagulation in diffuse DME (24). However, it should be noted that in these two studies the results were not confirmed by OCT.

In a recently published clinical trial, Sutter et al noticed that intravitreal triamcinolone has a temporary therapeutic effect for persistent DME unresponsive to adequate laser treatment (25).

The present study documented that two posterior subtenon injections of TA have no beneficial effect on VA and macular thickness of the eyes with severe DME. We should remind ourselves that some of our cases had HE at the center of the fovea or had macular ischemia; therefore, no visual improvement would be expected in these eyes. For this reason, lack of response may be in part due to the severity of maculopathy in some of our cases. It is supposed also that the sub-tenon route fails to show significant effect because of inadequate penetration through the sclera. Therefore, we would suggest the conduction of clinical trials for evaluating the effect of TA on refractory DME via other routes such as intravitreal injections or intracameral implants.

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