Intravitreal Triamcinolone Injection for Diffuse Diabetic Macular Edema with Foveal Cystoid Changes

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Abstract

Background: Diabetic macular edema causes visual loss in almost one-third of diabetic patients. There is currently no treatment for the accompanying cystoid foveal changes.

Objectives: To assess the clinical outcome, i.e., change in visual acuity, in patients treated with steroids for long-standing diabetic macular edema with foveal cystoid changes.

Methods: In the ophthalmology department of a tertiary care university-affiliated medical center and the ophthalmology service of a health management organization, 46 diabetic subjects (56 eyes) who had diabetic macular edema with cystoid foveal changes received one intravitreal injection of 4 mg triamcinolone acetonide.

Results: The mean baseline (pre-injection) visual acuity of 0.21 increased to 0.31 and 0.48 at 1 and 3 months, respectively, after which it decreased to 0.33 at 6 months. The mean intraocular pressure was 15.07 mmHg at baseline, 15.83 at day 1, gradually rising to 17.16, 18.38 and 18.57 mmHg at 1, 3 and 6 months respectively. Three patients suffered immediate visual decline after the injection.

Conclusions: Intravitreal triamcinolone acetonide may be a therapeutic option for long-standing diabetic macular edema with foveal cystoid changes.

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Diabetic macular edema affects approximately 29% of diabetic patients, with a disease duration of 20 years or more, and is responsible for a significant degree of visual loss in this population [1]. Eyes with diffuse macular edema carry an especially poor prognosis despite laser photocoagulation [2,3]. There is no treatment for the cystoid foveal changes that frequently accompany diffuse diabetic macular edema, but they have been shown to respond quickly and efficiently to sub-Tenon and intravitreal steroid injection in pseudophakic and inflammatory conditions [3–9]. Steroids are potent anti-inflammatory agents that are thought to inhibit the production of vascular endothelial growth factor and have been shown to decrease the breakdown of the blood-retinal barrier [10,11]. These qualities render steroids a potential treatment for certain types of diabetic retinopathy. The aim of this study was to investigate the role of steroids in a subgroup of patients who presented with diffuse diabetic macular edema accompanied by cystoid macular changes.

Patients and Methods

The study group comprised 46 diabetic individuals (both juvenile and adult-onset diabetes) who were diagnosed with clinically significant diabetic macular edema according to ETDRS criteria and cystoid foveal changes. There were fifty-six affected eyes. The diagnosis of these two entities was based on contact lens examination of the macular area and fluorescein angiography performed during 2 weeks prior to examination. Evaluation and management were conducted at the ophthalmology outpatient clinic of Tel Aviv Sourasky Medical Center and at the Maccabi Retina Service, Tel Aviv, by one of three retina specialists (A.B., M.G., A.L.) between April 2002 and April 2003. All eyes had previously received at least two prior sessions of laser photocoagulation according to ETDRS guidelines; the most recent laser treatment was given at least 3 months before the study began. All the investigated eyes had residual macular thickening and cystoid foveal changes with associated loss of visual acuity. No eyes had a history of ocular hypertension or glaucoma.

Suitable patients were offered intravitreal injection of triamcinolone acetonide (Kenalog™, 40 mg/ml, Bristol-Myers Squibb, Italy) to treat their macular edema, and each candidate provided informed consent to participate in this study. Baseline parameters were documented, including visual acuity (measured with the Snellen chart in a standardized examination room by trained ophthalmic nurses), intraocular pressure (using the Goldmann tonometer), lenticular status, and biomicroscopy by a retina specialist. Fluorescein angiography was performed on all patients prior to treatment, and it confirmed the diagnosis of diabetic macular edema with cystoid foveal changes.

All injections were given under strict antiseptic conditions in the outpatient clinic's minor surgery room. The eye was anesthetized with topical lignocaine HCL B.P. 2% (Rafa Laboratories Ltd., Jerusalem) gel followed by preparation with 4% povidone iodine solution. A cotton-tipped applicator soaked in tetracaine was then applied to the injection site 3.5 mm posterior to the limbus. Triamcinolone acetonide was injected slowly through

the inferior pars plana at a dose of 4 mg (0.1 ml), and through a 27-gauge needle. Indirect ophthalmoscopy was performed post-injection to confirm proper intravitreal localization of the suspension and perfusion of the optic nerve head. One drop of lacromycin was applied to the ocular surface, and the eye was patched and reexamined 1 hour later to evaluate acute pressure elevations. Another drop of lacromycin was then applied, and the eye was patched until the next morning when it was reexamined for any signs of infection or acute pressure elevations. All the study patients were placed on topical antibiotic, ciprofloxacin HCL 0.3%, four times daily for 5 days.

The primary outcome measured in the study was visual acuity. The secondary outcome was disappearance of clinically significant diabetic macular edema and cystoid foveal changes as assessed clinically by contact lens examination at 1, 3, and 6 month intervals after injection and by fluorescein angiography 3 and 6 months after injection. The tertiary outcome measured was intraocular pressure, which was examined at 1 hour, 1 day, 1 week, and 1, 3, and 6 months after injection. The final outcome measured was any sign of injection-related complications.

Statistical analysis

The mixed model analysis was applied to the data of the parameters intraocular pressure and visual acuity to study the effect of follow-up time. The time of examination was considered as the fixed effect and the subjects comprised the random effect. The mixed model was chosen to account for incomplete data. This analysis was performed for the entire sample as well as for adult-onset diabetes and juvenile diabetes separately. The SAS PROC MIXED version 8.1 was used to obtain restricted maximum likelihood estimates and for performing hypothesis tests.

Results

All 56 originally enrolled eyes completed 3 months of follow-up, and 52 of them had a follow-up of 6 months or more. The four patients who failed to come to the 6 month visit were contacted by one of the investigators at the time of this appointment to rule out any major ocular catastrophe (there were none), and these four were excluded from further analysis. Of the total of 56 patients 45 had adult-onset diabetes and 11 had juvenile diabetes. Of the adult-onset diabetics 34 were men and 17 were females. Mean age at the time of treatment was 64.2 ± 10.9 years. The duration of macular edema diagnosed was 14.2 ± 4 months. Of the 45 patients with adult-onset diabetes 20 had proliferative diabetic retinopathy and 25 had non-proliferative diabetic retinopathy. Of the juvenile-onset diabetics seven were male and four female. Mean age at the time of treatment was 63.4 ± 12.9 years. The duration of macular edema diagnosed was 14.0 ± 4 months. Of the 11 patients with juvenile-onset diabetes 5 had proliferative and 6 had non-proliferative diabetic retinopathy. The results from all injections performed between April 2002 and April 2003 were summarized and compared [Table 1].

Table 1. Results from all injections performed between April 2002 and April 2003

Parameter	Time trend	Significant difference between time points *
Visual acuity		
Whole sample	$P < 0.0001$	1 vs. 2, $P < 0.0001$
		2 vs. 3, $P = 0.0497$
		1 vs. 4, $P = 0.0012$
Adult diabetes	$P < 0.0001$	1 vs. 2, $P = 0.0005$
		2 vs. 3, $P = 0.0124$
		3 vs. 4, $P = 0.0771$
		1 vs. 4, $P = 0.0052$
Juvenile diabetes	$P < 0.0278$	1 vs. 2, $P = 0.0052$
		1 vs. 4, $P = 0.0878$
Applanation tonometry		
Whole sample	$P < 0.0002$	2 vs. 3, $P = 0.0663$
		1 vs. 5, $P < 0.0001$
Adult diabetes	$P < 0.0009$	2 vs. 3, $P = 0.007$
		1 vs. 5, $P = 0.0007$
Juvenile diabetes	$P < 0.0824$	1 vs. 5, $P = 0.0213$

* Time points: 1 = pre-injection, 2 = 1 week, 3 = 1 month, 4 = 3 months, 5 = 6 months

The pre-injection (baseline) mean visual acuity was 0.21 (20/100), 0.31 (20/64) at 1 month post-injection, increasing to

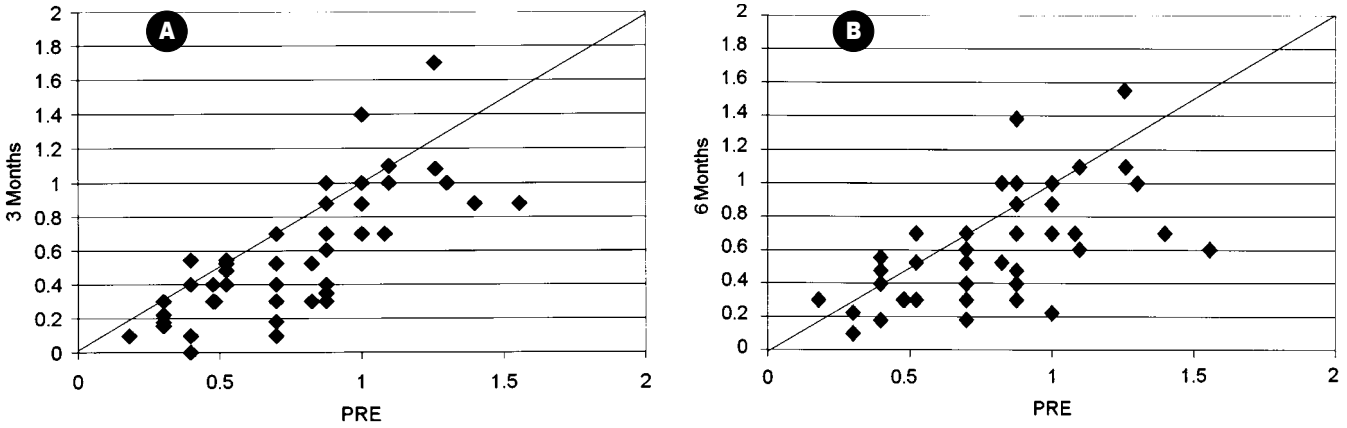

Figure 1. Graph showing the pre-and post-injection visual acuity for each patient at **[A]** 3 months and **[B]** 6 months after an intravitreal injection of triamcinolone acetonide. Visual acuity is presented in LOG (mean refraction).

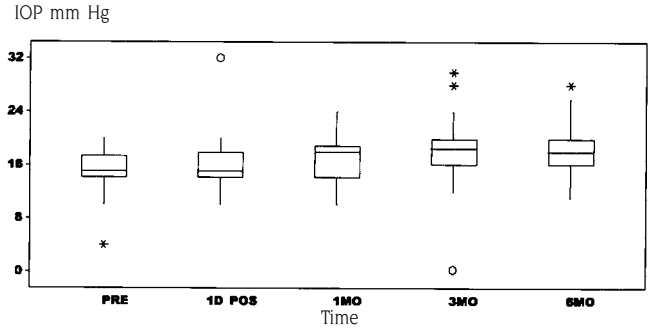

Figure 2. Box and whiskers plots showing the change in intraocular pressure after the intravitreal injection of triamcinolone acetonide. The box encloses the middle half of the intraocular pressure results. The box is bisected by a line at the value for the median. Extreme values are displayed as "*" for possible outliers and "O" for probable outliers. Possible and probable outliers are values that are outside the box boundaries by more than 1½ and 3 times the size of the box respectively. The vertical lines at the top and the bottom of the box indicate the range of intraocular pressure values.

0.48 (20/46) at 3 months and decreasing to 0.33 (20/60) at 6 months [Figure 1].

The results of the analysis of variance indicate an overall time trend for the whole sample as well as for the adult-onset diabetes and juvenile diabetes groups [Table 1]. Pair-wise comparisons between time intervals showed a significant difference between the first and second and between the second and third time points in visual acuity for the whole sample and for the adult-onset diabetes group. The difference between points 1 and 2 in the juvenile diabetes group was significant. When comparing changes in visual acuity from baseline for each patient, a change of more than 0.2 LOG MR was seen in 22 patients at 3 months after injection ($P < 0.002$, multiple regression test) and in 17 patients at 6 months ($P < 0.002$, multiple regression test) [Figure 1].

The mean baseline intraocular pressure was 15.07 and 15.83 mmHg at day 1, whereupon it gradually rose to 17.16, 18.38 and 18.57 mmHg at 1, 3 and 6 months, respectively [Figure 2]. The results of the analysis of variance indicate an overall time trend in both parameters for the whole sample, and for the adult-onset diabetes group [Table 1]. Patients in the juvenile diabetes group demonstrated a borderline change in intraocular pressure. Pair-wise comparisons between time intervals showed the difference between the first and fifth points to be significant for the whole sample and for the adult-onset diabetes group. The difference between points 2 and 3 was borderline for both the whole sample and for the adult-onset diabetes. There was a pressure elevation to more than 21 mmHg in 13 patients (25%), and elevations to more than 30 mmHg were recorded in 4 (7.6%) patients. All pressure elevations were controlled by anti-glaucoma medications. There was a clinical impression of complete resolution of diabetic macular edema and cystoid macular edema in 14 patients at 1 month and in 20 more patients at 3 months, but the total number dropped to 22 at 6 months, with the reappearance of both diabetic macular edema and cystoid foveal changes in 12 patients.

Complications

Neither endophthalmitis nor retinal detachment was detected among our study patients. Pseudohypopyon was observed in four patients (7%) (three pseudophakic, one phakic) on day 1 and it resolved without treatment. Four eyes (7%) of three patients, all with diagnosed proliferative diabetic retinopathy, had vitreous hemorrhage during the 6 month post-injection follow-up, and two of these eyes underwent vitrectomy 3 months post-injection due to non-clearing hemorrhage. Three patients (5.7%) suffered from severe (more than three line vision loss) decrease in visual acuity during the first week after injection. Patient 1, a 56 year old man with a 15 year history of diabetes mellitus, reported a severe decrease in his visual acuity immediately after injection. His pre-injection visual acuity was 20/50, and it dropped to 20/200 following the injection. A clinical examination revealed no signs of retinal vascular occlusion, and fluorescein angiography performed 2 weeks later showed a decrease in the amount of macular fluorescein leakage [Figure 3]. A visual field test revealed an altitudinal visual field defect, suggesting the diagnosis of anterior ischemic optic neuropathy. At that point, there was no evidence of optic nerve head swelling, but temporal pallor of the optic disk was detected 3 months later. Magnetic resonance scanning of the brain revealed no abnormality. This patient's visual acuity gradually improved to 20/50, with no change in the visual field defect.

Patients 2 and 3 had baseline visual acuities of 20/150 and 20/200 and post-injection visual acuities of 1 m/24 and finger counting, respectively. Fluorescein angiography performed 2 weeks after injection revealed that each had enlargement of the foveal avascular zone; there were no visual field defects or any other ocular or neurologic abnormalities. No abnormality was detected on their brain MR scans. Both patients' visual acuities remained stable, with no improvement by the end of the 6 month follow-up.

Discussion

The results of the current study showed a short-term significant improvement in the visual acuities of patients with diabetic macular edema and cystoid foveal changes who had been treated with a single intravitreal triamcinolone injection. The injection led to increased intraocular pressure in 13 patients (25%), while 3 patients (5.7%) suffered from severe (more than three line vision loss) decrease in visual acuity during the first week after injection. Four patients (7.7%) suffered vitreous hemorrhage during the first 6 months of follow-up.

The safety of intravitreal triamcinolone injection has been demonstrated in an animal model [12] and in human trials [13,14]. The complication rate was higher in our series than in previously reported studies, but to the best of our knowledge, and based on an extensive Medline search, our series is the largest to be reported in diabetic patients [15–18] – hence the greater chance for the emergence of a higher rate. We suspect that the post-triamcinolone injection response of decreased visual acuity in all three of our affected patients may be related to the small vessel closure that is associated with diabetic

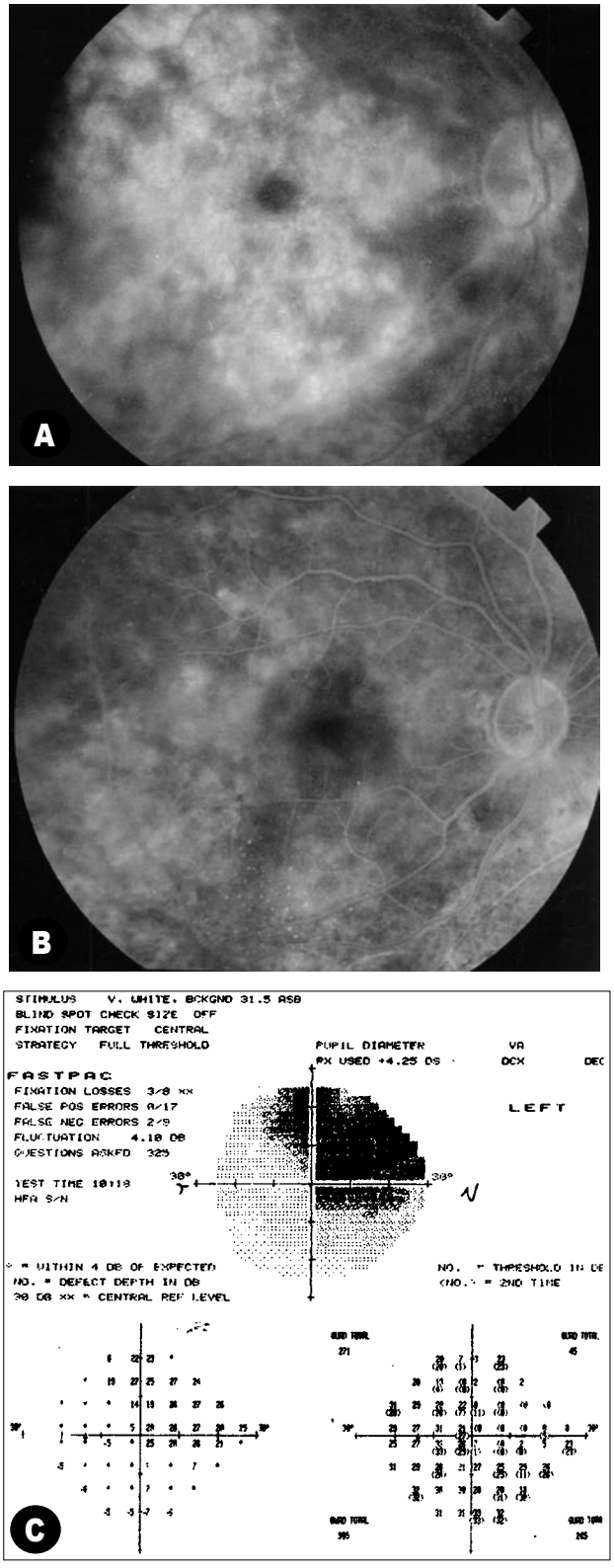

Figure 3. Patient no. 1 who suffered a severe decrease in his visual acuity immediately after one injection of triamcinolone acetonide. **[A]** Pre-treatment fluorescein angiography. **[B]** Fluorescein angiography performed 2 weeks post-injection, showing decrease in the amount of macular fluorescein leakage. **[C]** Visual field test resembling an altitudinal visual field defect, suggesting the diagnosis of anterior ischemic optic neuropathy.

pathogenesis. After our experience with these cases, we no longer inject triamcinolone to patients who show evidence of significant macular ischemia on fluorescein angiography or to those with a history of diabetic papillopathy.

Our results of transient improvement in visual acuity are encouraging. All 52 study eyes had diffuse macular edema that failed multiple laser sessions and exhibited cystoid changes. Eyes such as these had been shown to be difficult to treat [2,19]. The ETDRS demonstrated visual improvement of three or more lines in fewer than 3% of enrolled patients after photocoagulation [2]. Our patients showed transient visual improvement during the current study in which only a single injection was allowed for each eye. Multiple injections or different steroid delivery systems, such as an intravitreal long-term release device, may improve results for these difficult-to-treat patients. In the current study, we chose to inject 4 mg/ml triamcinolone based upon the numerous studies that used this concentration without complications. A higher dose (i.e., 25 mg) of triamcinolone, as used by Jonas et al. [20–25] in different settings may, however, give different and possibly better results.

The current study has several limitations. It is biased toward patients with type I diabetes. This does not reflect the far higher prevalence of type II diabetes in the general population. The study is also skewed towards the male population. Visual acuity was measured on a Snellen chart, as opposed to the more standardized ETDRS chart. Anatomic data are presented objectively and not in a quantitative fashion using optical coherence tomography. The duration of follow-up was also relatively short, and complications related to the corticosteroid medication, such as cataract progression and glaucoma, could be expected to occur over a longer period. Four eyes of three patients experienced vitreous hemorrhage during the 6 month follow-up. Two of these eyes underwent vitrectomy 3 months post-injection due to non-clearing vitreous hemorrhage. We decided to include these two eyes in the analysis, yet we are aware that vitrectomy is a significant confounding factor in the assessment of subsequent macular edema, thus the results may be skewed. Finally, we had no control group and, therefore, biased enrollment or some other unidentified flaw in study design may have confounded our results.

Despite the limitations and complications we encountered during the study, we believe that after refining the technique and collecting more information on dosage safety and complications, intravitreal triamcinolone injections have advantages that will make their use appealing for the treatment of diabetic retinopathy. The obvious advantages of this in-office procedure are its low cost and ease of administration. The medication is injected through the pars plana under topical anesthesia and any discomfort during and after injection is usually minimal. The Diabetic Retinopathy Clinical Research Network is initiating a multicenter, randomized clinical trial of triamcinolone acetonide injection for eyes with diabetic macular edema. The Intravitreal Steroid Injection Studies (ISIS), a multicenter prospective pilot uncontrolled study, is currently investigating this method for the treatment of macular edema secondary to diabetes, vein oc-

clusions, pseudophakia, and retinal telangiectasia. Thus, further essential information on this treatment modality will eventually become available.

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