A Comparative Study between Intravitreal and Subtenon Triamcinolone Acetonide in the Treatment of Diabetic Macular Edema

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Introduction:

Diabetic macular edema is the most common cause of visual loss among patients with diabetic retinopathy. [1]

The only proven treatment of diabetic macular edema consists of focal laser photocoagulation and is based on the results of the Early Treatment Diabetic Retinopathy Study (ETDRS). [2]

In the ETDRS, patients could receive multiple laser treatments if "treatable lesions" existed, defined as persistent leaking microaneurysms 500µ from the center of the macula if the vision was less than 20/40 and there was no perifoveal capillary dropout. Despite multiple attempts at photocoagulation, a significant number of eyes remained refractory to treatment, and the majority failed to have any improvement in vision. In fact the ETDRS reported that only 17% of eyes had any improvement in visual acuity, and less than 3% had a visual improvement of 3 or more ETDRS lines.[1]

The sequelae of chronic macular edema include permanent retinal damage and loss of visual acuity secondary to cystic degeneration, lamellar hole formation, epiretinal membrane formation, and atrophy of the outer retinal layers. Thus, other treatment modalities for diabetic macular edema had to be considered. [3]

Triamcinolone acetonide is a long acting corticosteroid that has been reported to be efficacious when administered by intravitreal injection for the treatment of diabetic macular edema. [4]

However, intravitreal injections carry considerable risk, including acute infectious endophthalmitis that has been reported at a rate of 0.83 %.[5]

Triamcinolone acetonide (TA) has also been efficient when given by intravitreal or subtenon injection as a treatment for Irvin-Gass syndrome, diabetic macular edema, uveitis, retinal vein occlusion, and age-related macular degeneration. [6, 7]

Subtenon injection may be safer, because of a lower incidence of endophthalmitis and intra-ocular pressure rise than with intravitreal injection.

Different studies have been performed to determine the intraocular concentration of TA after intravitreal injection. Although significant variability was found, they orbited around a concentration of 1.29 μg/ml when measured within an interval of 3-19 days after an injection of 4 mg. [8] Other studies measured the intraocular concentration after a subtenon injection of 40 mg and found it at an average of 0.6 μg/ml when measured within an interval of 1-29 days after injection. [9]

However, whether the clinical efficacy of this corticosteroid differs between these injection sites is unclear. We hope through this study to shed some light on this matter.

Aim of the work:

To compare the results of intravitreal and subtenon triamcinolone acetonide in the treatment of diabetic macular edema.

Patients and methods:

This study will include forty patients from the outpatient clinic at the Demerdash Hospital with the following inclusion criteria:

1- Clinically significant diabetic macular edema.
2- Retinal thickness in the central macular area > 250μ by OCT.
3- Best corrected visual acuity (BCVA) of 20/40 or worse.
4- Sufficiently clear ocular media to allow good retinal visualization.
5- Signed informed written consent.

Exclusion criteria will include:

1- History of raised IOP due to topical steroid therapy.
2- Systemic steroid therapy.
3- Any ocular surgery three months prior to the procedure.
4- Previous treatment for diabetic macular edema.

The patients will be divided into two groups each composed of twenty subjects. The first group will undergo intravitreal TA injection of 4 mg while the second group will undergo subtenon TA injection of 40 to 80 mg.

Before the procedure both groups will undergo the following:

1- BCVA.
2- IOP measurement.
3- Anterior segment and lens examination.
4- Fundus examination and photography.
5- Fundus fluorescein angiography (FFA).
6- OCT of the macular area.

Follow up of all patients will be as follows:

1- Slit lamp examination and IOP measurement on the first, third, seventh postoperative day, then weekly for the first month, then on the third, sixth and ninth month.
2- FFA will be performed at two weeks and four weeks then when necessary.
3- OCT will be performed at two weeks, four weeks then three, six and nine months.
4- BCVA will be measured at one, three, six and nine months.
5- Reinjection of patients will be considered if needed.

Results:

The results of both groups will be compared as regarding:

1- BCVA.
2- IOP rise.
3- Central macular thickness by OCT.
4- Vascular leakage by FFA.
5- The occurrence of any unwarranted complications.

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Contents

List of abbreviations

Abbreviation	Definition
AGE	Advanced glycation end products
A II	Angiotensin II
BRB	Blood retinal barrier
b-FGF	Basic fibroblast growth factor
CME	Cystoid macular edema
CMT	Central macular thickness
CSME	Clinically significant macular edema
DM	Diabetes mellitus
DME	Diabetic macular edema
ELM	External limiting membrane
ET	Endothelin
ETDRS	Early treatment diabetic retinopathy research study
FAZ	Foveal avascular zone
FFA	Fundus fluorescein angiography
GDNF	Glial cell derived neurotropic factor
ICAM-1	Intercellular adhesion molecule-1
IGF	Insulin-like growth factors
IL	Interleukin

IRMA	Intraretinal microvascular abnormalities
IVTA	Intravitreal injection of triamcinolone acetonide
MMP	Matrix metalloproteinases
NPDR	Non proliferative diabetic retinopathy
NVD	Neovascularization of the disc
NVE	Neovascularization elsewhere
OCT	Optical coherence tomography
PDR	Proliferative diabetic retinopathy
PDGF	Platelet-derived Growth Factor
PEDF	Pigment epithelium derived factor
PKC	Protein kinase C
PVD	Posterior vitreous detachment
RAGE	Advanced glycation end products receptors
RPE	Retinal pigmented epithelium
RVE	Retinal vascular endothelial cells
SD	Standard Deviation
STTA	Subtenon injection of triamcinolone acetonide
TA	Triamcinolone acetonide
TNF	Tumour necrosis factor
VEGF	Vascular endothelial growth factor
ZO	Zonula occludens

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Introduction

We are currently facing a worldwide epidemic of diabetes mellitus (DM). In the year 2000, more than 176 million people throughout the world suffered from DM. The World Health Organization has estimated that by the year 2030 there will be 370 million people affected with DM in the world, and every one of them will be at risk of developing retinopathy***(Arevalo,2009).***

The first report of diabetic retinopathy, specifically diabetic macular edema (DME), appeared in 1856. Prior to the advent of panretinal photocoagulation, proliferative diabetic retinopathy (PDR) was the main cause of diabetic blindness. Since the development of laser photocoagulation, DME has become the most common cause of visual loss in diabetic patients in the developed world. It is estimated that in the United States alone there are 500,000 patients with DME, with 95,000 new cases every year ***(Arevalo,2009).***

The percentage of cases of blindness attributed to age related macular degeneration, glaucoma, and diabetic retinopathy was 50%, 18%, and 17%, respectively ***(Morello,2007).***

Diabetic macular edema (DME) is the most common ocular complication of diabetes mellitus and presents a serious visual threat to patients. That being said, it's no wonder that so much literature has been dedicated to the various methods of its treatment and prevention of recurrence. Extensive research in the field of laser, medical and surgical therapy has cumulated over the years. Together with the advances in OCT and fundus imaging several treatment guidelines can be drawn to the benefit of our patients.

Diabetic macular edema is defined as retinal thickening within two disc diameters of the center of the macula. The intraretinal fluid comes from leaking microaneurysms or diffuses from capillary incompetence

areas. Sometimes the pockets of fluid are so large that they can be seen as cystoid macular edema (CME) ***(Singh et al.,2008).***

DME patients are categorized into clinically significant macular edema (CSME) and non CSME by the ETDRS. CSME includes any one of the following lesions:

1. Retinal thickening at or within 500µ from the center of the macula.
2. Hard exudates at or within 500µ from the center of the macula associated with thickening of the adjacent retina.
3. An area or areas of retinal thickening at least one disc area in size, at least a part of which is within one disc diameter of the center of the macula***(Singh et al.,2008).***

Diabetic macular edema was also classified as hyperfluorescent if there was predominantly widespread and ill-defined fluorescein leakage at the macular region on fundus fluorescein angiography (FFA), and as minimally fluorescent if there was little fluorescein leakage in late stages in the entire circumstance of the macula.

As might be expected, the prevalence of macular edema is directly related to the overall severity of the retinopathy, ranging from 3% among eyes with mild non proliferative diabetic retinopathy (NPDR) to 38% among eyes with moderate to severe NPDR and 71% among eyes with proliferative diabetic retinopathy ***(Klein et al.,1984).***

The risk factors for occurrence and progression of diabetic retinopathy include duration of diabetes, glycemic control, hypertension, nephropathy, genetics (patients with HLA DR4 and absent HLA DR3 were found to be at a greater risk of having PDR), serum lipid level, anemia and pregnancy ***(Singh et al.,2008).***

ETDRS has classified NPDR into mild, moderate, severe and very severe and PDR into early PDR and high risk PDR. This is as follows:

A. Mild NPDR: presence of at least one microaneurysm, definition not met for B, C, D, E, or F.
B. Moderate NPDR: Hemorrhages and/or microaneurysms more than standard photo 2A, presence of soft exudates, venous beading, IRMA definitely present, definition not met for C, D, E, or F.
C. Severe NPDR: Hemorrhages and/or microaneurysms more than standard photo 2A in all 4 quadrants, or venous beading in 2 or more quadrants, or intraretinal microvascular abnormalities (IRMA) > standard photo 8A in at least one quadrant, definition not met for D, E, or F.
D. Very severe NPDR: Any 2 or more of the changes seen in severe NPDR, definition not met for E, or F.
E. Early PDR: Presence of new vessels, definition not met for F.
F. High risk PDR: Includes any of the following characteristics: neovascularization of disc (NVD) > 1/4 to 1/3 disc diameter, (NVD) < 1/4 to 1/3 disc diameter with vitreous/preretinal hemorrhage, neovascularization elsewhere (NVE) ½ disc diameter with vitreous/preretinal hemorrhage. High risk characteristics were defined because if the patients were not treated urgently they were at a high risk of severe visual loss ***(ETDRS no 1,1991).***

The only proven treatment of diabetic macular edema not due to vitreous traction consists of focal laser photocoagulation and is based on the results of the ETDRS ***(ETDRS no 1,1985).***

In the ETDRS, patients could receive multiple laser treatments if "treatable lesions" existed, defined as persistent leaking microaneurysms 500µ from the center of the macula or 300µ from the center if the vision was less than 20/40 and there was no perifoveal capillary dropout. Despite multiple attempts at photocoagulation, a significant number of eyes remained refractory to treatment, and the majority failed to have any