Subject Area: Ophthalmology

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Peribulbar injection of triamcinolone acetonide as an outpatient clinic procedure in the management of mild to moderate macular edema

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Abstract

Background
Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus and is the most common and most blinding ophthalmic complication. Diabetic macular edema (DME) is an essential manifestation of diabetic retinopathy that occurs across all its severity levels. Several intraocular treatment modalities for diabetic eye disease exist, including per-bulbar steroid injections. This study was conducted aiming to study the clinical effect and central macular thickness decrease following an outpatient clinic simple procedure of peribulbar injection of prepared triamcinolone acetonide (TAA) as a single procedure.

Patients and methods
This study was performed on 100 eligible eyes in 70 consecutive patients. The study involved three times peribulbar injections of prepared TAA separated by 3-week interval with repeated follow-up of patients.

Results
The study revealed that repeated peribulbar injections of TAA resulted in significant visual acuity improvement and significant reduction in the central macular thickness in optical coherence tomography measurement. However, this was associated with a transient increase in intraocular pressure and lower lid edema (swelling). Our results confirm the usefulness of repeated peribulbar injections of TAA in mild to moderate DME management.

Conclusion
Peribulbar TAA injections should be regarded as a treatment for DME. Multicenter randomized trials must be performed comparing this therapy with other available and well-known modality treatments, and more extended follow-up periods are needed in future studies.

Keywords: Macular edema, peribulbar injection, triamcinolone acetonide

Introduction
Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus [1]. It is the most common and possibly the most blinding ophthalmic complication of diabetes [2]. DR is a burgeoning problem globally, currently affecting almost 100 million people worldwide and is set to become an ever-increasing health burden [3].

A healthy relationship was found between chronic hyperglycemia and the development and progression of DR [4]. DR falls into two broad categories: the earlier stage of nonproliferative diabetic retinopathy (NPDR) and the advanced stage of proliferative diabetic retinopathy (PDR) [5]. Diabetic macular edema (DME) is an essential manifestation of DR occurring in all DR severity stages of both NPDR and PDR and is the most common cause of vision loss in patients with DR.
DME emerges from the blood-retinal barrier diabetes-induced breakdown, with consequent vascular leakage into the neural retina of fluid and circulating proteins [5]. Fluid extravasation into the neural retina leads to irregular retinal thickening and sometimes macula cystoid edema [6]. Clinically significant macular edema is characterized as DME meeting at least one of these criteria: thickening of the retina at or within 500 µm of the center of the macula; hard exudates at or within 500 µm of the center of the macula, if associated with thickening of the adjacent retina (not counting residual hard exudates remaining after the disappearance of retinal thickening), or any zone (s) of retinal thickening one disc area or larger, any part of which is within one disc diameter of the center of the macula [7].

Intraocular treatment modalities for diabetic eye disease include laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factor (VEGF), steroid agents, and vitreo-retinal surgery [6]. Pan-retinal photocoagulation for PDR was first proposed in the 1960s based on the belief that thermal burns throughout the retinal periphery could promote the regression of retinal neovascularization, and its efficacy in reducing rates of severe vision loss in eyes with PDR was quickly and incontrovertibly demonstrated [8]. However, pan-retinal photocoagulation is an inherently destructive approach and is associated with well-documented adverse effects, including discomfort or pain [9], visual field loss [10], loss of color vision [11], reduction in contrast sensitivity [12], and choroidal effusions/detachment, leading to shallowing of the anterior angle, elevated intraocular pressure (IOP), and angle-closure glaucoma as well as possible misdirected or excessively intense burns resulting in lens damage, bleeding, or breaks in Bruch’s membrane [9].

Meanwhile, in the modern era, multiple phase 3 clinical trials have demonstrated the superiority of intravitreal anti-VEGF injections to laser monotherapy to reduce vision loss and improve vision gain rates in eyes with DME [13,14]. A recent comparative efficacy study of the three most commonly utilized anti-VEGF agents revealed that aflibercept, bevacizumab, and ranibizumab effectively improved vision over 1 and 2 years of treatment for DME [15]. However, intravitreal anti-VEGF injections were found to have some complications, which are unrelated to the underlying ocular disease, including [16] endophthalmitis [17], intraocular inflammation [18], IOP elevation [19], and subconjunctival hemorrhage [20]. Rare ocular adverse events include anterior ischemic optic neuropathy after bevacizumab injection [21], retinal venous occlusions after bevacizumab injection [22], retinal artery occlusions [23], and sixth nerve palsy following bevacizumab injection [24].

Given the apparent role of inflammation in DME’s pathogenesis, steroids have more recently been used for the treatment of DME [25]. Ophthalmic consequences of local application of steroids include cataract progression, elevated IOP, and when injected into the eye, a low risk of retinal detachment, vitreous hemorrhage, and endophthalmitis was reported [26].
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Exclusion criteria
The following were the inclusion criteria:
(1) Patients with poor visual acuity.
(2) Patients who have done any previous procedure for the management of clinically significant macular edema (laser or intravitreal injection of any material, or subtenon injection).
(3) Previous vitrectomy.
(4) DR with media opacification (dense cataract and corneal opacity).
(5) Double perforating trauma.
(6) Patients with chronic uveitis.
(7) Patients with glaucoma or steroid responder.
(8) Patients with rubeosis iridis.

Methods
Cases were assessed preoperatively. History taking included detailed medical history and detailed ocular history, including duration of symptoms, myopia, trauma, previous anterior segment operations (cataract surgery), and previous posterior segment procedures (laser photoocoagulation, previous intravitreal or subtenon injection, previous vitrectomy). Visual acuity was evaluated by a nonaided and aided method after the correction of errors of refraction using ETDR charts. Anterior segment examination was performed using slit-lamp with IOP measurement by slit-lamp mounted applanation tonometer. Detailed fundus examination was performed by indirect ophthalmoscope using 20 D lens and scleral indentation with a thimble depressor and slit-lamp biomicroscopy by 78 D lenses with an assessment of the following: integrity of retinal vasculature, the integrity of retinal background, macular status, presence of vitreous hemorrhage, posterior vitreous face status, epiretinal membranes, retinal or choroidal detachment, and choroidal effusion. Fundus fluorescein angiography was performed for proper diagnosis and followed up if needed. Moreover, OCT was performed to select inclusion cases, determine the baseline CMT, and follow-up after the third injection.

The TAA injection techniques were standardized. For preparation, one vial of TAA suspension (40 mg/1 ml) was aspirated in a 5-ml syringe, and 4-ml sterile balanced salt solution was added to complete the syringe, which was left upright to precipitate the TAA particles and washout its preservative (to make it less toxic and harmful on retro-orbital fat and tissue) for 15 min or until all particles were precipitated. The upper part of the syringe fluid was clear, then the washed preservative and balanced salt solution were pushed out, leaving particles of TAA in the syringe. Overall, 0.5 ml of mepivacaine hydrochloride 3% was added as a local anesthetic and dissolved the TAA crystals to facilitate injection and minimize pain during and after injection. Tip of 3-ml syringe (needle size 24GX1) was used for peribulbar injection in the same way of peribulbar injection of anesthesia: one drop of topical anesthetic eye drops was instilled, the lower lid pulled laterally with digital palpation to the site of injection, and then the needle was inserted through the skin of lower lid at the junction between medial two-thirds and lateral one-third of inferior orbital margin after sterilization with local povidone-iodine 10% solution for 30–60 s or cleaning with alcohol 70% solution till drying, passing it backward and laterally for not more than 24 mm and always keeping it away from the globe by directing it slightly downward. The injection was performed at the level of the equator, as shown in Fig. 1.

These injections were given, as described previously, three times separated by 3-week interval.

Cases were followed-up one day after the procedure and at 1, 2, and 3 weeks after each injection in the same way of preoperative assessment, that is, evaluation of visual acuity, anterior segment examination, detailed fundus examination, and IOP measurement. Any lower lid edema or ocular stiffness (local effect of TAA on retrobulbar fat) or lid hematoma after injection was recorded, and OCT was performed 1 month after the third injection.

Statistical analysis
Data were collected, revised, coded, tabulated, and analyzed using Statistical Package for Social Science (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp), version 20. The data were presented as numbers and percentages for the qualitative data; mean, SD, and ranges for the quantitative data with parametric distribution; and median with interquartile range for the quantitative data nonparametric distribution. A paired t test was used to compare two groups with quantitative data for before and after, and the parametric distribution and for the parametric data: Wilcoxon rank test were used in the comparison between two groups with quantitative data for before and after nonparametric distribution. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. So, the $P$ value was considered significant at the level of less than 0.05.

Results
A review of the included participants’ sociodemographic characteristics revealed that 50% were males, and 50% were females. Overall, 71.4% of them had diabetes, and 28.6% of them were both diabetic and hypertensive. Their ages ranged from 24 to 76 years, with a mean of $54.27 \pm 10.09$ years (Table 1).

Figure 1: The method of peribulbar injection.
Follow-up of patients revealed that the mean values of best-corrected visual acuity (BCVA) showed gradual improvement over time (Fig. 2), with highly statistically significant improvements following each of the three injections compared with the baseline BCVA (Table 2).

Follow-up of patients also revealed that IOP’s mean values showed a rise in the first week postinjection in each of the three injections, which gradually decreased (Fig. 3).

Moreover, comparison of follow-up mean values to baseline IOP revealed highly statistically reductions in the mean IOP, compared with baseline IOP, at 3 weeks following the first and third injections, as well as a highly statistically rise in the mean IOP, compared with baseline IOP, at 3 weeks following the second injection (Table 3).

Following each of the first and second injections, lower lid edema was noted in 100% of patients in the first week, which became mild edema in the second week and was resolved in the third week. Following the third injection, mild lower lid edema was noted in 100% of patients in the first week, which was resolved in the second and third weeks. Meanwhile, ocular motility was normal in 100% of patients in all follow-up visits following the three injections.

Eventually, follow-up of patients at 1 month following the third injection showed a highly statistically significant reduction in the mean CMT compared with its baseline level (Table 4 and Figs. 4–10).

**Discussion**

The present study revealed that 71.4% of the included patients had diabetes, and 28.6% were diabetic and hypertensive. A significant modifiable risk factor for DRR is hypertension [43]. Higher systolic blood pressure was also a risk factor for DR development in patients with diabetes [44]. This can be attributed to the destruction of the retinal capillaries’ automatic regulatory mechanism by high blood glucose, which causes the capillary endothelial cells to be vulnerable to hypertension injury, resulting in capillary injury, decreased retinal blood flow, and ultimately retinopathy [45].

The present study revealed highly statistically significant improvements in BCVA following each of the three injections compared with the baseline BCVA. Similar findings of improvement in the visual acuity following repeated peribulbar injections of steroids were reported in previous studies [41,46]. The effect of steroids can explain this in reducing muscle and soft tissue edema, decreasing optic nerve compression [41].

The present study revealed that repeated injections were associated with changes in IOP, with highly statistically reductions in the mean IOP, compared with baseline IOP.

<table>
<thead>
<tr>
<th>Table 1: Sociodemographic characteristics of the included cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
</tr>
<tr>
<td>DM</td>
</tr>
<tr>
<td>DM-HTN</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>Mean±SD</td>
</tr>
<tr>
<td>Range</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; HTN, hypertension.

<table>
<thead>
<tr>
<th>Table 2: Comparison of best-corrected visual acuity at 3 weeks following each of the three injections with baseline best-corrected visual acuity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCVA</strong></td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; injection</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; injection</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; injection</td>
</tr>
</tbody>
</table>

BCVA, best-corrected visual acuity.

**Figure 2:** Follow-up of mean values of BCVA. BCVA, best-corrected visual acuity.

**Figure 3:** Follow-up of mean values of IOP. IOP, intraocular pressure.
at 3 weeks following the first and third injections as well as a highly statistically rise in the mean IOP, compared with baseline IOP, at 3 weeks following the second injection. The most frequent adverse effect of triamcinolone ocular injections is increased IOP, but this tends to be transient and controlled in nearly all topical medication cases. Furthermore, the risk of inducing IOP increase is smaller with orbital steroids than subtenon or intravitreal injections [41].
The present study revealed that lower lid edema was noted following TAA injections. This finding comes in line with that published in 2015 in which orbital edema was noted following surgery under peribulbar anesthesia. This finding was attributed to surgical trauma during the administration of the peribulbar block [47]. Trauma during injection and ecchymosis possibly aids the spread of infection; therefore, an aseptic technique with minimal soft tissue trauma is recommended [48]. Skin preparation with povidone-iodine 10% is recommended before administering peribulbar injections and should be left for ~5–10 min to sterilize the surface [49].

The present study revealed that repeated injections of TAA resulted in a significant reduction of CMT. TAA injections were performed as a simple, less-invasive outpatient clinic procedure. Injections of triamcinolone have shown excellent results in treating tissue inflammation-related symptoms, which is predicted.
Ahmed: Peribulbar injection of TAA

Table 3: Comparison of intraocular pressure at 3 weeks following each of the three injections to baseline intraocular pressure

<table>
<thead>
<tr>
<th>IOP</th>
<th>Baseline</th>
<th>Third week</th>
<th>Paired t test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>1st injection</td>
<td>14.66</td>
<td>0.63</td>
<td>14.11</td>
</tr>
<tr>
<td>2nd injection</td>
<td>14.66</td>
<td>0.63</td>
<td>15.94</td>
</tr>
<tr>
<td>3rd injection</td>
<td>14.66</td>
<td>0.63</td>
<td>14.01</td>
</tr>
</tbody>
</table>

IOP, intraocular pressure.

Table 4: Comparison of central macular thickness at 1 month following the third injection with baseline central macular thickness

<table>
<thead>
<tr>
<th></th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre/CMT</td>
<td>265</td>
<td>410</td>
<td>372.95</td>
<td>30.69</td>
</tr>
<tr>
<td>1 month after</td>
<td>217</td>
<td>322</td>
<td>250.87</td>
<td>24.78</td>
</tr>
<tr>
<td>injection/CMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paired t test</td>
<td>40.731</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CMT, central macular thickness.

Figure 10: CT of preinjection and postinjection case no. 7. OCT, optical coherence tomography.

**Table 3: Comparison of intraocular pressure at 3 weeks following each of the three injections to baseline intraocular pressure**

- **1st injection:** Mean 14.66, SD 0.63 vs Mean 14.11, SD 0.47, t 6.171, P 0.001
- **2nd injection:** Mean 14.66, SD 0.63 vs Mean 15.94, SD 0.29, t −14.078, P 0.001
- **3rd injection:** Mean 14.66, SD 0.63 vs Mean 14.01, SD 0.12, t 8.750, P 0.001

**Table 4: Comparison of central macular thickness at 1 month following the third injection with baseline central macular thickness**

- Pre/CMT: Minimum 265, Maximum 410, Mean 372.95, SD 30.69
- 1 month after injection/CMT: Minimum 217, Maximum 322, Mean 250.87, SD 24.78

**References**


