Posterior subtenon versus intravitreal triamcinolone acetonide injection for the treatment of diabetic macular edema

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Background
Diabetic macular edema (DME) is the most common cause of loss of vision in diabetic patients. The role of inflammation in the pathogenesis of DME has been demonstrated. An intravitreal (IVT) injection of triamcinolone acetonide (TA) is a treatment option for DME. The high incidence of side effects, however, limits the routine use of IVT TA.

Aim
The aim of this study was to compare the efficacy and safety of an IVT injection of TA with the less invasive posterior subtenon (PST) injection of TA. We test the hypothesis that both techniques have equal efficacy and safety.

Patients and methods
This is prospective randomized noninferiority trial. Totally, 34 eyes from 30 patients with diffuse center involving DME were randomized in a 1: 1 ratio to receive a TA injection by either method. Baseline evaluation included measurement of best-corrected visual acuity (BCVA) and intraocular pressure (IOP), fundus fluorescein angiography, and optical coherence tomography to measure central macular thickness (CMT) and evaluation of the crystalline lens. After the injection, patients were seen at 1 week, 1 month, 3 months, and 6 months and their BCVA, CMT, IOP, and change in these measures from baseline as well as other complications were recorded. A Mann–Whitney *U*-test was used to compare the mean of quantitative variables and a χ^2-test was used to compare qualitative variables between the two groups.

Results
At baseline, both groups showed no statistically significant difference in age, sex, IOP, BCVA, and CMT. At 1, 3, and 6 months, both groups showed no statistically significant difference in the mean BCVA as well as change in BCVA from baseline. The average reduction of CMT was significantly higher only in the IVT group at 1 month ($P = 0.03$). The mean IOP and average IOP change from baseline were significantly higher in the IVT group than the PST group only at 3 months after injection ($P = 0.02$). Both groups showed a similar incidence of development of cataract ($P = 1.0$, χ^2).

Conclusion
IVT injection of TA is more effective than PST injection in improving CMT – that is, anatomical outcome. This is not, however, translated into a superior visual outcome. The risk of IOP elevation is also higher in IVT than PST injection. PST is a valid alternative to an IVT injection, especially from the functional perspective and when the risk of IOP elevation is significant.

Keywords:
diabetic macular edema, triamcinolone, subtenon

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Introduction

Cystoid macular edema (CME) is a frequent cause of visual impairment. It is a nonspecific pathologic sequel to many ocular insults. It occurs when fluid accumulates in the macular area secondary to disruption of the blood–retinal barrier (BRB) [1]. Diabetic macular edema (DME) is an important subset of CME and is the most common cause of reduced vision in diabetic patients. About one in four diabetic patients can be expected to develop DME in a lifetime and this places the central vision at risk [2]. CME can affect macular retinal functions such as contrast sensitivity. The latter explains visual difficulties experienced by CME patients even if they have good visual acuity [3].

The chronic presence of fluid in between retinal cells can irreversibly disturb retinal architecture and function. This highlights the importance of treating DME in a timely manner [4]. Furthermore, DME can also be associated with intracellular fluid inside Müller cells. This further contributes toward macular retinal dysfunction [5].

The pathogenesis of DME is multifactorial. Abnormal leakage of fluid and macromolecules, for example,

albumin from macular capillaries has been shown by fluorescein angiography (FA) and fluorophotometric studies. This disturbs the osmotic pressure balance between vascular and tissue spaces [6]. Chronic hyperglycemia contributes significantly toward damage of macular capillary endothelium and pericytes by accumulation of free radicals, activation of protein kinase, and accumulation of molecules called advanced glycation end products in the eyes of diabetic patients. These molecules have been linked to the damage observed in the eyes of diabetic patients. Eyes with DME show evidence of low-grade chronic inflammation [7,8]. Vitreous of patients with DME shows elevated levels of different inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β, angiogenic molecules, for example, vascular endothelial growth factor (VEGF) and platelet-derived growth factor and adhesion molecules such as intercellular adhesion molecule1. Levels of anti-inflammatory molecules such as pigment epithelium-derived factor are concurrently reduced. The main sources of inflammatory mediators are activated microglia, which initiates the inflammatory response by the release of tumor necrosis factor-α. This local inflammatory response recruits circulating leukocytes, further contributing toward the production of these factors. Interestingly, plasma levels of these mediators do not correlate with local high levels, meaning that the inflammatory response is locally driven. Therefore, a reasonable strategy in the treatment of DME is to reduce the levels of different molecules associated with tissue damage observed in diabetic retinopathy [9].

Triamcinolone acetonide (TA) is a corticosteroid used most commonly as a depot crystalline suspension. A proposed mechanism of anti-inflammatory action is induction of lipocortin synthesis, which inhibits phospholipase 2 enzyme [10]. At the BRB, corticosteroids act to maintain tight junction integrity by promoting tight junction protein expression and translocation to the endothelial/epithelial cell border [11] and by protecting against oxidative stress-induced disruption of tight junction proteins in retinal pigment epithelial cells [12]. In addition to reducing retinal vascular permeability, corticosteroids also promote retinal fluid clearance through their effects on transcellular aquaporin-4 and potassium channels, the two main channels controlling retinal fluid movement on retinal Müller cells [13].

Although anti-VEGF therapy has become first-line therapy in DME patients, especially those who are phakic, intravitreal (IVT) TA is sometimes used when access to anti VEGF agents is difficult due to cost, even in phakic patients [14].

In ophthalmic practice, TA is used as injections at a dose of 4–40 mg. Schindler *et al*.[15] showed that the rate of TA clearance following an IVT injection of 0.5 mg TA into rabbit eyes depends on the presence or absence of the vitreous or the crystalline lens. Normal eyes showed a longer duration of TA retention inside the eyes (41 days) than vitrectomized eyes and eyes with previous lensectomy. Vitreous levels of TA after posterior subtenon (PST) injections are variable. Kovacs *et al*. measured the vitreous of TA after a PST injection of TA. The vitreous concentration of TA reached a maximum at 1 day after injection then plateaued and reached a minimum 56 days after injection [15]. A similar study by Shen *et al*. [16] showed a fast distribution phase of TA in the aqueous and vitreous during the first 24 h after a PST injection of 40 mg TA. The vitreous concentration was 70–98 fold higher than the plasma concentration [16]. Moreover, clinical studies by Toda *et al*. [17] and Kaderli *et al*. [18] showed that systemically absorbed TA after PST did not lead to hormonal, metabolic, or blood pressure changes in diabetic patients [19-21].

Many studies in the last decade compared IVT and PST injections in DME patients. However, the heterogeneity of the results and the study designs makes a comparative assessment tenuous. Bonini-Filho *et al*. [22] and Cardillo *et al*. [23] showed that IVT leads to a more significant improvement in central macular thickness (CMT) and best-corrected visual acuity (BCVA) than PST at 1 and 3 months. Later, other studies by Choi *et al*. [24], Cellini *et al*. [25], Qamar *et al*. [26], and Luo *et al*. [27] showed no significant difference in BCVA and CMT between the two injection routes.

Patients and methods

This is a prospective randomized noninferiority trial that compares the efficacy and safety of two routes of TA injection (PST and IVT) in patients with DME.

The study followed the tenets of the Declaration of Helsinki. Approval of the ethics committee of the Faculty of Medicine, Assiut University, was obtained before patient enrollment. All patients signed a written informed consent before undergoing any study procedure.

Inclusion criteria included a diffuse center involving DME in one or both eyes, age 18 years or older, the ability to understand and sign the informed consent, and be able to comply with the study schedule. Exclusion criteria were age younger than 18 years, allergy to TA, media opacity interfering with the performance

of optical coherence tomography (OCT) or clinical evaluation of the vitreous and retina, previous viral retinitis or uveitis, toxoplasmosis scar, history of marked steroid induced intraocular pressure (IOP) elevation, or ocular hypertension in the study eye (>23 mmHg without treatment or >21 mmHg with treatment). Patients with active retinal or iris neovascularization and patients who received a local injection treatment for DME (either steroids or anti-VEGF) within 3 months before study enrollment were also excluded.

Outcome measures

The primary outcome measures are the mean BCVA of study eyes [converted into log magnification requirement (MAR) units from Snellen's visual acuity] at 1-, 3-, and 6-month time points and the mean change in BCVA at those times from baseline.

Secondary outcome measures included the mean change in the CMT as measured by OCT (central subfield 1 mm thickness) and the percentage of eyes that developed complications related to either injection technique.

Study procedures

Participants were recruited from the retina outpatient clinic, Ophthalmology Department, Assiut University Hospital, between January 2011 and August 2014 and were assigned randomly, in a 1: 1 ratio, to either a single IVT injection of 4 mg/0.1 ml TA or a single parametric static timing analysis (PSTA) 40 mg/1 ml on day 1 of the study; patients were assessed according to the schedule presented in Table 1.

Baseline evaluation

- Medical/ocular/surgical history and demographics.
- BCVA was measured by the Snellen chart through best correction

Table 1 Scheme of patient evaluation

Assessments	Day 1	Month 1	Month 3	Month 6
Timing/interval	1	±1 week	±1 week	±1 week
Medical/ophthalmic history	X	–	–	–
Demographics	X	–	–	–
Inclusion/exclusion criteria	X	–	–	–
Randomization	X	–	–	–
Ophthalmic examination[a]	X	X	X	X
OCT	X	X	X	X
IVT or PST TA injection	X	–	–	–
Concomitant medications	X	X	X	X
Adverse events	X	X	X	X

IVT, intravitreal; PST, posterior subtenon; OCT, optical coherence tomography; TA, triamcinolone acetonide; X, corresponding visit date. [a]Ophthalmic examination includes best-corrected visual acuity, intraocular pressure, dilated ophthalmoscopy, and indirect ophthalmoscopy with anterior and posterior slit-lamp examinations.

- Slit-lamp examination: examination of the anterior segment was performed at each visit including assessment of the cornea, angle, lens (presence of opacities and their grading according to the Lens Opacities Classification System II system of lens opacity grading), presence of an intraocular lens, or aphakia
- IOP: after a topical anesthetic was administered, IOP was measured by applanation tonometry
- Dilated indirect ophthalmoscopy: this was performed on all visits including visualization of the macula, optic nerve, retinal vessels, and peripheral retina
- Other treatments: patients were asked questions about the other medications and treatment that they had received for their condition and other concomitant medications, vitamins, and supplements that they had received during each visit
- Adverse events: patients were asked questions to determine whether they had any changes in health or side effects during the study at each study visit
- Color fundus photography and FA: the clinical grading of diabetic retinopathy was documented with color fundus photography and retinal angiography for all patients at baseline using a Topcon fundus camera. Five milliliter of a 10% sodium fluorescein solution was injected and the early, middle, and late phase images were captured up to 6 min to document leakage from retinal veins, capillaries, microaneurysms, abnormal new vessels, and optic disc as well as pooling of the dye in the center of the macula. Angiography was used for the determination of the stage of diabetic retinopathy and retinal capillary perfusion status and to exclude the presence of abnormal new blood vessels
- OCT: macular thickness was measured using either time domain OCT (Stratus 3 OCT, Carl Zeiss meditec, Heidelberg, Germany) or spectral domain OCT (RTvue, Optovue Inc., Fremont, CA, USA). For each patient, initial evaluation and follow-up was performed using the same device. Instrument software was used to calculate retinal thickness and macular volume. We used the central 1 mm of the OCT macular map for analysis.

Technique of parametric static timing analysis

- Before injection, topical anesthesia was administered at the injection site (superotemporal fornix): either benoxinate or subconjunctival lidocaine 1%
- Two to three drops of 5% Betadine were administered topically in the upper fornix. The eyelids were scrubbed with cotton-tipped applicators soaked in 5% Betadine

- TA was drawn up into a 3 ml syringe using a 20 G nonfiltered needle. The needle was switched to a 25 G 5/8 inch sterile needle. Air bubbles and excess volume were expelled to a final volume of 1 ml
- The patient was asked to look down and to the opposite side of the injected eye and 1 ml (40 mg) of TA was injected into the PST space through the superotemporal fornix.
- The eye was rinsed with eye wash or saline
- Indirect ophthalmoscopy was performed to verify adequate central retinal artery perfusion, absence of any other complications, and to verify correct placement of the study drug
- The IOP was measured within 10 min of injection.

Technique of intravitreal injection of triamcinolone acetonide

- Before the injection, topical anesthesia was administered at the injection site: either benoxinate or subconjunctival lidocaine 1%
- Administration of 2–3 drops of 5% Betadine topically in the lower fornix was performed. The eyelids were scrubbed with cotton-tipped applicators soaked in 5% Betadine
- TA vial was drawn up into a sterile syringe using a non-filtered 20 gauge needle. Needles were changed to sterile 30 gauge needle, and then air bubbles and excess volume were expelled to 0.1 ml preserved TA (Kenakort, Bristol-Myer Squibb, New York, USA).
- A sterile lid speculum was placed
- The patients were asked to look up and the injection site was marked 3.5–4.0 mm posterior to the limbus in the inferior quadrant with callipers
- Additional betadine was applied to the injection site and allowed to dry for 30 s before the injection
- 0.1 ml of TA was injected through the pars plana using a sterile 30 G needle
- The eye was rinsed with eye wash or saline
- Indirect ophthalmoscopy was performed to verify adequate central retinal artery perfusion and absence of any other complications, and to verify correct placement of the study drug
- IOP was measured within 10 min of injection.

Subsequent evaluation

After receiving their injections, all patients were scheduled to have at least three follow-up visits (2 weeks–1 month, 3 months, and 6 months after injection).

At each visit, every patient underwent a clinical evaluation similar to baseline and OCT for the assessment of CMT. FA was performed or repeated when clinically indicated and at the discretion of the study investigators on the basis of the overall clinical findings and disease course.

Statistical analysis

Data are shown as *n* (%) for categorical variables or as mean and SD for continuous variables. The *P* value was set at less than 0.05 to indicate statistical significance. The changes in logMAR visual acuity, CMT, and IOP were compared using the Wilcoxon's signed rank test. The differences between the two groups in logMAR visual acuity, CMT, IOP, and other continuous variables were compared using the Mann–Whitney *U*-test. The χ^2-test with used to compare the categorical variables between the two groups. The SPSS program was used to carry out an analysis (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics

Totally, 34 eyes from 30 patients with diabetic retinopathy and no active new vessels and center involving DME were included in the study. The demographic and clinical characteristics of the patients including age, sex, duration, and type of diabetes mellitus (Table 2).

Visual acuity

The mean ± SD visual acuity before TA injection and at 1 month, 3 months, and 6 months thereafter in both groups and the corresponding *P* values are shown in Table 3.

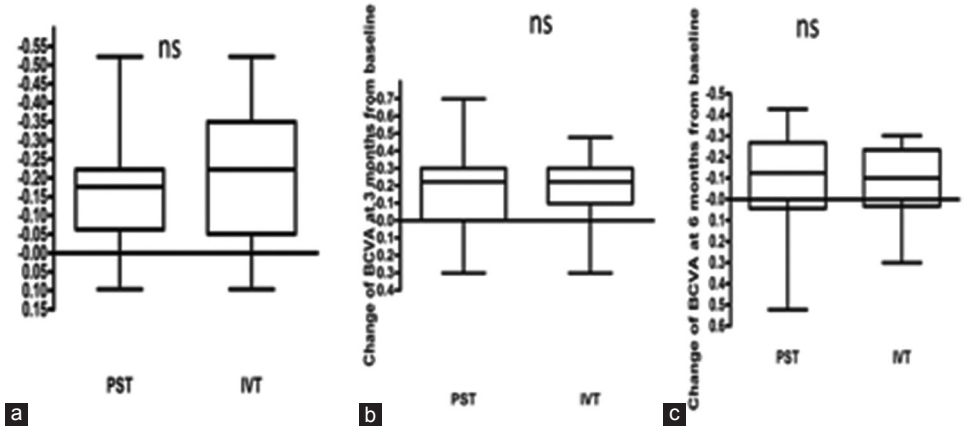
Table 3 shows the logMAR BCVA of both study groups at different time points and corresponding *P* values.

Also, the average change in logMAR BCVA in the eyes studied was calculated for both groups at 1, 3, and 6 months (Fig. 1).

Central macular thickness

The average change in CMT (Δ) from baseline measurements was calculated for both groups at 1 month, 3 months, and 6 months. We did not compare the mean directly because CMT values were obtained using different OCT machines with different protocols for CMT calculation. However, we used the same OCT for each single patient at different study points to validate calculation and use of the change in CMT achieved by every eye as an outcome measure (Tables 4 and 5).

Figure 1



Bar graphs showing the change in log magnification requirement best-corrected visual acuity from baseline at 1 month (a), 3 months (b), and 6 months (c) after injection. BCVA, best-corrected visual acuity; IVT, intravitreal; ns, difference is statistically insignificant between both groups; PST, posterior subtenon.

Table 2 Baseline characteristics of the study participants

Variables	PST group	IVT group	*P*
Number of eyes (total=34)	17	17	
Age (mean±SD) (years)	56.35±2.9	52.53±1.8	0.65 (Mann-Whitney)
Eyes by patient's; sex (male : female)	8 : 9	7 : 10	0.73 (χ^2)
Eyes by DM type (type 2 : type 1)	16 : 1	15 : 2	0.5 (χ^2)
Duration of DM (mean±SD) (years)	11.41±4.7	13.58±6.25	0.76 (χ^2)
Right : left eyes	8 : 9	8 : 9	1.0 (χ^2)

IVT, intravitreal; PST, posterior subtenon; DM, diabetes mellitus.

Table 3 Log magnification requirement best-corrected visual acuity of both study groups at different time points and the corresponding *P* values

	IVTA (*n*=17)		PSTA (*n*=17)		*P* between the two groups (Mann-Whitney)
	Mean±SD	*P* (Wilcoxon's signed rank)	Mean±SD	*P* (Wilcoxon's signed rank)	
Baseline	0.865±0.389	–	0.929±0.224	–	0.704
1 month	0.642±0.357	0.0051	0.759±0.214	0.025	0.34
3 months	0.672±0.396	0.0906	0.768±0.296	0.194	0.417
6 months	0.785±0.397	0.0002	0.855±0.338	0.0002	0.535

IVTA, intravitreal triamcinolone acetonide; PSTA, parametric static timing analysis.

Table 4 Mean change in central macular thickness from baseline in both study groups

Average change in CMT from baseline	IVT	PST	*P* (Mann-Whitney)
At 1 month	−128.88	−64.47	0.03
At 3 months	−124.24	−74.88	0.3
At 6 months	−50.1	−75.88	0.2

CMT, central macular thickness; IVT, intravitreal; PST, posterior subtenon.

Intraocular pressure

Also, the change in IOP from baseline at different study time points in both study groups is shown in Fig. 2.

Another way of examining the risk of IOP elevation is to show the percentage of eyes that developed an increase in IOP by 5 mmHg from the baseline value (which is reported to be a significant value) at different visits and to compare this risk in both study groups as shown in Table 6.

Although many eyes showed an increase in IOP from baseline, only one eye in each group showed an increase in IOP above 21 mmHg.

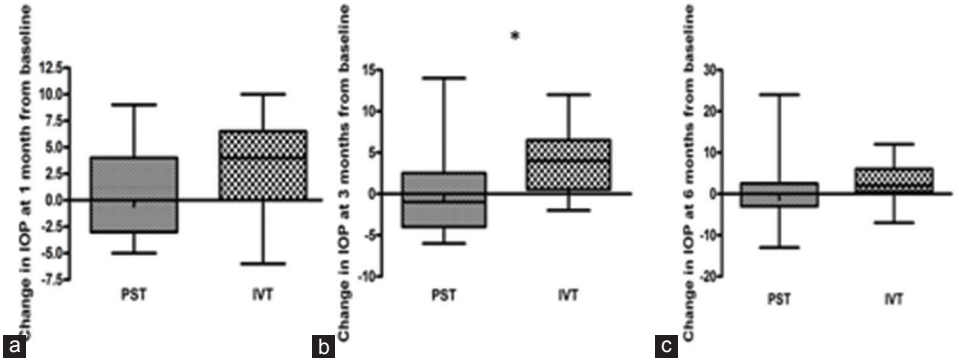
It is noteworthy that the eye in the PST group did not respond to medical treatment and was restored to normal IOP by excision of TA particles from the subconjunctival space. This approach has been described previously in the literature [19,20].

The eye in the IVT group that showed elevation to above-normal IOP required only medical treatment to restore normal IOP.

Crystalline lens changes

In patients receiving intravitreal triamcinolone acetonide (IVTA), 11 (64.7%) eyes were phakic, whereas six (35.3%) eyes were pseudophakic. In the

Figure 2



Bar graphs showing the change in intraocular pressure from baseline at 1 month (a), 3 months (b), and 6 months (c) after injection. The asterisk in (b) means that the difference is statistically significant between both groups. IOP, intraocular pressure; IVT, intravitreal; PST, posterior subtenon.

Table 5 Mean intraocular pressure in both study groups at different study time points with the corresponding *P* values

	IVTA (*n*=17)		PSTA (*n*=17)		*P* between the two groups (Mann-Whitney)
	Mean±SD	*P* (Wilcoxon's signed rank)	Mean±SD	*P* (Wilcoxon's signed rank)	
Baseline	14.35±2.66		15.53±2.9		0.5
1 month	17.17±5.24	0.026	16.29±4.3	0.626	0.59
3 months	18.71±4.51	0.0004	15.71±4.51	0.746	0.02
6 months	16.88 ± 3.59	0.0151	16±6.46	0.946	0.08

IVTA, intravitreal triamcinolone acetonide; PSTA, parametric static timing analysis.

Table 6 Eyes that showed elevation in intraocular pressure by 5 mmHg or more from the baseline values

Groups	At 1 month (*n* (%))	At 3 months (*n* (%))	At 6 months (*n* (%))	At any visit (*n* (%))
PST (*n*=17)	4 (24)	2 (12)	1 (6)	4 (24)
IVT (*n*=17)	6 (35)	8 (47)	5 (29)	10 (62)
P value (χ^2)	0.4	0.02	0.07	0.02

IVT, intravitreal; PST, posterior subtenon.

phakic group, two (18.8%) eyes showed progression or development of posterior subcapsular cataract by the end of the study (6 months after injection) and one (9.1%) eye required cataract extraction. In patients receiving PSTA, 11 (64.7%) eyes were phakic and six (35.3%) eyes were pseudophakic. In the phakic group, two (18.8%) eyes showed progression or development of posterior subcapsular cataract by the end of the study, whereas one (9.1%) eye required cataract extraction. χ^2 analysis showed that the development or the progression of cataract was independent of the method of triamcinolone injection (P = 1.0).

Other complications

No other side effects reported in the literature for both injection techniques were found in other cohorts – for example, retinal tears, detachment, vitreous hemorrhage, optic nerve damage, ptosis, and ocular perforation.

Discussion

DME continues to have increasing impact from the public health and economic perspectives. Globally, 422 million adults were living with diabetes in 2014 compared with 108 million in 1980. Ocular complications from diabetes place a huge economic burden on national and global health care systems that include direct medical costs (e.g. medications, investigations, rehabilitation, and hospital admissions) and indirect costs because of loss of productivity and negative impact on the national gross domestic product [21]. Different treatment modalities are described in the literature for DME. These include observation, laser photocoagulation, systemic and local pharmacological therapy, and surgery. Corticosteroids have been used for decades in a broad range of indications to suppress inflammation in ophthalmologic conditions. TA, a corticosteroid suspension, has been shown to reduce the breakdown of the BRB after an IVT injection. This, in addition to its anti-inflammatory and antiangiogenic properties, has led to its common use in the treatment of DME. However, the potential retinal toxicity of the drug carrier or preservative, the invasive nature of an IVT injection, the risk of injection technique-related complications such as retinal breaks, detachment and vitreous hemorrhage, and the risk of endophthalmitis are the main drawbacks of this treatment technique. The need for repeated injections further increases the likelihood of these complications and adds a burden to patients.

Periocular steroids have effectively been used for a long time in the treatment of uveitis. A growing body of research in the last decade has suggested that the proper technique of a periocular injection of TA can deliver an appreciable amount of TA adjacent to the macula and might be an equally effective and perhaps a safer alternative to IVT administration. In our study, we tested for potential differences in efficacy and side effects between IVT and posterior subtenon routes of delivering TA in patients with DME.

This study shows that both injection techniques led to a significant improvement in logMAR BCVA from the baseline. The mean logMAR BCVA was not statistically significant between both treatment groups. Also, the mean change in BCVA from baseline was not significantly different between the two groups at 1, 3, and 6 months.

However, IVT leads to a more significant reduction of CMT compared with baseline at 1 month after injection. After the first month, IVT is still associated with a greater average reduction of CMT, but the difference is no longer statistically significant.

Evaluation of the safety of both techniques showed that the mean IOP was higher in the IVT group at 1, 3, and 6 months after treatment, although this was only statistically significant at 3 months after injection. Also, the IVT group showed a significantly higher risk for elevation of IOP by 5 mmHg or more from baseline at 3 and 6 months.

The risk of cataract development and the need for cataract surgery were equal between the two treatment groups.

Other serious complications namely retinal tears, detachment, endophthalmitis, vitreous hemorrhage, and ocular perforation (with PST) were not encountered. This may be because of the relatively low number of patients, which did not result in enough power to detect these relatively uncommon events.

Many previous studies have examined the differences between PSTA and IVTA in DME patients [22–27]. The results of these studies are inconsistent.

Some studies, for example, Cardillo *et al.* [23] and Bonini-Filho *et al.* [22], which compared both techniques in patients with DME, showed a superior effect of IVT over PST by showing lower mean for CMT and BCVA at different study time points. However, the injection technique used in their study for the PST injection group entailed creating a conjunctival incision and injecting using a blunt cannula. This was associated with reflux of some TA, leading to suboptimal dosing.

In contrast, other studies showed that both injection techniques are equivalent as they showed similar mean BCVA and CMT over the study period [24–27]. Different designs and outcome measures, however, across different trials make it difficult to compare them directly. Some studies, for example, Cellini *et al.* [25] treated eyes with laser photocoagulation immediately before injection, whereas other studies excluded patients with previous laser photocoagulation. Moreover, some studies did not exclude patients with recent injections of steroids or anti-VEGF before inclusion in their protocol, which could have affected the results in some patients if they had been treated within a short time before enrollment.

Takata *et al.* [28] compared both injection techniques in conjunction with phacoemulsification in patients with cataract and refractory DME. However, the surgical trauma can exacerbate CME in some patients even if their surgery was uneventful and could unpredictably confound the results [28]. In contrast, other studies excluded patients who had undergone recent surgery.

Study outcome measures were also analyzed in different ways. Some studies compared the mean values of BCVA and CMT directly between treatment groups, whereas other studies compared the difference in BCVA and CMT from baseline values at different study time points between treatment groups.

All the above differences in the study design together with variable results explain the lack of consensus among these trials. Qi *et al.* [29] carried out a meta-analysis of studies that compared both techniques in DME patients to reach a general conclusion. They showed that IVTA leads to a more significant improvement in logMAR BCVA from baseline than PSTA in VA at 1 and 3 months. At 6 months, the difference was not significant. Improvements from baseline in CMT were more significant with IVTA than PSTA at 1 and 3 months, but not at 6 months. Evaluation of the effect of both techniques on IOP was described as a change of 5 mmHg or more and showed that at 3 months, patients with IVT developed a more significant elevation in IOP from baseline compared with the PST group [29].

However, meta-analyses are not substitutes for randomized trials.

This study is, to our knowledge, the first study to examine differences between the two TA injection protocols in DME, the main cause of CME, in Egypt. We excluded patients who had recently received steroid or anti-VEGF injections to minimize the confounding effects of these treatments, and yet, we did not exclude

eyes treated with previous laser treatment to simulate this common real-life scenario where cases with diffuse DME refractory to laser treatment are treated with pharmacologic treatment. We described the primary outcome measure (BCVA) in two different ways, that is, showing mean at different time points and changes from baseline, given that we had a relatively low number of participants in each group that may have resulted in a low power to detect changes if we had only compared the mean.

However, the secondary outcome measure of CMT could only be described as a change from baseline because the calculation of mean for values obtained by different acquisition protocols and devices is not appropriate.

Also, when we reported the effect of injections on IOP, we presented the results as mean and also as the risk of elevation by 5 mmHg or more from baseline, which is described as a clinically significant value by other investigators.

Our results show an early superior effect of IVT injections, especially on CMT improvement, consistent with the conclusion of the meta-analysis by Qi *et al.* [29]. The effect of both techniques on BCVA, however, was equal. This dissociation between improvements in CMT and BCVA was described previously in studies and is because of the fact that macular thickness is just one of the factors that determine VA in DME patients. Among other factors are baseline damage to photoreceptors, capillary loss at the fovea, and systemic factors [30,31].

Conclusion

IVT injection of TA leads to potentially greater reduction of CMT and improvement in visual acuity because of DME than PST injection, but these differences may be low enough to be clinically significant. Moreover, IVTA is associated with a higher risk of IOP elevation at certain time points. The peak increase in IOP occurs between 1 and 3 months after injection. Both techniques are equally associated with the development or progression of cataract, which may be visually significant within the short follow-up period of this study. PST injection of TA is a valid alternative to IVT in terms of functional outcome with a lower risk of IOP elevation. However, both techniques should be used with the appropriate discussion for cataract progression in phakic eyes and for the temporary nature of effect. One limitation to this study is that it may have been inadequately powered to test the noninferiority of one injection technique over another. However, the differences observed were thus more likely to be true. Also, the follow-up period was short. This was mainly a concern for the determination of complication rates such as cataracts, which may take additional time to develop. Also, time to repeat injections, and thus, duration of treatment efficacy, could not be assessed adequately.

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Conflicts of interest
There are no conflicts of interest.

References

1 Rotsos TG, Moschos MM. Cystoid macular edema Clin Ophthalmol 2008; 2:919–930.

2 Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes Ophthalmology 2009; 116:497–503.

3 Ibanez HE, Lesher MP, Singerman LJ, Rice TA, Keep GF. Prospective evaluation of the effect of pseudophakic cystoid macula edema on contrast sensitivity Arch Ophthalmol 1993; 111:1635–1639.

4 Guex-Crosier Y. The pathogenesis and clinical presentation of macular edema in inflammatory diseases. Doc Ophthalmol 1999; 97:297–309.

5 Ascaso FJ, Huerva V, Grzybowski A. The role of inflammation in the pathogenesis of macular edema secondary to retinal vascular diseases. Mediators Inflamm 2014; 2014:432685.

6 Stefansson E. Diabetic macular edema. Saudi J Ophthalmol 2009; 23:143–148.

7 Kim W, Hudson BI, Moser B, Guo J, Rong LL, Lu Y, *et al.* Receptor for advanced glycation end products and its ligands: a journey from the complications of diabetes to its pathogenesis. Ann N Y Acad Sci 2005; 1043:553–561.

8 Ramasamy R, Vannucci SJ, Yan SS, Herold K, Yan SF, Schmidt AM. Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. Glycobiology 2005; 15:16r–28r.

9 Dugel PU, Bandello F, Loewenstein A. Dexamethasone intravitreal implant in the treatment of diabetic macular edema. Clin Ophthalmol 2015; 9:1321–1335.

10 Jermak CM, Dellacroce JT, Heffez J, Peyman GA. Triamcinolone acetonide in ocular therapeutics. Surv Ophthalmol 2007; 52:503–522.

11 Aveleira CA, Lin CM, Abcouwer SF, Ambrosio AF, Antonetti DA. TNF-alpha signals through PKCzeta/NF-kappaB to alter the tight junction complex and increase retinal endothelial cell permeability. Diabetes 2010; 59:2872–2882.

12 Miura Y, Roider J. Triamcinolone acetonide prevents oxidative stress-induced tight junction disruption of retinal pigment epithelial cells. Graefes Arch Clin Exp Ophthalmol 2009; 247:641–649.

13 Zhao M, Bousquet E, Valamanesh F, Farman N, Jeanny JC, Jaisser F, Behar-Cohen FF. Differential regulations of AQP4 and Kir4.1 by triamcinolone acetonide and dexamethasone in the healthy and inflamed retina. Invest Ophthalmol Vis Sci 2011; 52:6340–6347.

14 Ciulla TA. Corticosteroids for diabetic macular edema. Rev Ophthalmol 2015;2:50–54

15 Schindler RH, ChandlerD, Thresher R, Machemer R. The clearance of intravitreal triamcinolone acetonide. Am J Ophthalmol 1982; 93:415–417.

16 Shen, L, You Y, Sun S, Chen Y, Qu J, Cheng L. Intraocular and systemic pharmacokinetics of triamcinolone acetonide after a single 40-mg posterior subtenon application. Ophthalmology 2010; 117:2365–2371.

17 Toda J, Fukushima H, Kato S. Systemic complications of posterior subtenon injection of triamcinolone acetonide in type 2 diabetes patients. Diabetes Res Clin Pract 2009; 84:e38–e40.

18 Kaderli B, Kivanc SA, Inan UU, Ersoy C, Yucel AA, Yilmaz S, Avci R. Effect of posterior subtenon injection of 40 mg of

triamcinolone acetonide on glycemic control and serum cortisol and adrenocorticotropic hormone in diabetic patients. Eur Rev Med Pharmacol Sci 2014; 18:2609–2614.

19 Okka, M, Bozkurt B, Kerimoglu H, Ozturk BT, Gunduz K, Yilmaz M, Okudan S. Control of steroid-induced glaucoma with surgical excision of sub-Tenon triamcinolone acetonide deposits: a clinical and biochemical approach. Can J Ophthalmol 2010; 45:621–626.

20 Chan LW, Hsu WC, Hsieh YT. Subtenon triamcinolone acetonide removal for uncontrolled ocular hypertension after posterior subtenon injection of triamcinolone acetonide. J Glaucoma 2016; 25:e268–e272.

21 WHO. Global report on diabetes. 2016; Available at: *http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf*. [Last accessed on 2016 Jun 21].

22 Bonini-Filho MA, Jorge R, Barbosa JC, Calucci D, Cardillo JA, Costa RA. Intravitreal injection versus sub-Tenon's infusion of triamcinolone acetonide for refractory diabetic macular edema: a randomized clinical trial. Invest Ophthalmol Vis Sci 2005; 46:3845–3849.

23 Cardillo JA, Melo LA Jr, Costa RA, Skaf M, Belfort R Jr, Souza-Filho AA, *et al*. Comparison of intravitreal versus posterior sub-Tenon's capsule injection of triamcinolone acetonide for diffuse diabetic macular edema. Ophthalmology 2005; 112:1557–1563.

24 Choi YJ, Oh IK, Oh JR, Huh K. Intravitreal versus posterior subtenon injection of triamcinolone acetonide for diabetic macular edema. Korean J Ophthalmol 2006; 20:205–209.

25 Cellini M, Pazzaglia A, Zamparini E, Leonetti P, Campos EC. Intravitreal vs. subtenon triamcinolone acetonide for the treatment of diabetic cystoid macular edema. BMC Ophthalmol 2008; 8:5.

26 Qamar RM, Saleem MI, Saleem MF. Comparison of the efficacy between an intravitreal and a posterior subtenon injection of triamcinolone acetonide for the treatment of diffuse diabetic macular edema. Eurasian J Med 2013; 45:185–190.

27 Luo D, Zhu B, Zheng Z, Zhou H, Sun X, Xu X. Subtenon vs intravitreal triamcinolone injection in diabetic macular edema, a prospective study in Chinese population. Pak J Med Sci 2014; 30:749–754.

28 Takata C, Messias A, Folgosa MS, Lucena LR, Lucena DR, Scott IU, Jorge R. Intravitreal injection versus subtenon infusion of triamcinolone acetonide during cataract surgery in patients with refractory diabetic macular edema. Retina 2010; 30:562–569.

29 Qi HP, Bi S, Wei SQ, Cui H, Zhao JB. Intravitreal versus subtenon triamcinolone acetonide injection for diabetic macular edema: a systematic review and meta-analysis. Curr Eye Res 2012; 37:1136–1147.

30 Larsson J, Zhu M, Sutter F, Gillies MC. Relation between reduction of foveal thickness and visual acuity in diabetic macular edema treated with intravitreal triamcinolone. Am J Ophthalmol 2005; 139:802–806.

31 Browning DJ, Glassman AR, Aiello LP, Beck RW, Brown DM, Fong DS, *et al*. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. Ophthalmology 2007;114:525–536.