Echography-Verified Retrobulbar Triamcinolone Injection in the Treatment of Uveitis

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Abstract

The Purpose: The aim of the present study is to assess the efficacy of sonography-verified retrobulbar injection (RBI) of Triamcinolone acetonide (TAA) in the treatment of uveitis and the management of persistent and refractory uveitic macular edema (ME).

Subjects and Methods: In this prospective study 26 eyes of 20 patients were included. Patients underwent RBI of TAA for intraocular inflammation and/or cystoid macular edema (CME) caused by chronic non-infective anterior, intermediate, posterior or pan uveitis. Patients with ocular hypertension or glaucoma were excluded from the study. The etiology of uveitis, Snellen visual acuity (VA) in decimal fraction, application intraocular pressure (IOP) were recorded, anterior segment findings were evaluated by slit lamp and posterior segment findings by ophthalmoscopy, slit lamp biomicroscopy or ultrasonography. Fundus fluorescein angiography (FFA) was performed whenever the ocular media allowed. The primary outcome measures were: Improvement of uveitis (inflammatory activity), angiographic appearance of CME at 6 months of follow-up and change in VA.

Results: There were 9 cases of Behcet's disease (45%), 4 cases of VKH (20%), 2 cases of intermediate uveitis (10%) and 5 cases of idiopathic uveitis (25%). There was a statistically significant improvement of visual acuity (VA) after injection in all patients with a $p$-value of 0.045. Complete resolution of anterior uveitis occurred in 6 eyes in the 1st week, 4 eyes in the 2nd week and 2 eyes in the 1st month. One case (2 eyes) failed to achieve complete resolution at the end of follow-up (7%). Regarding vitreous inflammatory activity, complete resolution occurred in 6 eyes in the 1st week, 4 eyes in the 2nd week, 3 eyes in the 1st month, 4 eyes in the 2nd month and 5 eyes in the 3rd month. 4 eyes failed to achieve complete resolution at the end of follow-up (14%). Although the IOP tended to be temporarily higher after injection, the increase in IOP was not statistically significant.

Conclusion: Sonographic confirmation of the paramacular location of depot steroids after RBI can potentially raise the therapeutic success in refractory uveitis and CME; although the effect may be transient. The procedure is relatively safe. Week 2 is the most probable time for the development of a high IOP. The most significant therapeutic effect of retrobulbarly-injected TAA on inflammatory activity appears at 4 weeks; however, its effect in terms of patient satisfaction and reduction in CME is maintained for as long as 4 months.

Key Words: Uveitis – Echography – Retrobulbar – Triamcinolone.

Introduction

THE average annual incidence of uveitis has been reported as approximately 14-17 per 100 000, rising to a peak in the working age (20-50 years) group [1]. Uveitis is the fifth commonest cause of visual loss in the developed world, accounting for about 10-15% of the cases of total blindness and up to 20% of legal blindness (World Health Authority definition). Macular pathology, as a sequel of intraocular inflammation, is responsible for a significant amount of the visual morbidity associated with uveitis [2]. Uveitic macular insult includes choroidal neovascularization (CNV), epiretinal membrane formation, macular hole, foveal atrophy, and ME [3]. Macular edema affects 26% of uveitic patients [1] and may be diffuse or cystoids (CME). Any type of uveitis can be complicated by CME, however, CME is more common with intermediate uveitis, posterior uveitis and panuveitis [4]. ME has been described as a common cause of visual loss in specific uveitic syndromes including Behçet’s disease, sarcoid uveitis and intermediate uveitis [5]. The pathogenic mechanisms underlying uveitic CME are multi-factorial and involve disruption of the inner blood-retinal-barrier (BRB) secondary to inflammation and vitreous traction, choroidal inflammation and retinal pigment epithelial (RPE) dysfunction [4].

Peribulbar injections of long acting corticosteroids have been used with proven effectiveness in conditions with a break down in the BRB, such as intermediate uveitis and CME. Depot corticosteroid injection has been tried in CME secondary to uveitis [6] or intraocular surgeries, as well as diabetic ME. The use Triamcinolone acetonide, a
corticosteroid suspension, for the treatment of CME and/or vitritis in chronic anterior, intermediate, posterior and pan uveitis is well established [7]. This targeted approach to therapy is used to avoid initiation of or increase in dose of systemic steroids whenever the activity of the disease requires an increase in medication. Owing to the maximal local concentration of the depot steroid after periocular injection, its effect is prolonged with minimal systemic side effects [6]. Several methods and routes of injection have been advocated including subconjunctival, anterior and posterior sub-tenon (PST), trans-septal, intravitreal, orbital floor and retrobulbar injections (RBI) [6,7,9].

The therapeutic response manifested by improvement in macular function may be related to the proximity of the corticosteroid to the macular area. Drug localization to the macula is important in obtaining maximum therapeutic effect. Lack of therapeutic response to repository corticosteroids may be because of placement at a site relatively far from the target zone [8]. Based on this fact the efficacy of intravitreal injection of steroids has been proposed to be higher than other routes for the treatment of macular edema [10]. Nevertheless, the intravitreal route is more invasive, needs special settings to be performed and is associated with a higher risk of potential complications [11]. Studies have reported the incidence of endophthalmitis to be between 0.5% and 0.87% after intravitreal TAA injection [12].

Growing evidence is indicating the usefulness of the transscleral pathway in delivering drugs to the retina [13]. However, one case series has echographically demonstrated that corticosteroid was deposited over the macula in only 11 of 24 cases injected with subtenon TAA [8]. This therapeutic failure may be the main limitation of the peribulbar route. Weijtens et al. [14] reported that the intravitreal concentration of the steroid increased after its peribulbar injection. Recent studies have shown that trans-tenon's retrobulbar infusion and posterior subtenon injection of the corticosteroids are effective in treating posterior inflammation and ME that is associated with uveitis [15]. Because of localization of drug in the macula, posterior subtenon and RBI are equally effective in the treatment of CME [11]. Freeman et al., have shown by ultrasound B-scan that the temporal placement technique results in more accurate placement of steroids near the macula [8].

Based on these reports, a hypothesis can be postulated that the retrobulbarly-injected TAA is located on macular area in most cases and that its therapeutic effect on the retina and choroid may depend on whether or not it has been localized to the macular area. This can be verified using B-scan ultrasonography.

The aim of the present study is to assess the efficacy of sonography-verified RBI of TAA in the treatment of uveitis and the management of persistent and refractory uveitic ME (diffuse or cystoid).

**Patients and Methods**

This is a prospective study that includes 26 eyes of 20 patients undergoing retrobulbar steroid injection for intraocular inflammation and/or CME caused by chronic non-infective anterior, intermediate, posterior or pan uveitis. This study was done at Kaser El Aini Ophthalmology department in the period between March 1, 2005 and February 28, 2008.

The main inclusion criteria were the presence of visually significant CME or vitritis that were resistant to topical and systemic anti-inflammatory treatment or were clinically severe enough to require periocular injection of steroids primarily. Patients with ocular hypertension or glaucoma were excluded from the study. In addition, cases suspected to have infectious uveitis or intraocular lymphoma were excluded.

The following clinical parameters were recorded: The aetiology of uveitis, Snellen visual acuity (VA) in decimal fraction, Goldmann applanation intraocular pressure (IOP), anterior segment findings by slit lamp and posterior segment findings by ophthalmoscopy, slit lamp biomicroscopy (90 D lens) or ultrasonography. Anterior chamber and vitreous cells were graded as 0.5+, 1+, 2+, 3+ and 4+ according to the guidelines of the Standardization of Uveitis Nomenclature Working Group 16 and Nussenblatt et al. [17]. Improvement or worsening of activity of inflammation was assessed according to the Standardization of Uveitis Nomenclature Group’s directions. Cataract progression was assessed clinically by slit lamp throughout the follow-up period and was defined as: New or increase in any type of lens opacification after TAA injection (arbitrary scale 1-4). IOP elevation was defined as any rise above baseline record. On one occasion IOP was greater than 22mm Hg; medical anti glaucoma agents was initiated. Fundus fluorescein angiography (FFA) was performed whenever the ocular media allowed. Clinical characteristics of the patients are summarized in Table (1).
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Pt No = Patient number.
Lat = Laterality.
Age = Age in years.
VA = Visual acuity.
IOP = Intraocular pressure.
US = Ultrasoundography.
KPs = Keratic precipitates.
After a signed informed consent was obtained, each eye was injected with 1ml of 40mg/ml Sterile TAA Suspension (Kenakort-A IM, Bristol-Meyers Squibb Company, Egypt) mixed with 0.5ml of 2% lidocaine (lidocaine) using a 1.25 inch 23 gauge needle. The needle was inserted at the inferotemporal aspect of the lower lid aiming in the direction of the orbital apex. The patient was asked to look straight a head while the globe was pushed towards the superior orbit with the index finger of the non-injecting hand. A quick wiggle of the needle, in absence of any eye movement, assures non penetration of the globe. Once the needle was positioned in the muscle cone near the posterior pole, the solution was slowly injected. B-scan ultrasound (Compact Sono Med; US) was performed within 1 hour of the injection. Special emphasis was paid to the integrity of the ocular contour. Standard longitudinal, vertical transverse and axial planes were imaged. In patients with relatively clear media, indirect ophthalmoscope exam with indentation was done to exclude any accidental globe perforation. Patients in which the injected drug was found to be localized to the macular area (Fig. 3) were then followed up after 1 day, 1 week, 2 weeks, 1 month, 2 months and 3-6 months. On the other hand, cases in which the drug could not be visualized or was not localized to the macular area as seen by ultrasound received a second RBI using the same technique. The ultrasound was then repeated to confirm that the TAA was deposited over the macula. These patients were also followed-up according to the schedule described.

The primary outcome measures were: Improvement of uveitis (inflammatory activity), angiographic appearance of CME or diffuse ME at 6 months and change in VA. At the final follow-up the minimum difference from baseline to be considered as significant was two Snellen lines of change in VA at all follow-up periods with an average of 0.249 and a range from finger counting at 50cm to 0.8. On the second week postoperatively the mean postoperative VA was 0.18 with a standard deviation of 0.246 and a range from 0.016 to 1.0. On the first month postoperatively, the mean VA increased to 0.15 with a standard deviation of 0.21 and a range from finger counting at 50cm to 0.8. On the second week postoperatively the mean postoperative VA was 0.23 (approximately 6/24) with a standard deviation of 0.246 and a range from 0.016 to 1.0. On the first month postoperatively, the mean postoperative VA was 0.26 with a standard deviation of 0.29 and a range from 0.016 to 0.8. Approaching the second month postoperatively, the mean postoperative VA was 0.29 and a range from 0.016 to 0.9. There was a statistically significant improvement of VA at all follow-up periods with an average p-value of 0.045 (Fig. 1).

Although the improvement in VA was more noted in cases of Behcet’s disease than other causes of uveitis, this difference was not found to be statistically significant (Fig. 2).

There was a dramatic improvement in anterior chamber activity in all the patients (p-value <0.05). Flare and cells were detected in 14 eyes (12 cases) before injection. Improvement started on the first day post injection in 8 eyes, on the 1st week in 5 eyes and on the 2nd week in 1 eye. Complete

Results

Demographic and preoperative data:

This study included 26 eyes of 20 patients with refractory uveitis who were recruited for echo-
resolution of anterior uveitis occurred in 6 eyes in the 1st week, 4 eyes in the 2nd week and 2 eyes in the 1st month. One case (2 eyes) failed to achieve complete resolution at the end of follow-up (7%).

There was an improvement in vitreous activity in all patients. Vitritis was present in all cases (26 eyes) before injection. Complete resolution occurred in 6 eyes in the 1st week, 4 eyes in the 2nd week, 3 eyes in the 1st month, 4 eyes in the 2nd month and 5 eyes in the 3rd month. 4 eyes failed to achieve complete resolution at the end of follow-up (14%) (Table 2).

The post injection IOP showed a spike of elevation above baseline, which was greatest from the second to the fourth week (Table 2). This increase in IOP was not statistically significant (p-value=0.13). Three cases (3 eyes) were found to have elevation of IOP above 22mmHg (11%) of which two cases were controlled with B blockers and one case was controlled with B blockers in addition to dorzolamide. Refractory or intractable glaucoma was not reported in this study. The IOP returned to normal range by the end of the second month.

In this study, apart from the increase in IOP, no major complications were encountered such as hemorrhage, globe perforation, retinal or choroidal occlusion, orbital abscess, ptosis, extraocular muscle necrosis or systemic toxicity. None of our patients had a posterior subcapsular cataract development or progression. Two patients developed focal dermal hypopigmentation at the site of injection which was treated with topical antibiotics.

Reattacks:

Although all the cases showed an improvement in their VA and decrease in the inflammatory activity, only 22 eyes were completely resolved. Inflammation did not resolve completely in 4 eyes. In addition, 4 patients (5 eyes) developed reactivation of uveitis (19%). The second attack was much milder than the original one. None of them developed CME. These recurred attacks developed later than expected. The time free interval varied in the 4 patients ranging from 3 months in 2 cases to 6 months in one case. These patients were again treated using the same technique and they were followed-up with the same protocol previously described.

![Post-injection change in visual acuity](image1)

**Fig. (1):** Post injection change in VA in different follow-up periods (in bilateral cases the mean VA of both eyes is considered).

[Source: HMGP=0, CF 50 cm=0.008, 1/60=0.01, 2/60=0.03, 3/60=0.05, 4/60=0.06, 5/60=0.08, 6/60=0.1, 6/36=0.17, 6/24=0.25, 6/18=0.33, 6/12=0.5, 6/9=0.67, 6/6=1].

![Mean change in VA in various uveitis types](image2)

**Fig. (2):** Mean change in VA in different types of uveitis.
Table (2): Postoperative data: Change in VA & IOP [expressed as Mean ± Standard deviation (Range)].

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<th></th>
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<th>Second week</th>
<th>First month</th>
<th>2nd month</th>
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<td>0.11±0.158 (HM)</td>
<td>0.15±0.21 (CF)</td>
<td>0.18±0.246</td>
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<td>(0.7)</td>
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<td><strong>IOP</strong></td>
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<td>14±2.22 (8-18)</td>
<td>17.85±9.03 (8-42)</td>
<td>17.85±7.51 (8-42)</td>
<td>14±4.13 (2-24)</td>
<td>13.5±3.4 (2-18)</td>
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Fig. (3): B-scan ultrasonography: Echolucent area is present (arrow) representing the depot steroid over the macula.

**Discussion**

The peribulbar injection of steroids has been used in the treatment of CME and the inflammation associated with uveitis by many investigators [6-9,11,15,18]. The retrobulbar approach, although not free from complications, is clearly less invasive than the intravitreal route [20]. However, the efficacy of the peribulbar route in achieving a therapeutic dose of steroids at the level of the retina, particularly at the macula, has been questioned [19]. Drug localization to the macular area is considered important for optimal therapeutic effect. Tolentino and coworkers documented the retrobulbar location of corticosteroid by B-mode ultrasonography in 15 of 16 eyes given retrobulbar injections for inflammatory CME [11]. On the contrary, in another study, only 17 of 24 eyes (71%) with inflammatory CME given a sub-Tenon’s injection of corticosteroid using a 5/8 inch needle were found to have the bolus of medication posterior to the equator by B-mode ultrasonography [8]. Of the remaining eyes, six were found to have the drug deposited into the orbit while one eye was found to have the drug deposited in the vicinity of the equator. In current study, only 3 eyes out of 26 ones enrolled the injection had to be repeated as the drug could not be detected by ultrasound.

Numerous researchers have evaluated the efficacy of peribulbar TAA in uveitic cases. Tanner et al., reported improved VA and diminished vitreous cellular activity in 21 out of 28 eyes (75%) that were given PST-TAA (40mg). In most cases, a recovery was detected within 2 weeks from injection [21]. Another study by Lafranco and coworkers documented the effectiveness of PST-TAA on 58 eyes with posterior uveitis. Snellen VA improved significantly from 0.4±0.03 to 0.79±0.07 with the resolution of inflammatory activity [22]. However Buiquoc et al., reported a lower effectiveness after PST-TAA injection (52.45% of 32 patients with non-infective posterior uveitis). VA improved by more than two lines and the inflammation resolved as documented angiographically [23]. In Our study, there was a significant improvement in the VA and reduction of flare and cellular activity in all cases. Our report showed a comparable rate of resolution of inflammation to that previously reported in the literature, in the form of 93% rate of complete resolution (24 out of 26 eyes) regarding anterior chamber activity and 86% (22 out of 26 eyes) concerning vitreous activity. However, the improvement of visual acuity and the reduction of inflammatory activity was earlier and persisted longer than other reported studies not confirmed with ultrasonography.

Steroid-induced elevation of IOP is one of the major side effects, which are most often discussed in combination with corticosteroids. Elevation in IOP (>21mm Hg) after PST-TAA injection occurred in 6 patients in Helm and Holland’s study [6] with onset at a mean of three weeks after initial injection;
the mean interval to peak increase was 14 weeks after the injection. Similarly, an IOP spike after PST TAA injection was documented in a study by Buiquoc et al., where IOP rose in 13 patients. Surgical excision of periocular steroid deposit was required in 3 cases in which medical treatment was unsuccessful [23]. Other complications have been reported in literatures, that was not reported in our study, such as the accidental injection directly into the choroidal or retinal circulation, perforation of the globe, occlusion of the central retinal artery cataract, blepharoptosis, orbital fat atrophy, strabismus, conjunctival necrosis and orbital abscess [20,25].

The effect of a single TAA injection usually lasts in the eye for about (4-6) weeks in posterior subtenon route and up to 3 months in intravitreal route after which a second attack is possible. Consequently, the retrobulbar administration of corticosteroids is only effective for a few weeks (26), which means that it is necessary to repeat the injections at 6 weekly intervals to maintain stability of the inflammation as well as the ME. In our study, the effect in our cohort lasted a much longer time. This could be due to the fact that TAA was acting directly at the required site of action, while in other reports a fair amount of TAA is absorbed systemically with consequent short duration of action.

This study has attempted to simplify the transcutaneous RBI technique even further by using a 23 gauge (1.25") needle, generally used for parabulbar anesthetics in cataract surgery. In contrast to PST injection, this approach made it possible to administer the injection without having to create a surgical opening in the conjunctiva to access the subtenon space, thus improving patient compliance with this therapy.

When we use the retrobulbar approach for TAA injection it is very important to make a careful echographic examination to determine the correct location near the macula of the drug. Without echography we cannot determine whether an unsatisfactory therapeutic response is secondary to the disease process or to misdisplacement of the TA (therapeutic failure). We think that our good results with the retrobulbar TAA approach in this study is related to the correct placement of TA near the macular area displayed with the echographic images.

Recurrence of uveitis and ME occurred in some patients in this study as would be expected from the known short-term effect of peribulbar TAA in many other studies with uveitic and diabetic ME. However the TAA clearly prevented the short term exacerbation of ME that can be associated with blood ocular breakdown due to intraocular inflammation. It seems logical to use a drug, even if with a known short-lived effect, in this way visual outcome potentially improved until longer lasting alternatives are produced. Nowadays there are many studies investigating the safety and efficacy of intravitreal implanted slow release devices in the treatment of refractory uveitis. The aim is to decrease the recurrence rate of uveitis for a longer period than a single intravitreal injection dose and reducing the risk of complications from repeated injection [27].

One major limitation of this study was the inability to capture good quality fluorescein or OCT images because of the anterior chamber and vitreous turbidity and so it was not possible to follow the patients by measurement of macular thickness. However, it is well documented that CME and macular thickness correlate with VA reduction and uveitis activity [28]. The relatively short duration of follow-up is also a limitation of this clinical study.

This trial, as in many other similar studies, proved that sonography-verified retrobulbar TAA has raised the therapeutic success of refractory uveitis and CME, although the effect seems to be transient. A number of conclusions can be drawn based on the results of this study: (1) Retrobulbar TAA injection is a relatively safe procedure; (2) Week 2nd is the most probable time for the development of a high IOP and the time at which anti-hypertensive medication may necessary; (3) Retrobulbar TAA-related high IOP is usually controllable by one drug (4) The most significant therapeutic effect of TAA on inflammatory activity appears at 4 weeks; however, its effect in terms of patient satisfaction and reduction in CME is maintained for as long as 4 months.

References


