Subconjunctival injections of triamcinolone acetonide to treat uveitic macular edema

Yi Qu

Peking Union Medical College Hospital

Xinshu Liu

the fourth people's Hospital in Shenyang

Anyi Liang

Peking Union Medical College Hospital

Chan Zhao

Peking Union Medical College Hospital

Fei Gao

Peking Union Medical College Hospital

Zhang Meifen (✉ meifen_zhang@hotmail.com)

Peking Union Medical College Hospital <https://orcid.org/0000-0002-7581-6800>

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Abstract

Background: To evaluate the efficacy and safety of subconjunctival triamcinolone acetonide (TA) injections for treating uveitic macular edema (UME).

Methods: This retrospective case series study included patients with UME who received subconjunctival TA injections with a minimum follow-up period of 6 months. The main outcome was central macular thickness. The secondary outcomes included the best corrected visual acuity, recurrence rate and intraocular pressure.

Results: In total, 68 patients (83 eyes) were enrolled in this study. The mean CMT decreased from $456.9 \pm 171.1 \mu\text{m}$ at baseline to $324 \pm 175.9 \mu\text{m}$, $305.6 \mu\text{m} \pm 147.7 \mu\text{m}$, $331.8 \pm 154.3 \mu\text{m}$ and $281.1 \pm 147.6 \mu\text{m}$ at 1, 2, 3 and 6 months postinjection, respectively (all $P < 0.01$). A total of 21/83 eyes exhibited elevated IOPs, which was controlled with topical IOP-lowering agents in 14 eyes, whereas 7 eyes got subconjunctival TA deposit surgically removed.

Conclusion: subconjunctival TA injections appear to be safe and effective for UME.

Key Words: Triamcinolone acetonide; subconjunctival injection; uveitis; macular edema

Background

Macular edema (ME) is a common complication of uveitis and is responsible for a substantial amount of visual impairment among patients with uveitis^{1,4–6,24}. ME is believed to result from fluid leakage across the blood-retinal barrier and fluid accumulation in the macular region, sometimes with a characteristic distribution in the outer plexiform layer and subretinal area¹. Corticosteroids are the first choice for treating uveitic macular edema (UME), while long-acting and sustained release implants represent the newest treatment method. However, immunosuppressants such as cyclosporine, methotrexate, azathioprine and mycophenolate mofetil can only be used specifically for chronic and intractable UME. Moreover, various newly developed biological agents, such as anti-VEGF, interferon- α and anti-TNF, have provided options for UME pharmacotherapy²⁴.

Triamcinolone acetonide (TA), a long-acting glucocorticoid, is still widely used because of its efficacy and affordable cost, but the use of local applications is controversial. Periocular²² or intraocular injections of TA have been previously reported in detail^{7–10,20}. However, few studies have been conducted on subconjunctival injections of TA for treating UME^{13,19,23}.

This study aimed to evaluate the efficacy and safety of subconjunctival TA injections in treating UME.

Methods

This was a retrospective study with standardized longitudinal preinterventional and postinterventional imaging. The study was performed in accordance with the ethical standards stated in the 1964 Declaration of Helsinki.

Patient Eligibility and Exclusion Criteria

The clinical data of UME patients who received subconjunctival TA injections from January 2009 to December 2018 in the Ophthalmology Department of Peking Union Medical College Hospital were collected and analyzed. The inclusion criteria were as follows: A definite diagnosis of UME, subconjunctival TA injection and regular follow-up for at least 6 months. The exclusion criteria were as follows: other eye diseases (e.g., diabetic retinopathy or retinal vascular obstruction) that may be complicated by macular edema; periocular or intraocular drug injections within 6 months before treatment; or subconjunctival TA injections with an increasing oral dose of glucocorticoids or immunosuppressants. Data were collected at 1, 2, 3 and 6 months after the injection; if the data were not available, missing value substitutes were not used. If a patient underwent repeated injections, data were collected for a minimum of 6 months beyond the last injection in the study period.

Examination and Treatment Procedures

The procedure was performed in the outpatient department. Patients received subconjunctival injections of TA while in a supine position. To anesthetize the injected eye, a single application of 0.4% oxybuprocaine hydrochloride eye drops (Santen Pharmaceutical Co., Ltd.) was applied. Injection of 20mg Triamcinolone acetonide (Kunming Jida Pharmaceutical Co., Ltd., concentration: 40 mg/mL) was injected with a 1 mL syringe into the inferior fornix, and the drug deposit could be seen under the conjunctiva. Patients were asked to monitor their eye pressure every 2 weeks after the intervention.

The main outcome was central macular thickness (CMT) measured by optical coherence tomography (OCT). The secondary outcomes included the best corrected visual acuity (BCVA), recurrence rate and intraocular pressure (IOP) within 6 months after the injection.

OCT Acquisition

The CMT was measured using an Optovue OCT (Optovue, Fremont, CA) or 3D-OCT 2000 (Topcon Corporation, Japan) devices. The same device was used for the follow-up examination of each patient. AutoRescan features were used to ensure that the follow-up scans matched the baseline scan.

Statistical Analysis

Statistical analysis was performed using IBM SPSS software, version 25.0 (IBM SPSS, USA). Visual acuity was obtained from each patient's medical records and converted to a logarithm of the minimal angle of resolution (logMAR) for statistical analysis. Paired t-tests were performed to analyze logMAR visual acuity and CMT. A P value < 0.05 was considered significant.

Results

In this retrospective, observational case series study, 68 patients (17 males and 51 females, 83 eyes) were enrolled. The ages of included patients ranged from 11 to 78 (49.2 ± 14.1) years; 38/68 patients (55.88%) received only one injection, while other patients received several injections in one eye or in both eyes. The baseline characteristics of the patients are shown in Table 1.

The mean CMTs of the subconjunctival TA-injected eyes, as measured with OCT, were significantly reduced. The mean CMT decreased from $456.9 \pm 171.1 \mu\text{m}$ before subconjunctival TA injection to $324 \pm 175.9 \mu\text{m}$ ($P < 0.01$), $305.6 \mu\text{m} \pm 147.7 \mu\text{m}$ ($P < 0.01$), $331.8 \pm 154.3 \mu\text{m}$ ($P < 0.01$) and $281.1 \pm 147.6 \mu\text{m}$ ($P < 0.01$) at 1, 2, 3 and 6 months after injection, respectively (Figure 1). A total of 22/83 eyes (26.51%) relapsed within 6 months; 10/22 eyes received a second injection, and the efficacy was still very good.

The secondary outcome was the mean visual acuity, which increased from logMAR 0.5 ± 0.3 at baseline to logMAR 0.4 ± 0.3 ($P < 0.01$) in the 1st month after the injection, to logMAR 0.4 ± 0.3 ($P < 0.01$) in the second month, to logMAR 0.4 ± 0.4 ($P < 0.01$) in the third month and logMAR 0.4 ± 0.3 ($P < 0.01$) in the sixth month. None of the patients received any additional medications during the six-month follow-up (Figure 2).

In our study, 21/83 eyes (25.30%) exhibited to experience elevated IOPs above 21 mmHg (1 mmHg = 0.133 kPa). Fourteen eyes of these instances were well controlled by 1 or 2 kinds of topical IOP-lowering agents, while 7 patients ultimately needed an operation to remove the persistent subconjunctival TA deposit. Figure 3 is the Kaplan-Meier survival analysis of the patients with an IOP > 21mmHg, which indicated that elevated IOPs were observed more frequently within the first 2 months after the injections.

Discussion

UME is frequently encountered in patients with uveitis (20.5% in the clinic)^{2,3} and can cause permanent vision loss. The management strategies vary significantly as no optimal strategy exists. Periocular injections or intraocular injections of TA and intraocular sustained-release glucocorticoid implants have been previously reported in detail^{9,11}. Recently, the POINT trial compared the effectiveness of 3 methods of administering regional corticosteroids for UME, including periocular injections of 40mg TA (periorbital floor or posterior sub-Tenon's approach), intraocular injections of 4mg TA and a 0.7 mg dexamethasone intravitreal implant. The results showed that all treatment groups had clinically meaningful reductions in central subretinal thickness compared with baseline¹². However, subconjunctival injections of TA have rarely been reported^{13,19,23}.

CMT

In our study, subconjunctival injection of TA was effective in controlling UME, particularly in patients with unilateral macular edema and in those with bilateral UME under systemic medication who still exhibited

aggravated unilateral ME. In these cases, topical TA injection could prevent systemic glucocorticoids side effects.

In the first month after 20 mg TA injection, 62/71 eyes (87.32%) showed a reduction in CMT. In addition, 59/71 eyes (83.09%) showed an obvious reduction in CMT (at least 20%).

A previous article²⁷ compared the efficacy and tolerability of subconjunctival injection of TA, subtenon TA and intravitreal dexamethasone implants and showed improvements in CMT of 88% at one month with no significant differences among the three groups. Bae et al.¹⁴ reported that 53.1% of the eyes treated with peribulbar injections of 40 mg TA showed reductions in CMT after 1 month. However, the curative effect declined after 3 months. Similarly, Henry A. Leder et al.¹⁵ also reported that 53% of the eyes treated with a single posterior-subtenon TA injection had clinically resolved 1 month after the injection, and 57% of the eyes had clinically resolved 3 months after the injection. However, another recent study administered periocular injections of 40 mg TA using a periorbital floor or posterior subtenon approach, and the percentage of CMT reduction was only 23% after 2 months⁹.

Although our study reduced the dose of TA by half, the efficacy and persistence were similar or even better than those reported previously.

Relapse

Twenty-two eyes (22/83, 26.51%) had UME relapse within 6 months; 10 patients received a second injection and still effective. Among these eyes, 5 eyes (22.73%) relapsed at 2 months, 7 eyes (31.82%) relapsed at 3 months and 10 eyes (45.45%) relapsed at 6 months. In one patient in the present study, the effect of the first injection lasted for 6 months, but the effect of the second injection 1.5 years later lasted for only 2 months. However, over the past decade, we did not observe any other similar cases. One patient received 7 injections within 10 years with a good response to TA every time, and the injection had an efficacy that lasted for more than 6 months. Furthermore, no correlation was found between the duration of TA efficacy and the number of injections.

During the follow-up, 5 patients did not respond to the therapy. One patient was diagnosed with Vogt-Koyanagi-Harada (VKH) disease complicated by choroidal neovascularization, but ME resolved after an anti-VEGF injection.

IOP

In this study, elevated IOP was the only side effect of subconjunctival TA injections. An elevated IOP was observed in 21/83 eyes (25.30%). However, Byun et al.¹⁷ reported that 18 eyes (11.3%) required glaucoma medications after a posterior-subtenon injection. Another study reported that 34.9% of the patients after a posterior-subtenon injection had elevated IOPs, and 4.7% of the patients needed trabeculectomy after a posterior-subtenon injection with 40 mg TA¹⁸.

Previous literature reported that an anterior subtenon injection of TA was 2.4 times more likely (95% CI, 1.02–5.9) to cause elevated IOPs than a posterior subtenon injection¹⁶. A higher level of aqueous humor triamcinolone may be associated with a higher incidence of IOP elevation. However, our data showed similar rate of IOP elevation as posterior subtenon injection, and thus, further randomized controlled trials are needed to verify these findings.

According to our clinical experience, the elevated IOP can be well controlled. The Kaplan-Meier survival analysis of the patients with an IOP > 21mmHg is illustrated in Figure 3, which indicated that elevated IOP was more frequently observed within the first 2 months after the injection. Therefore, IOP should be closely monitored every 2 weeks within the first 2 months after the injection.

For patients with elevated IOP, topical IOP-lowering agents should be applied first. For example, topical beta-blockers, carbonic anhydrase inhibitors, and alpha-agonists are the usual first-line treatments. For patients with IOP above 35 mmHg that cannot be controlled with topical eye drops, removal of the TA deposit is suggested. In our study, 7 eyes (7 patients) underwent removal of the subconjunctival TA deposit, and IOP of all 7 eyes returned to normal within 1 month after TA deposit removal.

Subconjunctival hemorrhage is also a well-known but trivial side effect. One case²⁵ of conjunctival ulceration caused by a subconjunctival injection of 40 mg triamcinolone has been reported; other reported side effects of subconjunctival triamcinolone acetonide include infectious scleritis, blepharoptosis, mydriasis, conjunctival ischemia²³ and conjunctival necrosis²⁶. These side effects were not observed in our patients, which may be due to the halved dose.

There are some limitations in our study, including missing data due to the retrospective nature of the study and the different follow-up intervals. The efficacy rate may be influenced by confounding factors, such as the presence of cataracts or epiretinal membrane.

From our point of view, subconjunctival injection, which could be performed in the outpatient department, is much easier to administer than posterior subtenon injection and intravitreal injection, which must be performed in the operating room. On the other hand, subconjunctival injections are more likely to cause IOP elevation, although elevated IOP could be well controlled by application of 1 or 2 types of topical IOP-lowering agents. Furthermore, subconjunctival TA deposit removal may cause less damage than intravitreal injection or posterior subtenon injection in patients suffering IOP elevation who require pars plana vitrectomy or trabeculectomy.

Conclusion

In conclusion, subconjunctival TA injections appear to be safe and effective for UME. Elevated IOP was the only side effect but could be well controlled. Nevertheless, large-scale prospective studies are needed to compare subconjunctival injections of TA with other regional corticosteroid administration methods in UME patients.

List Of Abbreviations

TA: triamcinolone acetonide

UME: uveitic macular edema

OCT: optical coherence tomography

BCVA: best corrected visual acuity

IOP: intraocular pressure

logMAR: logarithm of the minimal angle of resolution

Declarations

- Ethics approval and consent to participate: Yes

The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Peking Union Medical College Hospital, and written informed consent was obtained from all patients. While the participants are children (under 16 years old), the written informed consent was obtained from their parents.

- Consent for publication: Not applicable
- Availability of data and materials: We have uploaded an excel of the 68 patients collecting IOP and CMT database
- Competing interests: The authors declare that they have no competing interests.
- Funding: Not applicable
- Authors' contributions:

YQ, XL and AL collected the data, while YQ wrote this article. CZ, FG and MZ reviewed and edited the manuscript. All authors read and approved the manuscript.

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Tables

TABLE 1. Baseline characteristics of 68 patients

Uveitis diagnosis	48.53% Idiopathic		
	27.94% Vogt-Koyanagi-Harada disease		
	4.41% Tuberculosis-associated		
	4.41% JIA-associated		
	2.94% Sarcoidosis		
	2.94% Bechçet disease		
	1.47% HLA-B27 associated		
	7.35% Other		
Sex	75%	Female	
	25%.	Male	
Age	Range from	11 to 78	
	Mean±SD	49.2 ± 14.1	
Periocular steroid injection times	unilateral	53 patients	77.94%
	bilateral	15 patients	22.06%
	7times	1 patient	1.47%
	6times	1 patient	1.47%
	5times	1 patient	1.47%
	4times	5 patients	7.35%
	3times	7 patients	10.29%
	2times	15 patients	22.06%
	1times	38 patients	55.88%
	Systemic Therapy	64.7% of all patients	
8.8% prednisolone alone			
36.8% prednisolone + 1 second line agent			
11.8% prednisolone + 2 second line agents			

4.4% 1second line agent

2.9% 2second line agent

Figures

Figure 1

Mean baseline CMT and the changes over time. The mean CMT decreased from $456.9 \pm 171.1 \mu\text{m}$ at baseline to $324 \pm 175.9 \mu\text{m}$ ($P < 0.01$), $305.6 \mu\text{m} \pm 147.7 \mu\text{m}$ ($P < 0.01$), $331.8 \pm 154.3 \mu\text{m}$ ($P < 0.01$) and $281.1 \pm 147.6 \mu\text{m}$ ($P < 0.01$) at 1, 2, 3 and 6 months after injection, respectively.

Figure 2

Mean baseline visual acuity (VA, logMAR) and the changes over time. The mean visual acuity increased from logMAR 0.5 ± 0.3 at baseline to logMAR 0.4 ± 0.3 ($P < 0.01$), logMAR 0.4 ± 0.3 ($P < 0.01$), logMAR 0.4 ± 0.4 ($P < 0.01$), logMAR 0.4 ± 0.3 ($P < 0.01$) at 1, 2, 3 and 6 months after injection, respectively.

Figure 3

Kaplan-Meier survival analysis for patients with IOP > 21 mmHg

Supplementary Files

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- [Additionalfile1originaldataset.xlsx](#)