Subconjunctival injections of triamcinolone acetonide to treat uveitic macular edema

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Research article

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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 measure was central macular thickness. The secondary outcome measures included 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 ± 171.1 μm at baseline to 324 ± 175.9 μm, 305.6 μm ± 147.7 μm, 331.8 ± 154.3 μm and 281.1 ± 147.6 μm at 1-, 2-, 3- and 6-months post injection, respectively (all $P < 0.01$). A total of 21/83 eyes exhibited elevated IOPs, of which 14 were controlled with topical IOP-lowering agents and 7 eyes underwent surgical removal of subconjunctival TA deposit.

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

Background

Macular edema (ME) is one of the most common complications of uveitis which may result in visual impairment and even blindness[1-4]. The mechanism of 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 area[1]. While corticosteroids remain the first line treatment for uveitic macular edema (UME), immunosuppressants such as cyclosporine, methotrexate, azathioprine and mycophenolate mofetil are usually required for chronic and intractable UME. Sustained-release corticosteroid implants[5], anti-VEGF agents and anti-TNF-α agents are recently emerged options for UME[1, 6].

Despite the advantages of the corticosteroid implants, triamcinolone acetonide (TA), a long-acting glucocorticoid, is still widely used for its efficacy and affordable cost[7]. While reports on periocular[8] or intraocular injections of TA are numerous[9-13] , however, few studies have been conducted on subconjunctival injections of TA for treating UME[14-16].

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

Methods

This study was a retrospective cases series of UME patients who underwent subconjunctival TA with regular follow up. Written informed consent was obtained from all participants before the subconjunctival TA injection(s) and any other invasive procedures/examinations. The study adhered to 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 Department of Ophthalmology, Peking Union Medical College Hospital were collected and analyzed. The inclusion criteria were as follows: a) new onset of unilateral UME, or bilateral UME with unilateral aggravation, of any anatomical type (anterior, middle, posterior or pan uveitis); b) if the patients was on systemic corticosteroid, the dose should be ≤15 mg prednisone or equivalent; c) absence of significant ocular inflammation that require, or the patient refused or has contraindications for, initiation or up titration of systemic corticosteroids and/or immunosuppressants; d) had been regularly followed up to at least 6 months after the (last) subconjunctival TA injection. e) patients with complete clinical data at baseline and the 1-, 2-, 3- and 6-months post-injection visits. The exclusion criteria were as follows: a) history of any other ocular disease (e.g., diabetic retinopathy or retinal vascular obstruction) that may cause macular edema; b) received periocular or intraocular injections within 6 months before the (first) subconjunctival TA injection; c) presence or development of posterior synechia or media opacity such as cataract that compromise satisfactory fundus evaluation and quality of (optical coherence tomography) OCT images.

Examination and Treatment Procedures

The procedure was performed in the outpatient department. Patients received subconjunctival injections of TA 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. 1 mL syringe contained 20mg Triamcinolone acetonide (Kunming Jida Pharmaceutical Co., Ltd., concentration: 40 mg/mL) was injected 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 intervene. Systemic corticosteroids or immunosuppressants were not initiated or up-titrated. Corticosteroid eye drops and topical NSAIDs were not used in any of the cases. While Topical IOP-lowering agents were applied as first line treatment for IOP elevation, such as beta-blockers, carbonic anhydrase inhibitors, and alpha-agonist. For patients with IOP over 30 mmHg that cannot be controlled with topical eye drops, surgery to remove TA deposit is recommended

The main outcome measure was central macular thickness (CMT) measured by OCT. The secondary outcome measures included best corrected visual acuity (BCVA), recurrence rate and 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. In order to follow-up, the same device was applied for each patient. AutoRescan features were used to ensure that the follow-up scans matched the baseline.

Statistic Analysis

Statistic 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 statistic 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 age 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. Of the 15 patients with both eyes included, none received bilateral subconjunctival TA injection simultaneously. The demographic features of patients at baseline were shown in Table 1.

The mean CMTs of the subconjunctival TA-injected eyes were significantly reduced. The mean CMT decreased from 456.9 ±171.1 μm before the injection to 324 ± 175.9 μm (P<0.01), 305.6 μm ± 147.7 μm (P < 0.01), 331.8 ± 154.3 μm (P < 0.01) and 281.1 ±147.6 μm (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 were still responsive.

BCVA 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) and logMAR 0.4 ± 0.3 (P<0.01) at the 1-, 2-, 3- and 6-months post-injection visits, respectively. (Figure 2).

Elevation of IOP (≥21 mmHg) was observed in 21/83 (25.30%) eyes. Among them, 8/21 (38.09%), 6/21 (28.57%) and 3/21 (14.29%) eyes had peak IOPs between 21 and 25 mmHg, 25 and 30mmHg, 30 and 35mmHg, respectively; and 4/21(19.05%) eyes had peak IOPs over 35mmHg."14/21(66.67%) eyes were well controlled by 1 or 2 kinds of topical IOP-lowering agents, while 7 eyes (33.33%) underwent surgical removal of the subconjunctival TA deposit. Figure 3 was the Kaplan-Meier survival analysis of the patients with elevated IOP, which revealed that the time frame for IOP rise was the first 2 months after the injections.

Discussion

ME is frequently encountered in patients with uveitis[17, 18] and may cause permanent vision loss. The management vary significantly among different centers. Options of local corticosteroids included periocular or intraocular injections of TA and intraocular sustained-release glucocorticoid implants[11, 19]. Of interest is the POINT trial which compared the effectiveness of 3 treatment modalities of local corticosteroids in UME, in particular 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[15]. The results showed that all treatment groups had clinically meaningful reductions in central subretinal thickness compared with baseline[15]. However, subconjunctival injections of TA have rarely been reported[14-16].

Regarding CMT

In the first month after injection of 20mg TA, 62/71 eyes (87.32%) showed a reduction in CMT with 59/71 eyes (83.09%) by at least 20%, which is very close to the overall response rate (88%) observed in a previous study[20] aiming to compare sub-tenon TA, intravitreal TA and intravitreal dexamethasone implants. Other studies, however, revealed lower levels of effectiveness. Bae and colleagues[21] reported that 53.1% of the eyes treated with peribulbar injections of 40 mg TA showed reduction in CMT after 1 month. Henry A. Leder et al.[22] observed that UME was clinically resolved in 53% and 57% of treated eyes 1 and 3 months respectively after a single posterior-subtenon TA (40mg) injection. Furthermore, CMT reduction was observed only in 23% eyes 2 month after a periocular injections of 40 mg TA[11].

Regarding relapse

As presented previously, twenty-two (22/83, 26.51%) eyes underwent relapse of UME within 6 months. Among these eyes, 5 (22.73%), 7 (31.82%) and 10 (45.45%) eyes relapsed less than 2 months, 2 to 3 months, and 3 to 6 months after the injection, respectively. Some cases are worthy of note. In one patient, the first injection resulted in resolution of UME for 6 months, however, but the therapeutic effect of the second injection given 1.5 years later lasted only 2 months. Another patient received 7 injections with good responsiveness observed every time in a 10-year follow up period, and the longest resolution lasted for more than 6 months.

Regarding IOP

An elevated IOP was observed in 21/83 eyes (25.30%) in our study. However, Byun et al.[23] 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 ultimately[24].

Anterior subtenon injection of TA was found to be 2.4 times more likely (95% CI, 1.02–5.9) to cause elevated IOPs than posterior subtenon injection[25], which could be explained by the notion that a higher aqueous level of TA is associated with a higher incidence of IOP elevation. However, our data showed a similar rate of IOP elevation as compared to posterior subtenon injection. In addition, Elevated IOP was observed mainly (16/21 eyes) within the first 2 months after the injection in our study. However, 5 eyes develop IOP rise later than 2 months with the latest observed up to 15 weeks after the injection. While IOP-lowering eye drops were sufficient for majority of the patients, 7 eyes (7 patients) underwent surgical removal of the subconjunctival TA deposit and IOP returned to normal within 1 month after the surgery.

Subconjunctival hemorrhage is also a well-known but trivial side effect. Other reported side effects[16] of subconjunctival TA such as conjunctival ulceration[26], ischemia, necrosis[27] and infectious scleritis, were not observed in our patients.

From our point of view, subconjunctival injection of TA (20mg) has several advantages over other periocular injections. It is technically an easier procedure and could be safely performed in the outpatient clinic; Even though it may be more likely to cause IOP elevation, topical IOP-lowering agents are usually sufficient to control the IOP, and surgical removal of subconjunctival TA deposits is easy and effective when intractable IOP elevation occurs.

There are some limitations for our study, including inhomogeneity of the included patients, inevitable biases, missing data and the different follow-up intervals among different patients due to the retrospective nature of the study.

Conclusion

In conclusion, subconjunctival TA injections appear to be safe and effective for UME. Increased IOP is a concern but could be well controlled by IOP-lowering eye drops and surgical removal of TA deposit when necessary.

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. Written informed consent was obtained from all participants before the subconjunctival TA injection(s) and any other invasive procedures/examinations. 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 dataset of the 68 cases included IOP and CMT data.
- 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, edited and reviesed the manuscript. All authors read and approved the manuscript.

- Acknowledgements: Not applicable

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Table

TABLE 1. Demographic features of the 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
Lens condition	51.47% no cataract
	26.57% already with complicated cataract
	22.06% IOL eyes
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 immunosuppressant
11.8%	prednisolone + 2 immunosuppressant
4.4%	1 immunosuppressant
2.9%	2 immunosuppressant

Figures

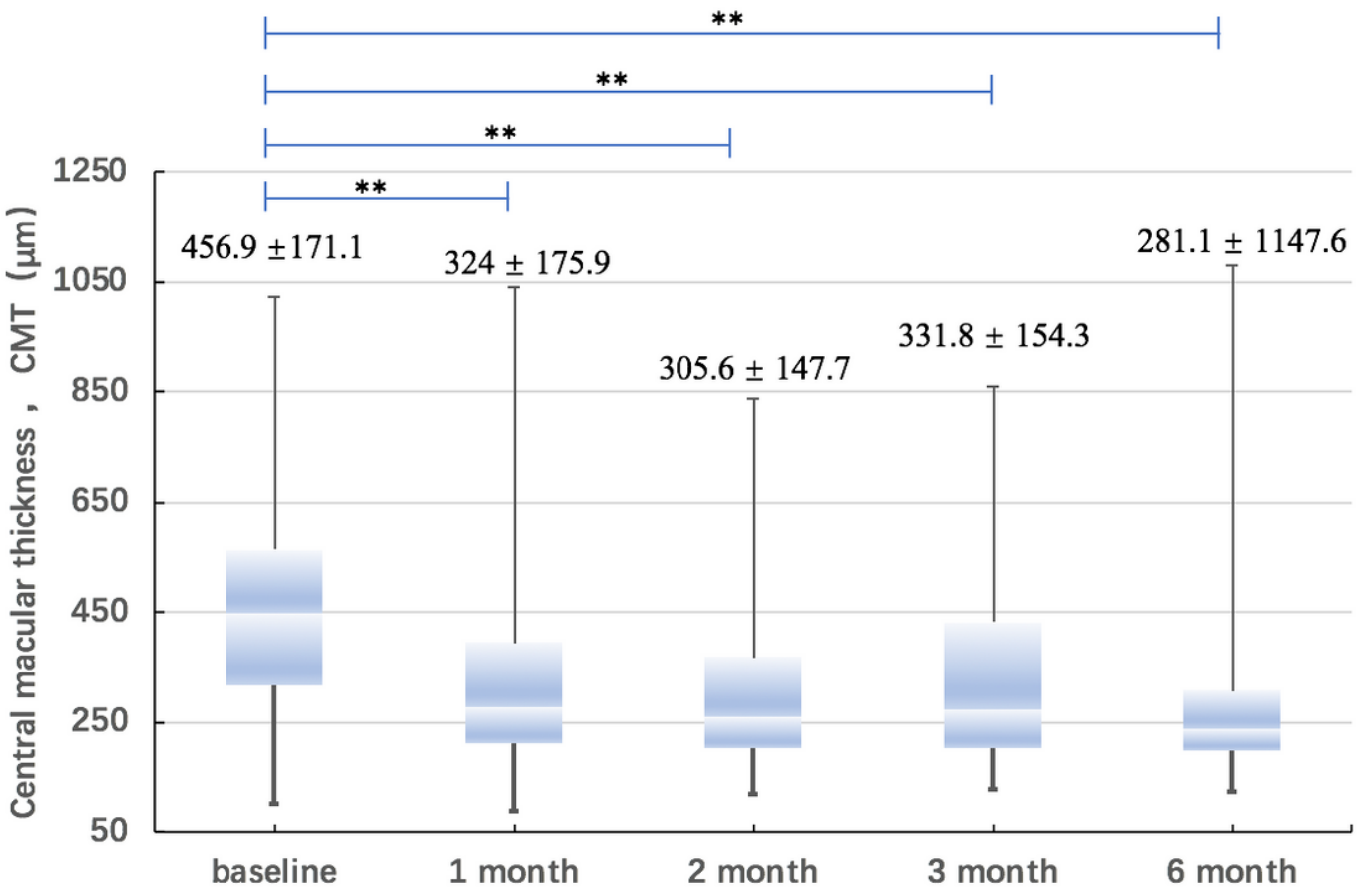

Figure 1

CMT changes after the treatment with subconjunctival injection of TA CMT: Central macular thickness. Asterisk: '*' stands for p<0.05; '**'stands for P<0.01 ; '***' stands for P<0.001

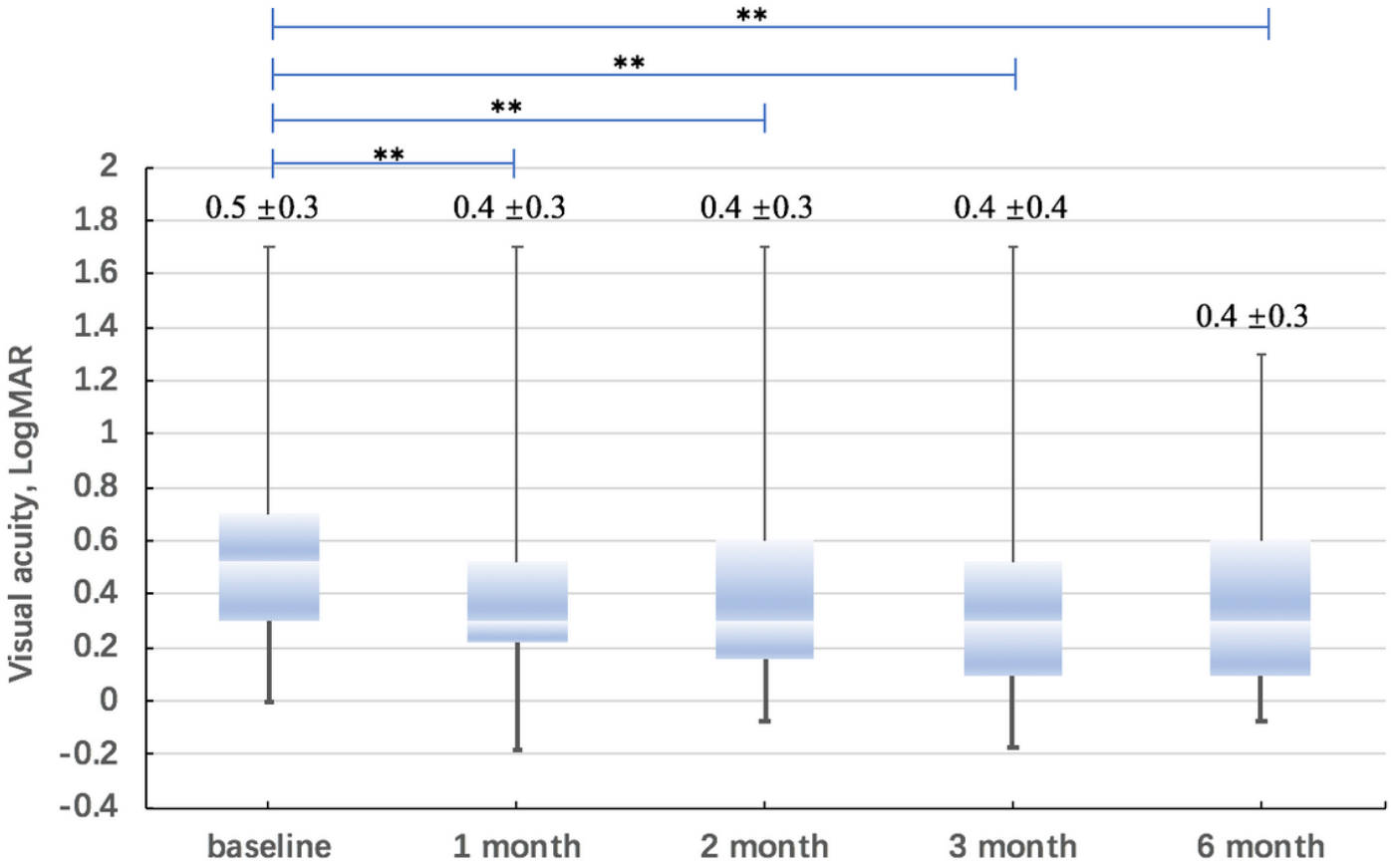

Figure 2

Mean baseline visual acuity and the changes over time. VA: Visual acuity; logMAR : logarithm of the minimal angle of resolution Asterisk: '*' stands for p<0.05; '**'stands for P<0.01 ; '***' stands for P<0.001

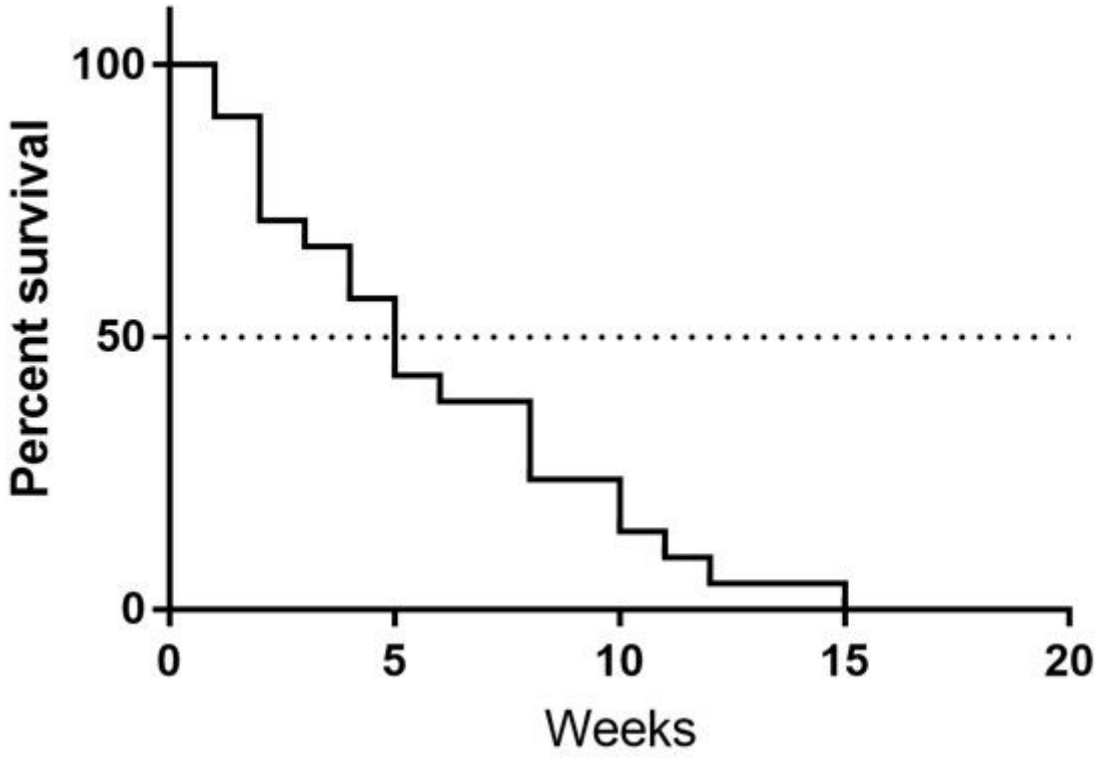

Figure 3

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

Supplementary Files

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- Additionalfile1originaldataset.xlsx