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Research Article

# THERAPEUTIC EFFECTS AND ADVERSE EVENTS OF SINGLE DOSE OF INTRAVITREAL TRIAMCINOLONE ACETONIDE INJECTION IN MACULAR EDEMA

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**ABSTRACT**

**Objective:** The objective of the study was to study the therapeutic effects and adverse events of single dose of intravitreal triamcinolone acetonide (TA) in macular edema (ME).

**Methods:** This prospective observational study was conducted for a period of 18 months in a tertiary care hospital. A total of 100 patients who received intravitreal injection of TA 4 mg were followed up within 1 month of injection and thereafter monthly for 3 months. Therapeutic effect was noted by improvement in visual acuity and reduction in macular thickness. Safety was assessed based on adverse events reported during the study period. The quantitative variables were analyzed by paired t-test and the qualitative variables by Wilcoxon signed-rank test and Chi-square test.

**Results:** The mean age was 58.66±11.21 years with majority of patients (46%) in 46–60 age group. Diabetic retinopathy was the most common etiology. Fifteen patients experienced improvement in vision within 1 month, 51, 84, and 91 patients had better visual acuity after 1, 2, and 3 months, respectively, which were statistically significant (p=0.001). The mean macular thickness of 497.79±115.08 at baseline reduced to 448.62±112.48 within 1 month which further reduced to 383.72±105.79, 327.33±86.49, and 263.83±68.68 at the end of the 1st, 2nd, and 3rd months, respectively (p=0.001). The adverse events of rise in intraocular pressure, cataract, redness, pain, floaters, and subconjunctival hemorrhage were not found to be statistically significant (p>0.05).

**Conclusion:** Intravitreal TA injection may be an effective and safe treatment option for ME due to various etiologies.

**Keywords:** Macular edema, Diabetic retinopathy, Retinal vein occlusion, Triamcinolone acetonide.

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## INTRODUCTION

Macular edema (ME) occurs in a wide variety of ocular diseases [1]. It is the most common cause of vision loss in patients with diabetic retinopathy and other ischemic retinopathies such as branch retinal vein occlusion (BRVO) and central retinal vein occlusion. ME is also a frequent complication of uveitis regardless of its etiology and is commonly seen in patients with retinitis pigmentosa. Thus, ME is a component of many and different types of pathological conditions and is an enormous clinical problem [1].

ME occurs as a result of accumulation of fluid in the outer plexiform and inner nuclear layers of the retina [2,3]. Vision loss in ME is due to breakdown of blood retinal barrier (BRB) due to capillary leakage and abnormal proliferation of intraocular cells. In addition, release of vascular endothelial growth factor (VEGF), cytokines, and other inflammatory mediators play an important role in the pathophysiology of ME [4,5].

ME is diagnosed by a battery of tests including visual acuity test using Snellen chart, fundus examination, optical coherence tomography (OCT), and fluorescence angiography [6]. Previously, focal or grid laser photocoagulation was the standard treatment, which is practiced as per the recommendation of various study groups like early treatment diabetic retinopathy study (ETDRS) group, branch vein occlusion study group, and central vein occlusion study group [7-9]. The current standard of treatment is intravitreal injection and the drugs used are anti-VEGF agents such as bevacizumab, ranibizumab, and corticosteroids like triamcinolone acetonide (TA) [6].

Although intravitreal injection with anti-VEGF agents is the most effective treatment in ME, the disadvantage of high cost and monthly repeat injections has limited their use [6]. TA by inhibiting VEGF, other cytokines and growth factors, regulates the endothelial cell tight junctions. In addition, they inhibit prostaglandin and leukotriene synthesis that reduces edema locally [10]. To achieve desired therapeutic intraocular concentration of TA, it is used as intravitreal injection in the dose of 4 mg [11-13].

TA is considered safe and well tolerated with lasting effects on ME. It has been shown to be devoid of ocular toxicity in various experimental and clinical studies [14-16]. However, certain complications can rise following Intravitreal injection of TA [17-20]. The complications can be drug related or injection related. Drug-related complications include rise in intraocular pressure (IOP) (glaucoma), cataract, and floaters while injection-related complications include pain, retinal detachment, subconjunctival hemorrhage, and vitreous hemorrhage [5].

## METHODS

A prospective observational study was conducted in the Department of Ophthalmology of a Government Medical College in Central Kerala from December 1, 2017, to June 1, 2019 (18 months), in patients with ME, who received intravitreal injection of TA. After getting approval from the Institutional Review Board (IRB No:153/2017), 100 patients who gave informed consent of age 18 years and above of any gender were recruited. Patients with previous administration of intravitreal TA injection and ocular surgery within the past 6 months were excluded. Patients with vitreomacular traction, epimacular membrane, and thickened posterior hyaloid attached at macula as seen in OCT were also excluded from the study.

After taking patient demographics and history, basal visual acuity using Snellen chart, cataract status of the lens, macular thickness using OCT,

and IOP using Schiotz tonometer were recorded in the structured pro forma before injection, within 1 month and then monthly for 3 months following injection. Patients were observed for 1 h for immediate complications after intravitreal injection of 4 mg of TA and then followed up within 1 month and monthly for 3 months. Therapeutic effects were studied from improvement in visual acuity and reduction in macular thickness. Adverse events were identified by recording incidence of redness, pain and floaters which indicated infection, rise in IOP, development, or worsening of cataract following the injection. Rise in IOP above 21 mm of mercury was considered as elevated IOP [21].

The data recorded were entered into MS Excel spreadsheet and were analyzed at the end of study using SPSS software 16.0 trial version. The quantitative variables were analyzed by paired t-test and the qualitative variables by Wilcoxon signed-rank test and Chi-square test.

## RESULTS

This was a prospective observational study done among 100 patients attending the ophthalmology outpatient department, with ME due to various etiologies. The mean age of the patients was 58.66±11.21 years of which 54% were male and 46% were female. Majority (91%) had diabetes mellitus, 46% had hypertension, and 23% had undergone cataract surgery.

As shown in Table 1, the most common etiology was proliferative diabetic retinopathy with clinically significant ME (35%).

As shown in Table 2, there was an improvement in visual acuity scores as evident by decrease in number of patients from counting fingers (CF) 1/2 m to visual acuity of 6/36 1, 2- and 3-month post-injection compared to pre-injection levels.

The visual acuity scores CF ½ m to 6/6 was coded from 0 to 10 accordingly for the purpose of analysis. On comparing the participant's visual acuity before and within 1 month after triamcinolone injection 15 patients became better, nine had experienced a lower visual acuity while 76 had the same visual acuity. Wilcoxon signed-rank test did not elicit a statistically significant (p=0.321) change in the visual acuity and the median visual acuity score was the same (4) for both before and within 1 month after injection.

In the 1 month follow-up, the visual acuity of 51 patients was better compared to before the treatment, four had experienced a lower visual acuity while 45 had the same visual acuity. Wilcoxon signed-rank test showed a statistically significant (p=0.001) change in the visual acuity 1 month after injection and the median visual acuity score improved from 4 to 5.

Two months after injection, visual acuity of 84 patients was better compared to before the treatment, two had lower visual acuity while 14 had the same visual acuity. Wilcoxon signed-rank test showed statistically significant (p=0.001) change in the visual acuity 2 months after injection and the median visual acuity score after 2 months was 5.

Visual acuity of 91 patients was better compared to before the treatment, one had lower visual acuity while eight continued to have the same visual acuity, 3 months after injection and the Wilcoxon signed-rank test was statistically significant (p=0.001) and the median visual acuity score changed to 5.5.

All had visual blurring prior to injection; while 5%, 27%, 53%, and 65% had no visual blurring during subsequent follow-ups.

As shown in Table 3, the number of patients with macular thickness <300 μm increased from 0 to 73% at the end of 3 months following IVTA injection. There was a decline in the number of patients with severe ME (macular thickness >600 μm) from 21% to 4% 1 month after IVTA injection. None of the patients had severe ME 2 and 3 months post-injection.

The mean OCT macular thickness before injection was 497.79±115.03 μm which was reduced to 448.62±112.480 μm, within 1 month post-injection which was found to be statistically significant (mean difference=49.17±47.61 μm, t=10.327, p=0.001).

The patients were assessed for the development of cataract, increase in IOP, presence of redness, pain, floaters, and any other adverse events following IVTA injection.

**Table 1: The etiopathogenesis of macular edema**

| Diagnosis | Number of patients, n (%) |
|---|---|
| Diabetic macular edema | |
| PDR with CSME | 35 (35) |
| Mild NPDR with ME | 8 (8) |
| Moderate NPDR with ME | 17 (17) |
| Severe NPDR with ME | 9 (9) |
| Very severe NPDR with ME | 5 (5) |
| Unstable PDR with ME | 6 (6) |
| Retinal vein occlusion | |
| CRVO with ME | 6 (6) |
| BRVO with CME | 10 (10) |
| Macular BRVO with CME | 2 (2) |
| Retinal macroaneurysm with ME | 1 (1) |
| Combined retinopathy with CSME | 1 (1) |
| Total | 100 (100) |

CRVO: Central retinal vein occlusion, ME: Macular edema, PDR: Proliferative diabetic retinopathy, CSME: Clinically significant macular edema, NPDR: Non-proliferative diabetic retinopathy, BRVO: Branched retinal vein occlusion, CME: Cystoid macular edema

**Table 2: Visual acuity scoring of patients before and after intravitreal triamcinolone acetonide injection**

| Visual acuity score | Code | Percentage of patients (%) | | | | |
|---|---|---|---|---|---|---|
| | | Pre-injection | Within 1 month post-injection | 1 month post-injection | 2 months post-injection | 3 months post-injection |
| CF 1/2 m | 0 | 9 | 6 | 0 | 0 | 0 |
| CF 1 m | 1 | 14 | 11 | 8 | 2 | 0 |
| CF 2 m | 2 | 3 | 10 | 7 | 4 | 3 |
| 5/60 | 3 | 4 | 2 | 34 | 0 | 0 |
| 6/60 | 4 | 30 | 32 | 14 | 28 | 24 |
| 6/36 | 5 | 16 | 12 | 26 | 24 | 23 |
| 6/24 | 6 | 24 | 22 | 3 | 13 | 18 |
| 6/18 | 7 | 0 | 3 | 8 | 6 | 7 |
| 6/12 | 8 | 0 | 2 | 0 | 17 | 20 |
| 6/9 | 9 | 0 | 0 | 0 | 4 | 4 |
| 6/6 | 10 | 0 | 0 | 0 | 1 | 1 |
| Total | - | 100 | 100 | 100 | 100 | 100 |

CF: Counting fingers

**Table 3: Distribution of macular thickness pre-injection and post-injection**

| Macular thickness (μm) | Percentage of patients (%) | | | | |
|---|---|---|---|---|---|
| | Pre-injection | Within 1 month | 1 month post-injection | 2 months post-injection | 3 months post-injection |
| <300 | 0 | 4 | 16 | 40 | 73 |
| 300–400 | 28 | 34 | 48 | 39 | 23 |
| 401–600 | 51 | 50 | 32 | 21 | 4 |
| >600 | 21 | 12 | 4 | 0 | 0 |
| Total | 100 | 100 | 100 | 100 | 100 |

Among the 100 subjects, 19 patients (19%) had Grade 1 cataract, 35 patients (35%) had Grade 2 cataract, 9 patients (9%) had Grade 3 cataract, and 17 patients (17%) had posterior chamber intraocular lens (that is, had undergone cataract surgery previously).

As shown in Fig. 1, even though there was an increase in the number of patients with IOP more than 21 mmHg post-injection during the initial follow-ups, at the end of 3 months, all had normal IOP similar to pre-injection level.

The mean IOP before injection was 13.754±2.678 mmHg which changed to 15.458±11.218 mmHg, within 1 month, to 19.025±33.382 mmHg after 1 month, and to 14.515±3.4927 mmHg 2 months post-injection, however, the changes were not statistically significant. The mean IOP became 13.675±2.130 mmHg 3 months post-injection and comparable to pre-injection level.

Only one patient experienced pain, redness, floaters, and subconjunctival hemorrhage on the day of injection.

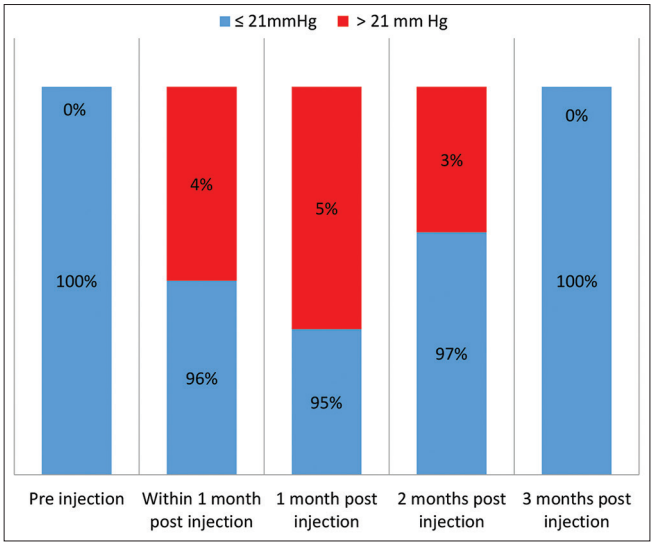


**Fig. 1: Intraocular pressure before and after IVTA injection**

## DISCUSSION

This was a prospective observational study on the therapeutic effects and adverse events of a single dose of intravitreal injection of TA 4 mg for ME due to various etiologies in 100 patients. The mean age was 58.66±11.21 years and majority of patients (46%) belonged to 46–60 age group. In the study by Ahmed *et al.*, it was seen that majority of patients belonged to the 51–60 age group [22]. Jain *et al.* found that the mean age of the patients was 51.3±15.8 years, which was in concurrence to our study [23].

Diabetic retinopathy is the most common cause of ME followed by BRVO [24]. In this study also in concurrence with the literature, we found that diabetic retinopathy was the most common etiology followed by BRVO. Edema caused by leaking microaneurysms and capillaries results in diabetic maculopathy [25]. Among diabetic retinopathy patients, majority (41%) had proliferative diabetic retinopathy (PDR and unstable PDR included). In contrast to our study in the study by Ahmed *et al.*, the maximum number of cases belonged to non-proliferative diabetic retinopathy group as compared to proliferative diabetic retinopathy [22].

Even though, ETDRS study recommends macular laser photocoagulation as the gold standard for the treatment of diabetic macular edema; the clinical outcomes are not promising. Therefore, during the last decade, several studies supported the use of intravitreal pharmacotherapies as adjuncts or alternative treatments to laser photocoagulation. TA by virtue of its stabilization of BRB, anti-VEGF action, and action at cellular levels has been proven to be effective in the management of ME [26]. Two concomitant diseases were considered, which were diabetes mellitus and systemic hypertension. It was seen that majority of patients (91%) had diabetes while only 46% had systemic hypertension. According to Sankara Nethralaya-Diabetic Retinopathy Epidemiology and Molecular Genetic Study-1, duration of diabetes was significantly associated with DR prevalence [27].

On analyzing visual acuity before and after injection, it was found that the median score remained same as 4 before and within 1 month of injection. During the 1st and 2nd months, the score became 5 and later on increased to 5.5 in the 3rd month postinjection. While only 15 patients experienced improvement in vision within 1 month, 51, 84, and 91 patients had better visual acuity after 1, 2, and 3 months, respectively, which were statistically significant (p=0.001). Fernandez *et al.* showed that following IVTA, improvement in visual acuity was recorded in 30.77%, 47.37%, and 52.63%, at 1, 3, and 6 months, respectively (p<0.05 at 3 months) [28]. Jain *et al.* showed that the mean visual acuity at 2 months (1.12±0.45 log of minimum angle of resolution units) and 4 months (1.08±0.46 log MAR unit) after the injection was significantly better than baseline measurements (1.32±0.3 log MAR units) [23].

The mean macular thickness of 497.79±115.08 before injection reduced to 448.62±112.48 within 1 month which further reduced to 383.72±105.79 1 month post-injection, which were statistically significant (p=0.001). Further statistically significant reduction was noted 2 months and 3 months post-injection with mean macular thickness value of 327.33±86.49 and 263.83±68.68 (p=0.001). Ciardella *et al.* showed that mean (SD) OCT macular thickness decreased from 476 (98.32) micrometer at baseline to 277.46 (96.77) micrometer, 255.33 (95.73) micrometer, and 331.25 (146.76) micrometer at 1, 3, and 6 months follow-up period, respectively [29]. Tewari *et al.* observed a 44% and 52% decrease in the central macular thickness at 1 month and 3 months after injection showing effectiveness of IVTA in decreasing macular thickness [30].

Visual blurring, which is a subjective finding, was also assessed and was noted that all 100 patients had visual blurring initially. With IVTA, the blurring decreased and at 3 months post-injection, only 35 patients complained of blurring.

The mean value of IOP pre-injection was found to be 13.75±2.68 mmHg which increased to 15.46±11.22 within 1 month of injection. However, this change was found to be statistically not significant (p>0.05) even though 4% of patients had IOP more than 21 mm Hg. Similarly, there were 5% and 3% of patients, respectively, 1 month post-injection and 2 months post-injection with IOP value more than 21 mmHg, with mean

IOP of 19.025±33.382 and 14.515±3.4927. These changes were also statistically not significant (p>0.05). The mean IOP value 3 months post-injection was 13.675±2.130 and all 100 patients had values less than 21 mmHg. Throughout the 3 months follow-up, there were 11 patients with raised IOP of more than 21 mmHg. In all the cases, the IOP was normalized by topical glaucoma medications and none of the patients required surgery. Jain *et al*. showed that even though IOP significantly increased after the injection at day 1 and day 7, the change in IOP at 1 month, 2 months, and 4 months was not statistically significant which is in concurrence with our study [23].

On assessing the cataract status of the lens, it was found that there were no cases of progression of cataract or development of new cataract throughout the 3 months follow-up. This may be due to the short duration of follow-up. Islam *et al*. showed that the time to first documentation of significant cataract was 16.2 months, with a range of 3–29 months and the majority were posterior subcapsular in nature [31].

The presence of redness and pain was also assessed in the study subjects and was found that only 1% each had any of these adverse events. Even though many patients may experience floaters due to the presence of TA in the vitreous, only one patient complained of floaters that affected the vision. We also looked for the presence of any other adverse events such as retinal detachment, endophthalmitis, and subconjunctival/vitreous hemorrhage. It was seen that only one patient had subconjunctival hemorrhage.

Chang *et al.* found that IOP elevation was the most common complication among all adverse events (11/17, 64.7%), followed by pain in the eye (1/17, 5.9%), floaters (1/17, 5.9%), vitreous hemorrhage (1/17, 5.9%), retinal detachment (2/17, 11.8%), and cataract removal surgery due to advanced cataract formation (1/17, 5.9%) [32]. No cases of sterile or infectious endophthalmitis were observed during this period of study. Similarly, in a study by Sorensen *et al*., no cases of endophthalmitis, retinal detachment, or any other complication caused by the injection procedure other than subconjunctival hemorrhage were noted [33]. In concurrence to our study in that by Spandau *et al.*, none of the study groups showed an infectious or sterile endophthalmitis, pseudoendophthalmitis, or a marked progression of cataract [34].

The study was done in a single center and the follow-up was limited to 3 months. This limitation could be overcome by multicentric study with longer follow-up periods.

## CONCLUSION

Our study suggests that IVTA may be effective in the management of ME of all etiologies. All patients showed significant decrease in mean macular thickness and improvement in visual acuity post-injection. The adverse events recorded were minimal, making this a safe option for the treatment of ME. None of the eyes showed recurrence of ME within 3 months of the injection, suggesting that the effect of drug remains until this time.

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## AUTHORS' CONTRIBUTIONS

Dr. Brighty Mathew: Study design, data collection, and data analysis

Dr. Syam Sreedharan: Provided guidance and data review

Dr. Padmasree Kamala Madhavan: Guidance and data review

Dr. Aparna Retnayyan: Data collection and review.

## CONFLICTS OF INTEREST

The authors confirm that this article content has no conflicts of interest.

## FINANCIAL COMMITMENTS

None.

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