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Research Article

# The Efficacy of Ranibizumab and Triamcinolone on Macular Edema Following Cataract Surgery in Diabetic Retinopathy Patients

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## Abstract

**Purpose:** To compare the efficacy and safety of Intravitreal Triamcinolone Acetonide (IVTA) and Intravitreal Ranibizumab (RAN) in Diabetic Macular Edema (DME) patients Schedule for Cataracta surgery.

**Methods:** The study included 42 eyes of 42 patients. All patients had advanced Cataracta with DME and underwent an uneventful phacoemulsification and intraocular lens implantation. Patients were divided in to 3 groups.The first group received Intravitreal RAN injection (n=12), second group received IVTA (n=10) and the third group did not received any injections (n=20). Follow-up examinations were performed at 1 week, 1 and 3 months postoperatively. A complète ophthalmic examinations and SD-OCT Imaging were performed at each visit.

**Results:** There were 27 (64.3%) female and 15 (35.7%) male patients. The mean age was 64.82±8.0 years. Compared to control Visual acuity significantly improved only in group 1 at 1st and 3rd months. (p<0,05).There were no significant differences for fovéal thickness and intraocular pressure between the three groups. (All p>0.05) Visual acuity significantly improved at 1st months visit in all groups. (All p<0.05) Fovéal thickness showed a réduction only in group 2 at 1st month. It increased in group 1 and 3. (All p<0.05) Intraocular pressure showed an insignificant elevation in group 2 at 1st and 3rd months. (p>0.05)

**Conclusions:** No significant differences were found between the injection groups. Ranibizumab showed a transient increase in visual acuity and IVTA was more effective in reducing foveal thickness.

**Keywords:** Cataract Surgery; Diabetic Macular Edema; Ranibizumab; Triamcinolone

## Introduction

Diabètesaccelerates the formation of visually significant cataracts and patients

Benefit from cataract surgery [1,2]. However, studies have shown that cataract surgery, the definitive treatment for this type of visual impairment, may worsen the underlying diabetic retinopathy and macular edema [3-7]. Thus, ophthalmologists have searched for methods to minimize exacerbation of the retinopathy and to optimize the outcome following cataract surgery. This goal has led to several studies on peri-operative injections of steroids and anti Vascular Endothelial Growth Factor (VEGF) agents to prevent progression of diabetic retinal disease.

Funatsu et al. [8] showed that in diabetic patients, aqueous levels of Vascular Endothelial Growth Factor (VEGF) and interleukin-6 at the time of cataract surgery were significantly correlated with worsening of macular edema postoperatively. In a study by Patel et al. [9] concentrations of angiogenic and anti-angiogenic growth factors were altered after cataract surgery and this alteration may cause progression of diabetic maculopathy. It is possible that eyes of patients with diabetes have higher levels of growth factors, which modulate vascular proliferation and permeability, and this may compromise the ability of retinal vasculature to recover from the injury and subsequent inflammation caused by cataract surgery [10].

Ranibizumab is a human monoclonal anti body which inhib-

its all VEGF-A isoforms. A detailed analysis of phase 3 clinical trials has generated évidence-based guidelines for using ranibizumab for the treatment of Diabetic Macular Edema (DME) [11]. Optical Coherence Tomography (OCT) studies [12,13]found intravitreal steroidal agents to be effective in reducing macular edema. The mechanism of action in diabetic macular edema appears to include inhibition of VEGF and its anti inflammatory effects [14,15].Cataract surgery can be an ideal setting to administer intravitreal medications becausesurgery is performed in a surgically sterile field with full control of the globe and excellent İntraOcular Pressure (IOP) management [16].

The purpose of this study was to compare the efficacy and safety of Intravitreal Triamcinolone Acetonide(IVTA) and Intravitreal Ranibizumab (RAN) in DME patients Schedule for Cataract surgery, to provide a Framework for the future treatment of patients.

## Methods

This prospective clinical study was conducted between 2014 and 2015 in accordance with the principles of the Declaration of Helsinki. The trial protocol has been approved by the Medical Ethical Committee of the University of Kırıkkale. The study included 42 eyes of 42 patients.

All patients had advanced Cataract with DME and underwent an uneventful phacoemulsification and intraocular lens implantation at Kırıkkale University Hospital. Patients were divided in to 3 groups.The first group received RAN injection (n=12), second group received IVTA (n=10) and the third group did not receive any injections (n=20).

Inclusion criteria were sight-limiting Cataract in DM patients with poor fundus view precluding adéquate monitoring and/or macular laser treatment and the presence of macular edemaas determined by flourescein angiography and Spectral Domaine Optical Coherence Tomography (SD- OCT).

Patients with active intraocular inflammation, intractable glaucome, Age-related macular degeneration, a history of ocular trauma or intraocular surgery with in the previous 3 months, any kind of Intravitreal drug injections with in the previous 3 months, retinal laser treatment of me with in the previous 3 months and any known history of adverse reactions to anti-VEGF drugs were excluded.

Initially ophthalmological examinations findings were included; Best-Corrected Visual Acuity (BCVA) which was measured with the Snellen chart and then converted to Logarithme of the Minimum Angle of Resolution (log MAR), Intraocular Pressure (IOP) by Goldmann applanation tonometry and biomicroscopic anterior-posterior segment findings, SD-OCT (OCT Advance Nidek RS-3000; Nidek Co. Ltd., Gamagori, Japan) and Fluorescéine Angiography (FA). After Cataract surgery, Follow-up examinations were performed at 1 week, 1 and 3 months postoperatively. A complete ophthalmic examination and SD OCT imaging were performed at each visit.

All Cataract surgeries were performed Under topical anesthesia by the same surgeon. A clear corneal side incision was made using a 2.75 mm incision technique. The anterior chamber was filled with an ophthalmic viscosurgical device (hydroxypropyl methyl cellulose) and a continuous curvilinear capsulorhexis was created. After phacoemulsification of the nucleus and aspiration of epinucleus and cortical material, a foldable hidrophylic intraocular lens was implanted in to the capsular bag. A 0.05 ml of a solution containing 0.5 mg of ranibizumab (Lucentis, Novartis Pharma AG, Basel, Switzer land.) or triamcinolone acetonide as a off-label drug (prapered from 4 mg/0.1 ml- Kenacort®-A 40; Bristol-Myers Squibb, New York, NY, USA) was injected intravitreally in operating room conditionsat the end of surgery.

SPSS 18.0 statistical program was used for the analysis (SPSS, Inc., Chicago, IL) Parametric differences between the groups were assessed using a multivariate analysis. Paired t test was used to compare the continuous variables. A p value below 0.05 was regarded as statistically significant.

## Results

42 eyes of 42 patients with DME and Cataract who underwent phacoemulsification Cataract surgery with intravitreal injection of 0.5 mg of RAN or 4 mg IVTA were included in the study. There were 27 (64.3%) female and 15 (34.7%) male patients. The mean age was 64.82±8.0 years (range, 51-84 years).

Twelve patients were included in group 1 (RAN). The median hemoglobin value was 8.80 (8.84 ±1.31, range 6.77-11.70), including 9 women (75.0%) and 3 men (75.0%), who had a median age of 65.0 years (mean=64.08±8.57, range 51-83). Ten patients were included in group 2 (IVTA). The median hemoglobin value was 8.71 (8.71±1.19, range 6.77-10.23) including 4 women (40.0%) and 6 men (60.0%), who had a median age of 65 years (mean=63.22±8.16, range 51-83). And 20 patients were included in group 3 (control). The median hemoglobin value was 9.62 (8.23±2.3, range 7.20-12.74) including 14 women (70.0%) and 6 men (30.0%), who had a median age of 65.0 years (mean=66.0±5.61, range 55-76).

In all groups, there were no significant differences in termes of age and HbA1c values. (All p>0.05) At baseline, none of the patients received Prior treatment (either macular laser photocagulation or intravitreal injection) for macular edema. (Table-1) lists the demographic and clinical parameters in study groups.

| Group | N | Age | HbA1C | Va0 | Va1 | Va3 | FT0 | FT1 | FT3 | To0 | To1 | To3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 12 | 64 | 8.8 | 0.85 | 0.63 | 0.67 | 374.1 | 392 | 443.4 | 17 | 15.5 | 15.7 |
| 2 | 10 | 63.2 | 8.71 | 0.76 | 0.43 | 0.43 | 412.6 | 376.2 | 440 | 17.7 | 18.3 | 19.1 |
| 3 | 20 | 66 | 9.63 | 0.74 | 0.39 | 0.39 | 357.6 | 429.9 | 373.8 | 15.5 | 16.1 | 16.3 |
| total | 42 | 64.8 | 9.18 | 0.76 | 0.56 | 0.47 | 351.8 | 392.4 | 394 | 15.8 | 15.6 | 16.7 |

**Table 1:** Demographics and clinical parameters in study groups.

HbA1C=Hemoglobin A1C, Va0=Best corrected visual acuity at baseline, Va1=Best corrected visual acuity at1st month, Va3: Best corrected visual acuity at 3thmonth, FT0=Foveal thickness at baseline, FT1=Foveal thickness at 1st month, FT3=Foveal thickness at 3th month, To0=Intraocular pressure at baseline, To1=Intraocular pressure at1st month, To3=Intraocular pressure at 3th month.

Compared to controls BCVA significantly improved only in group 1 at 1st and 3rd months. (p<0,05). There were no significant differences for Foveal Thickness (FT) and IOP between the three groups. (All p>0.05) (Table-2).

| Groups | Va0 | Va1 | Va3 | FTo | FT1 | FT3 | To0 | to1 | to3 |
|---|---|---|---|---|---|---|---|---|---|
| 1-2 | 0.96 | 0.744 | 0.573 | 0.711 | 0.405 | 1 | 0.961 | 0.405 | 0.158 |
| 1-3 | 0.69 | 0.001 | 0.001 | 0.254 | 0.993 | 0.077 | 0.054 | 0.467 | 0.517 |
| 2-3 | 0.997 | 0.425 | 0.382 | 0.083 | 0.95 | 0.207 | 0.121 | 0.198 | 0.228 |

**Table 2:** Results of statistical comparisons between the groups (p values).

Va0=Best corrected visual acuity at baseline, Va1= Best corrected visual acuity at1st month, Va3: Best corrected visual acuity at 3rd month, FT0= Foveal thickness at baseline, FT1= Foveal thickness at 1st month, FT3=Foveal thickness at 3rd month, To0= Intraocular pressure at baseline, To1= Intraocular pressure at1st month, To3=Intraocular pressure at 3thmonth.

In all groups, BCVA significantly improved at 1stmonths visit. (All p<0.05) At month 3, significant improvement continue in group 2 and 3. (p<0.05) Foveal thickness showed a reduction only in group 2 at 1st month. It increased in group 1 and 3. Changes in FT did not reveal any significance in the study groups. (All p<0.05) Intraocular pressure showed an insignificant elevation in group 2 at 1st and 3rd months. (p>0.05) (Table-3).

| Groups | Va0-val | va0-va3 | va1-va3 | FTo -FT1 | FT0-FT3 | FT1-FT3 | to0-to1 | To1-to3 | To0-to3 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.027 | 0.177 | 0.503 | 0.27 | 0.051 | 0.151 | 0.059 | 0.27 | 0.072 |
| 2 | 0.019 | 0.019 | 0.952 | 0.225 | 0.337 | 0.074 | 0.627 | 0.457 | 0.259 |
| 3 | 0.015 | 0.017 | 0.845 | 0.013 | 0.092 | 0.062 | 1 | 0.854 | 0.837 |

**Table 3:** Comparisons between pre- and postoperative BCVA, FT and IOP changes in study groups.

Va0= Best corrected visual acuity at baseline, Va1= Best corrected visual acuity at1st month, Va3: Best corrected visual acuity at 3rd month, FT0= Foveal thickness at baseline, FT1= Foveal thickness at 1st month, FT3= Foveal thickness at 3rd month, To0= Intraocular pressure at baseline, To1= Intraocular pressure at1st month, To3= Intraocular pressure at 3th month.

No intraoperative complications (posterior capsular rupture, vitreous loss and dropped lens fragments) and postoperative complications (endophthalmitis, retinal tears, and retinal détachement) were observed in the groups.

## Discussion

Eyes with DR have been associated with an increased incidence of postoperative macular edema. The macular edema after Cataract surgery in diabetic patients could be the consequence of Cataract surgery, diabetic retinopathy or both, but it is not usually easy to differentiate between these two entities.

Diabetic macular edema results from multiple biochemical and cellular changes That eventually cause leakage and exudation. Increased permeability factors, interleukin-6 and VEGF and impaired blood-retina barrier may lead to the passage of intravascular fluid in to the intra retinal and sub retinal space through the microaneurysms and abnormal capillaries [18].

Corticosteroids are very potent anti-inflammatory drugs. They not only inhibit the release of VEGFs but also various cytokines as well [19]. Triamcinolone acetonide is almost the first

intravitreal agent used in ophthalmology. The effective concentration of TA in human vitreous humor has not been studied yet, but a similar steroid, fluocinolone acetonide has been reported to be effective at concentrations>0.1 μg/ml [20]. The therapeutic dose of an IVTA injection in human eye is known to be 4 mg/ml. Beer at al reported the pharmacokinetics occurring after direct injection of IVTA in to the vitreous humor [21]. After a single intravitreal injection of triamcinolone acetonide, the mean elimination half-life was 18.6 days in non-vitrectomized patients. The half-life in a vitrectomized eye was shorter (3.2 days). In their study, there was a considerable intra-individual variations among peak concentration, concentration-time curve values and elimination half-lives. After Intravitreal injection, mesurable concentrations of triamcinolone acetonide would be expected to last for approximately 3 months (93 ± 28 days) in the absence of vitrectomy.

In this study, BCVA improved and FT reduced in triamcinolone acetonide injected eyes. The therapeutic effect decreased at 3 months, as expected. Takata et al. [22] found significantly decreased FT and improved BCVA in 12 diabetic patients with refractory diffuse macular edema during 24 week follow up. They measured the lowest FT at 1 month. A gradual increase was observed after 2 months and it reached to baseline level at 6 months. Lam et al. Followed 17 DME patients after combined cataracta surgery and TA injection for 6 months. They found significantly improved BCVA and reduced FT at 2 months. There were no significant differences at 6 months [23] In our study, no significant IOP elevations were found, topical medications were needed only in two patients.

Recent studies [24-26] have established a strong link between alterations in angiogenic growth factors and pathogenesis of DR. Angiogenic growth factors, such as VEGF, induce subclinical and clinical worsening of DR [9,10] and are biochemical mediators of progression of DR and maculopathy after uneventful cataract surgery. Vascular endothelial growth factor is a potent endothelial cell mitogen angiogenic factor and a powerful mediator of vascular permeability. It leads to breakdown of the blood retina barrier, resulting in leakage of intravascular fluid from abnormal retinal capillaries.

Krohne et al. Measured RAN concentration in human aqueous samples and reported the data on the intraocular pharmacokinetics of RAN [27]. They found an aqueous half-life of 7.19 days. Aqueous and vitreous values in some animal models indicate that RAN half-life measurements derived from aqueous samples are a good representation of the vitreous values [28-30]. Muether et al. Measured VEGF suppression in the aqueous humor and showed that the therapeutic effect disappeared after 33.7 ± 5.1 days (31). Pate et al. Measured VEGF levels in 7 diabetic patients after cataracta surgery [9]. There was a Ten fold increase at first day and by the end of first month VEGF levels showed a significant reduction (2.5 fold).

Anti-VEGF drugs may prevent postoperative ME in cataract patients with DR. Chen et al. Reported significant visual improvement and FT reduction after bevacizumab injection in 15 patients [32]. Akıncı et al. Found similar results, but They added grid laser photo coagulation at first month [33]. Cheema et al. Did not observe any significant improvement in FT and visual acuity during the 6 months follow up [34].

The effect of ranibizumab on postoperative ME in DR patients has been shown in a Small number of studies. Rauen et al. Used ranibizumab in 11 refractory DME patients undergoing cataract surgery [35]. There was no control group in their study. The Authors reported that BCVA improved at 4, 8 and 12 weeks. Six patients received macular laser photocoagulation due to increased FT at 4 weeks. They did not find any significant difference in FT postoperatively and linked this to the refractory nature of ME. Chae et al. Investigated the effect of ranibizumab following cataract surgery in 76 DR patients with out ME [36]. They had 39 patients in phacoemulsification group and 37 patients served as controls. There was no significant differences for FT, BCVA at 6 months follow up. Only total macular volume significantly differed in ranibizumab patients. In our study, BCVA improved significantly in RAN patients compared to baseline at month one. Nevertheless, it began to decrease at 3rd month. Foveal thickness increased at 1st month and it continued up to 3rd month. The change was statistically insignificant.

In conclusion, we compared the efficacy and safety of ranibizumab and triamcinolone acetonide in macular edema following cataract surgery in diabetic patients and we found no significant differences between injection groups and non-injection control group. Ranibizumab group showed a transient increase in BCVA and TA group was more effective in reducing foveal thickness. Future studies are still needed to better understand the effect of these drugs on diabetic macular edema following cataract surgery.

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