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Original Article – Clinical Science

Diabetic retinopathy progression 6 months post cataract surgery with intravitreous bevacizumab versus triamcinolone: A secondary analysis of the DiMECAT trial

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Clinical Trial Registration
-Registration SITE: Royal Victorian Eye and Ear Hospital
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ABSTRACT

Importance: Diabetic retinopathy (DR) may progress following cataract surgery due to surgery-induced inflammation. The effect of intravitreal bevacizumab (BVB) and triamcinolone acetonide (TCA), which have differing anti-inflammatory properties, on DR progression following cataract surgery has not been reported.

Background: To report the progression of DR in diabetic patients undergoing cataract extraction treated with intravitreal BVB or TCA during the surgery.

Design: Post-hoc analysis of 6 month data from a prospective, randomized, double-masked clinical trial

Participants: Diabetic patients with clinically significant cataract and fovea involving diabetic macular oedema (DME), or a recent history of DME.

Methods: Participants were randomly allocated 1:1 to receive intravitreal BVB 1.25 mg or TCA 4 mg during and post cataract surgery as needed. The rate of DR progression between groups was compared.

Main Outcome Measure(s): DR progression

Results: There were 61 eyes included. Patients receiving BVB were older than those receiving TCA (70.2 vs. 64.3 years; $P<0.05$). Three participants (10.7%) in the BVB and three (9.09%) in the TCA group had a 1-step progression, while none in BVB and only one (3%) in the TCA group demonstrated 2-step DR progression. In the majority of these patients, DR progression was from mild to moderate NPDR.

Conclusion and relevance: In this study, BVB and TCA groups had a similar, and lower rate of DR progression compared to previous studies where no adjunctive

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treatment was administered, suggesting that patients with DME may benefit from either intra-operative intravitreous BVB or TCA injection to reduce the risk of DR progression following cataract surgery.

Keywords: Diabetic retinopathy, Cataract surgery, intravitreal bevacizumab, Intravitreal triamcinolone acetonide

1. INTRODUCTION

Cataract remains the leading cause of blindness worldwide.[1] Of the 36 million people who are blind, over a third are due to cataract.[2] The presence of cataract is by nature more common in older people, yet its development may be significantly accelerated in people with diabetes mellitus.[2] Therefore, as the rate of diabetes increases, the presence of cataract in persons with diabetes will be more prevalent and the magnitude of cataract surgery in the presence of diabetic retinopathy (DR) and diabetic macular oedema (DME) becomes more pronounced.

Cataract surgery has very high published success rates.[3] However, in persons with diabetes, cataract surgery-induced progression of diabetic retinopathy (DR) has been the subject of debate.[2,4-8] A number of studies have reported that cataract surgery may significantly increases the progression of DR,[4-6,9] whereas other studies have suggested that it does not.[10-12]

Cataract surgery may introduce some degree of inflammation which causes disruption of the blood-retinal barrier.[2,9,13,14] In the context of diabetes, where prolonged low-grade inflammatory processes have already occurred, one may speculate that the effect of surgically-induced inflammation and blood-retinal barrier disturbance might be multiplied, thus significantly affecting the progression of DR.[2,9,13,15] In support of this, previous evidence by Cheema and associates showed that perioperative intravitreal bevacizumab (BVB),[16] which is known to inhibit vascular endothelial growth factor (VEGF) and improve retinal vascular permeability,[17] may prevent the

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progression of DR after cataract surgery. In addition, there is also evidence suggesting that the administration of intravitreal triamcinolone acetonide (TCA), which has potent anti-inflammatory and some anti-angiogenic effect,[18,19] may also reduce the deterioration of DR.[20,21] Nevertheless, there have been no studies that provide direct comparison between these two agents in reducing the risk of DR progression following cataract surgery.

The Diabetic Macular Edema at the time of Cataract Surgery Trial (DiMECAT) is a prospective, double-masked randomized trial aiming to compare the effect of intravitreal BVB versus TCA on visual and anatomical outcomes when administered as an adjunct at the time of cataract surgery, and as needed post operatively, in patients with diabetes undergoing cataract surgery.[20,21] In this paper, we reported the progression of DR following cataract surgery among participants given intravitreal BVB versus TCA.

As there is good evidence that inflammation attributable to cataract surgery occurs within 1 month after the surgery and will return to pre-operative levels thereafter, the effect this may have on DR progression would be expected to be apparent by 6 months post-surgery.[20,21] This post hoc analysis of patients recruited in the DIMECAT trial was thus performed in order to assess the relative effect of bevacizumab and triamcinolone on the progression of diabetic retinopathy when administered for treatment of DME at the time of cataract surgery.

2. METHODS

2.1 Study Design and Participants

This was a secondary analysis of the DiMECAT trial, assessing progression of DR as the primary outcome in this study. The detailed methodology of DiMECAT has been previously described.[20,21] In brief, DiMECAT is a prospective, randomized with 1:1 allocation ratio, double-masked with parallel treatment, comparison clinical trial.

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The study protocol adhered to the tenets of the Declaration of Helsinski and ethical approval was obtained from the Human Research Ethics Committee of the Royal Victorian Eye and Ear Hospital (RVEEH), Melbourne, Australia. Written informed consent was obtained from all study participants prior to their participation.

This study included diabetic patients with fovea-involving diabetic macular edema (DME), or refractory DME within 24 months of study entry or a recent history of treated DME, plus visually significant cataract. Patients with other potential causes of macular edema were excluded. Eligible participants were recruited from the Medical Retina Clinic at RVEEH between June 2012 to August 2017 and were randomly allocated to receive either intravitreous BVB or TCA following their consent. We excluded all patients who had macular laser within 12 weeks of enrolment or intravitreal BVB within 3 weeks or TCA within 10 weeks.

2.2 Cataract Surgery

All patients underwent standard ophthalmic examination prior to surgery, including biometry, IOL Master (Zeiss, Carl Zeiss Meditec Ltd, Jena, Germany) or an A-Scan. Phacoemulsification with intraocular lens (IOL) implantation was performed using standard technique under topical or regional anesthesia. The AcrySoft SN60WF (Alcon, Inc, Fort Worth, TX) IOL was used in all cases. Intravitreous injections were administered following the surgery using 30-gauge needle for BVB or 27-gauge for TCA. Prednisolone acetate 1% (Prednefrin Forte, Allergan) and Chloramphenicol 0.5% (Chlorsig, Sigma Pharmaceuticals, Australia) eye drops were prescribed 4 times daily for 1 week, after which the topical steroids only were continued and tapered off within 4 weeks after surgery. In the event of complicated surgery, patients were withdrawn from the trial without administration of study treatment.

2.3 Patients Assessment and Follow-up

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All study participants were assessed at baseline (up to two weeks before the surgery) and followed-up at 1 week post-surgery and monthly thereafter. Participants' characteristics including age, gender, diabetes history, HbA1c, use of medication and any ophthalmic history, including laser photocoagulation or previous intravitreal injection were documented.

Routine ophthalmic assessment was performed at each follow-up. This included best corrected visual acuity (BCVA) testing using logarithm of the minimum angle of resolution (LogMAR) with an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, intraocular pressure (IOP) measurement using a Goldmann applanation tonometer, slit lamp biomicroscope and fundus examination. Macular thickness over a 6 mm macular area was assessed using spectral-domain optical coherence tomography (OCT) (Heidelberg Engineering, Heidelberg, Germany).

2.4 Retinal Photography and Diabetic Retinopathy Grading

Seven-field fundus photographs were obtained from all participants after pupil dilation at baseline and at 6 month visit using Topcon TR50EX (Topcon Inc, Tokyo, Japan). Fluorescein angiography was performed only at 6 months. All imaging procedures were done by trained and certified personnel masked to any participant's characteristic or study treatment. DR was graded based on ETDRS DR severity grading scale and further categorized according to the international clinical diabetic retinopathy disease severity scale by the American Academy of Ophthalmology (AAO) as follows: No DR (ETDRS level 10), Mild Non-Proliferative DR (NPDR) (ETDRS level 20), Moderate NPDR (ETDRS levels 35, 43, 47), Severe NPDR (ETDRS levels 53 A-E), Proliferative DR (PDR) (ETDRS levels 61, 65, 71, 81, 85).[22,23] DR grading was performed by certified and experienced graders at the Singapore Eye Research Institute (SERI) Ocular Reading Centre.

2.5 Methods of Literature Search

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We performed a systematic literature search to identify all studies reporting the progression of DR following cataract surgery. Search terms “diabetic retinopathy AND progression AND cataract surgery” were used to retrieve all English-published articles available from Medline, EMBASE, Current Contents, EBSCO, JSTOR and Science Direct. A total of 182 citations were identified to July 2018 after excluding duplicate citations. Irrelevant title and abstracts were then also excluded and after further review of the remaining articles’ full texts, only 18 relevant articles were identified.

2.6 Statistical Analyses

We used intention-to-treat analyses including all data from baseline to 6 month follow-up. Completed baseline and 6-month assessment for DR grading was achieved in 56 eyes (91%). Participants without 6-month fundus images were considered to have the same DR level as the previous follow-up using the last value carried forward (LVCF). DR progression was defined as a 1-level increase in the international clinical DR disease severity scale by the AAO (e.g. mild NPDR to moderate NPDR or severe NPDR to PDR), or the development of active neovascularization in previously treated (with PRP laser treatment) inactive PDR.

Baseline characteristics were analyzed as continuous or categorical variables, and comparisons between BVB and TCA groups were tested using independent t-test for continuous variables and chi-square test for categorical variables. Number and proportion of participants with different DR severity at baseline and 6 months follow-up was cross-tabulated and DR progression from baseline to 6 months was tested using chi-square test.

3. RESULTS

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There were 61 participants (61 eyes) included in this analysis. The baseline characteristics of both treatment groups were similar, except for age where the mean age in the group receiving BVB was statistically older (70.2 vs. 64.3; P<0.05) (**Table 1**). The distribution of DR severity at baseline and any treatment procedures prior to study enrolment was also not statistically different between the groups.

Table 1: Baseline characteristics of study participants and eyes, by treatment group

Characteristics per person	**BVB (N=28 eyes)**	**TCA (N=33 eyes)**
Age (at time of surgery), years, mean (CI)	70.2 (67.4 – 73.0)	64.3 (61.1 – 67.5)*
Male gender, n (%)	18 (64.3)	24 (72.7)
HbA1c % (at time of surgery), median (IQR)	7.5 (7 – 8.6)	7.5 (6.3 – 8.4)
Diabetes type, n (%)		
Type 1	0	1 (3.0)
Type 2	28 (100.0)	32 (97.0)
Characteristics per eye		
Right eye, n (%)	64.3	54.5
BCVA at baseline, letters, mean (CI)	55.1 (48.7 – 61.4)	50.5 (45.3 – 55.8)
IOP, mmHg, median (IQR)	11.7 (6 – 19)	13.5 (9 – 19)
DR severity at baseline, n (%)		
Mild NPDR	1 (3.6)	6 (18..8)
Moderate NPDR	13 (46.6)	11 (33.3)
Severe NPDR	3 (10.7)	5 (15.1)
PRP only (inactive PDR)	9 (32.1)	11 (33.3)

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Active PDR	2 (7.1)	0
DME presence at baseline, n (%)	22 (78.6)	26 (78.8)
Prior treatment of study eye, n (%)		
Any treatment (BVB, TCA or focal laser)	14 (50.0)	20 (60.6)
Macular laser	13 (46.6)	18 (54.6)
PRP laser	10 (35.7)	9 (27.3)
BVB	3 (10.7)	3 (9.1)
TCA	1 (3.6)	0

* indicates P-value <0.05

Abbreviations: **BCVA**, Best Corrected Visual Acuity; **CI**, 95% confidence interval; **IOP**, Intra Ocular Pressure; **IQR**, interquartile range; **DR**, Diabetic Retinopathy; **NPDR**, Non-Proliferative Diabetic Retinopathy; **PDR**, Proliferative Diabetic Retinopathy; **PRP**, Pan Retinal Photocoagulation; **DME**, Diabetic Macular Edema; **BVB**, Bevacizumab; **TCA**, Triamcinolone Acetonide

Table 2 shows the progression of DR in both treatment groups over the 6 month post-operative period. There were three participants (10.7%) in the BVB group and three (9.09%) in the TCA group who developed a 1-level DR progression (P=0.6). Furthermore, there was one (3%) participant in the TCA group who had a 2-level DR progression, while none in BVB group progressed to this extent (P=0.8).

Table 2: Progression of DR through to 6 months after cataract surgery, by treatment group

Retinopathy Severity change from baseline to 6 months	Treatment group		P-value
	BVB	TCA	
No progression	25 (89.3)	29 (84.9)	

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1-step progression	3 (10.7)	3 (9.09)	0.609
2-step progression	0 (0.0)	1 (3.03)	0.8

P-value was estimated using Chi-square test, with no progression as comparison

1-step progression was defined as a 1-level increase in severity scale (e.g. mild to moderate NPDR, moderate to severe NPDR)
2-step progression was defined as a 2-level increase in severity scale (e.g. mild to severe NPDR)

Figure 1 shows DR severity levels at baseline and at 6 months in the BVB and TCA treatment groups. In the BVB group, one participant progressed from mild to moderate NPDR and two progressed from moderate to severe NPDR. There was also one participant with persistent active PDR who did not experience further deterioration. In the TCA group, three participants progressed from mild to moderate NPDR, and one participant progressed from mild to severe NPDR over the 6-month period.

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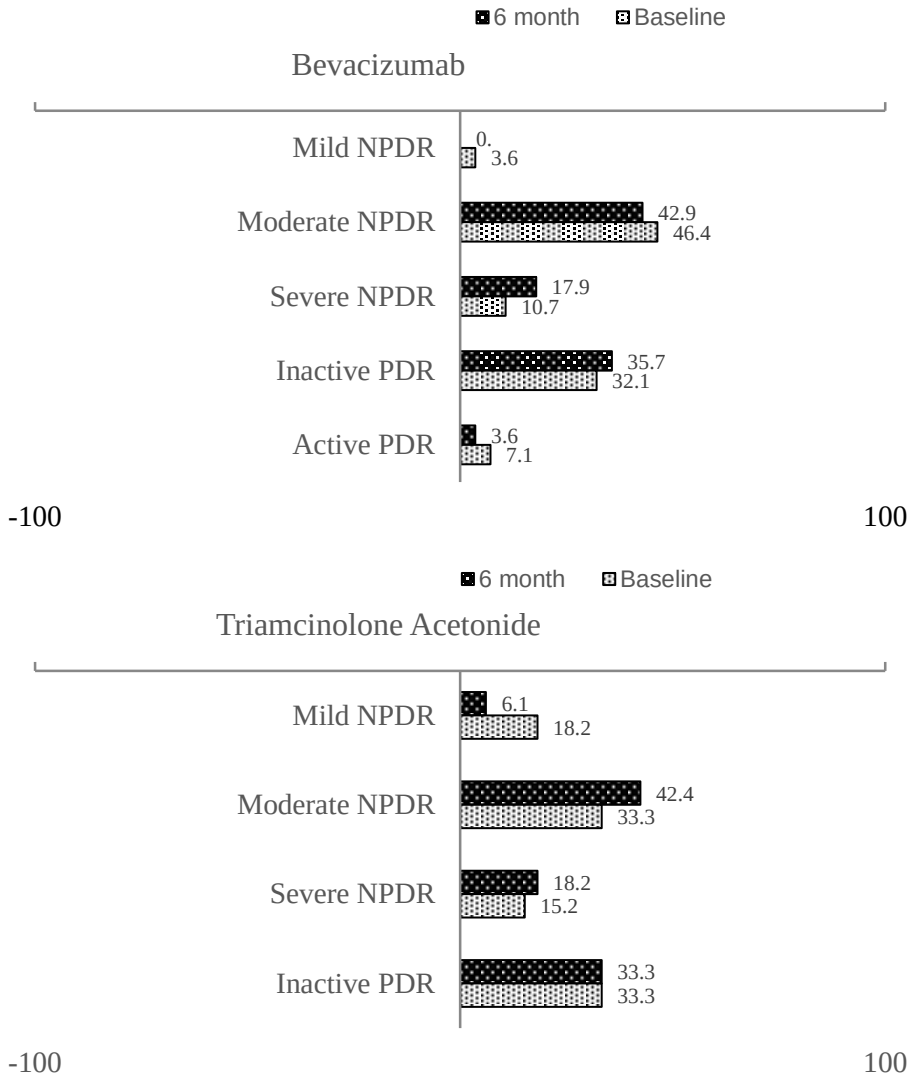

Figure 1: DR severity at baseline and 6 months in the Bevacizumab and Triamcinolone Acetonide treatment groups

NPDR, Non-Proliferative Diabetic Retinopathy; **PDR**, Proliferative Diabetic Retinopathy

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4. DISCUSSION

This study demonstrated that the rate of DR progression within 6 months after cataract surgery was low in eyes treated with BVB and those treated with TCA. Thus, our findings suggest that both intravitreous BVB and TCA appear to slow the progression of DR in patients with diabetes requiring cataract surgery, when compared with diabetic patients observed in earlier studies who were not given adjunctive therapies.

Our study is the first to directly compare DR progression of diabetic patients with additional intravitreal BVB and TCA injections at the time of cataract surgery, and post-operatively as required. A very recent meta-analysis reported that a comparable rate of DR progression among patients undergoing cataract surgery with prophylactic intravitreal BVB was 9.7% within 6 months.[24] A previous study by Cheema and associates also showed a significantly lower rate of DR progression in those with combined cataract surgery and intravitreal BVB injection compared to cataract surgery alone (11.4% vs. 45.5%; $P<0.05$).[16] In contrast, there have been few prospective studies of the use of TCA in this situation. A small prospective study by Habib et al. demonstrated that the rate of DR progression among study participants undergoing cataract surgery with intravitreal TCA was 33% over at least 5 months, higher than the rate reported in our study.[25]

Progression of DR in diabetic patients after cataract surgery has been a subject of debate over the last two decades, with two opposing conclusions regarding whether or not cataract surgery increased, or did not increase, the risk of DR progression post-operatively.[4-6,9-11,13,26] In **table 3**, we have outlined all existing studies of DR progression following cataract surgery with various surgical techniques. Overall, the rate of DR progression following cataract surgery ranged from 12% to 50% within 6 to 12 months post-operatively. These variations were similar regardless of

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surgical technique. While some studies showed relatively low DR progression after cataract surgery (less than 20%),[26-28] most of these studies suggested that the rates of DR progression were greater than 25%, significantly higher than found in this study. Unfortunately, we were unable to perform a meta-analysis and obtain a pooled progression rate due to the marked heterogeneity and lack of good quality data owing to the varying study designs. Nonetheless, it is worth nothing that a large, prospective cohort study by Hong and colleagues demonstrated that the risk of DR progression was almost doubled following cataract surgery (without adjunctive treatment) over 12 months, thus providing strong evidence that cataract surgery does indeed increase the risk of DR progression.[9]

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Table 3: Summary of previously-published studies that examine DR progression after cataract surgery

Author (Year)	Study Design	Study Population	Progression of DR	Cataract Surgery Technique	Author's Recommendation
Jaffe et al. (1988)[4]	Prospective	8 patients with NPDR	To severe, exudative DR in 6 months	ECCE and ICCE	Cataract surgery causes progression of DR
Pollack et al. (1991)[8]	Retrospective	89 patients with various stages of DR	38.2% progressed in 6 months	ECCE and ICCE	Risk of progression of DR after cataract surgery is high

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Pollack et al. (1992)[29]	Retrospective	33 patients with DR previously treated with PRP	18% progressed in 3 months, 12% progressed within 6 months	ECCE and ICCE	Laser treatment should be applied at least 3 months prior to cataract surgery
Jaffe et al. (1992)[5]	Prospective	21 patients with symmetric NPDR	74% progressed in 18 months	ECCE and ICCE	Cataract surgery increases the risk of DR progression
Hykin et al. (1993)[30]	Retrospective	56 patients with PDR	50% had deterioration of PDR	ECCE	Active PDR is a poor prognostic indicator after cataract surgery

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Henricsson et al. (1996)[31]	Prospective	70 patients with various stage of DR	39% progressed 2 step and 4% progressed 3 step in 18-32 months	ECCE and Phacoemulsification	Poor glycemic control is predictor of DR progression
Wagner et al. (1996)[12]	Prospective	223 patients with diabetes	18.4% developed DR and 27.6% progressed in 6 months	Phacoemulsification	Progression of DR after cataract surgery is due to the natural course of DR
Sadiq et al. (1999)[26]	Retrospective	118 patients with diabetes and 118 non-diabetics	16.1% patients with diabetes had DR progression	ECCE and Phacoemulsification	Cataract extraction may initiate or progress DR
Kato et al. (1999)[6]	Prospective	66 patients with DR and no DR	36.3% progressed in 12 months	Phacoemulsification	Surgical intervention accelerate the progression of DR

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Mittra et al. (2000)[7]	Retrospective	119 patients with diabetes	25% progressed in 6 to 10 months	Phacoemulsification	NPDR, longer surgical duration and inexperience surgeon increases the rate of progression
Squirrell et al. (2002)[11]	Prospective	50 patients with type 2 diabetes	20% progressed in 12 months	Phacoemulsification	Uncomplicated cataract surgery does not cause DR progression
Chung et al. (2002)[32]	Prospective	75 patients with DR and no DR	30.6% progressed in 12 months	Phacoemulsification	Presence of preoperative macular edema and poor renal function increase the progression of DR postoperatively

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Krepler et al. (2002)[27]	Prospective	42 patients with mild-moderate NPDR	12% progressed within 12 months	Phacoemulsification	Modern cataract surgery has little influence on the progression of NPDR
Chatterjee et al. (2004)[33]	Retrospective	30 patients with type 2 diabetes	23.4% progressed in 6 months	Phacoemulsification	Afro-Caribbean ethnicity has higher rate of DR progression
Hauser et al. (2004)[13]	Retrospective	48 patients with diabetes		Phacoemulsification	Poor diabetes control increases the risk of DR progression

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Suto et al. (2006)[34]	Prospective	87 patients with type 2 diabetes	19.5% progressed in 12 months	Phacoemulsification	Rapid perioperative glycemic control increases the risk of progression of DR and maculopathy
Romero-Aroca et al. (2006)[10]	Prospective	132 patients with diabetes	23.5% had progression of DR	Phacoemulsification	Uncomplicated phacoemulsification does not cause DR progression
Hong et al. (2009)[9]	Prospective	1994 general cataract patients, 190 with diabetes with various stage of DR	28.2% developed DR, 35.6% progressed in 12 months	Phacoemulsification	Phacoemulsification substantially increases the risk of developing DR and progression of DR

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Abbreviations: **DR**, Diabetic Retinopathy; **ECCE**, Extracapsular Cataract Extraction; **ICCE**, Intracapsular Cataract Extraction; **NPDR**, Non-Proliferative Diabetic Retinopathy; **PDR**, Proliferative Diabetic Retinopathy

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Our findings that additional intravitreal BVB and TCA injection may slow the progression of DR after cataract surgery can be well explained. In the event of cataract surgery, patients with diabetes may undergo a series of unfavorable changes in intraocular inflammatory cytokines and VEGF levels.[13,14] Such changes cause disruption of retinal perfusion homeostasis, causing breakdown in the blood retina barrier, and thus accelerate the progression of DR.[35,36] Fundamentally, BVB and TCA work in different ways. BVB has been widely known for its ability to inhibit intraocular VEGF and improve vascular permeability,[17] whereas TCA is known to have both anti-inflammatory and anti-angiogenic effects.[19] There is additional empirical evidence that the use of intravitreous steroid may improve the degree of ischaemia in the peripheral retina.[37] In our DIMECAT trial, 70.6% of the BVB group required additional injections in the 6 month post-operative period, compared to only 16.7% of the TCA group ($P<0.001$).[20,21] Furthermore, the mean number of re-treatment injections in BVB and TCA groups were 1.76 and 0.17 respectively ($p>0.05$).[20,21] Nonetheless, albeit that BVB and TCA might work differently, the use of either of these agents as adjunct therapy at the time of cataract surgery may potentially reduce the adverse consequence of cataract surgery on DR progression.

Our study has important clinical implications. In addition to the existing literature suggesting that intravitreal BVB injection may help prevent DR progression after cataract surgery in patients with diabetes, we were able to show that intravitreal TCA injection may also have a beneficial and notably similar effect to BVB in slowing the progression of DR. If confirmed, considering that TCA is cheaper and more widely available than BVB, these study findings may be applied to various situations where BVB is not easily available (e.g. remote areas, limited healthcare resources). The main concern of intravitreal TCA administration has been its side effect in increasing intraocular pressure (IOP).[38] However, a recent prospective randomized

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clinical trial comparing periocular TCA versus intravitreal TCA versus the dexamethasone implant found that all three regimens resulted in only a subtle IOP increase, with no significant difference found between the degree of IOP rise induced by intravitreous TCA when compared with the dexamethasone implant.[39]

Strengths of this study include its prospective design with a well-established protocol, comprehensive patient examinations by experienced retinal specialists and patient recruitment from large public hospital, which provides a more heterogeneous patient population that may be more representative of the general population. However, we acknowledge that there are some limitations to this study, which include its small size, absence of a control group and post-hoc analysis. The DIMECAT trial was designed specifically to investigate the effect of Bevacizumab and triamcinolone on DME at the time of cataract surgery and not DR progression. The factors that led to a smaller than anticipated sample size in this trial have been discussed elsewhere[20] and included a sudden increase in wait times for cataract surgery part way through the study that negatively impacted patient recruitment, and high rates of medical co-morbid events requiring exit from the study. Whether a larger sample size would show a different result deserves further study. Second, the baseline age of participants was significantly different in the group treated with BVB compared to TCA. Nonetheless, as the actual age difference was only 5.9 years, it is unclear whether an individual's response to BVB or TCA injections would be influenced by this age difference. Therefore, we cannot speculate if this age difference may or may not have influenced our findings. Finally, the original aim of the DiMECAT trial was to compare the efficacy of intravitreous BVB vs. TCA on DME at the time of cataract surgery, with the primary outcomes being vision and central macular thickness.[21] As such, the trial did not have an untreated control group, particularly since doing so would entail withholding Pharmaceutical Benefit Scheme (PBS) approved treatment in these patients. Nevertheless, we performed an extensive literature search and provided results from previous studies for comparison.

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In conclusion, our study demonstrated a lower rate of DR progression in diabetic patients undergoing cataract surgery with additional intravitreal BVB or TCA injections at the time of the surgery, as compared to existing evidence with patients without any adjunctive treatment. These findings suggest that patients with diabetes may benefit from either intravitreous BVB or TCA injection at the time of the surgery and as required post-operatively, to slow the deterioration of DR following cataract surgery.

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