

Treatment History as a Predictor for Change in Visual Acuity After Surgical Correction of Diabetic Retinal Traction Detachment

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Received Nov. 24, 2021; Accepted for publication Jan. 26, 2022; Published online April 29, 2022
<https://doi.org/10.17161/kjmvoll5.16036>

ABSTRACT

Introduction. Tractional retinal detachment remains a leading cause of severe, persistent vision loss in those with diabetic retinopathy. The purpose of this study was to investigate factors in treatment history associated with outcomes of surgical repair for diabetic tractional retinal detachments.

Methods. A retrospective, cohort study design was used. Data on 64 eyes that underwent surgical correction for diabetic tractional retinal detachment were analyzed. For eyes that received any treatment within three months of surgery, the entire treatment history was recorded and analyzed. Eyes with no recorded treatment or only remote treatment outside of three months prior to surgery were considered treatment naïve.

Results. Of all eyes, 56% (n = 36) had received treatment for proliferative diabetic retinopathy in the three months prior to surgery. Among those treated, 50% (n = 18) of eyes had both laser and bevacizumab treatments and 44% (n = 16) had only bevacizumab injections. Average best corrected visual acuity (BCVA) for all eyes improved from 1.68 LogMAR (20/1,000) pre-operatively to 1.34 (20/400) post-operatively, p = 0.0017. Average BCVA in eyes with pre-operative treatment history improved from 1.73 (20/1,000) pre-operatively to 1.09 (20/250) post-operatively, p = 0.0006. Average BCVA in treatment-naïve eyes was 1.60 (20/800) pre-operatively and 1.66 (20/1,000) post-operatively, p = 0.638. Eyes treated only with intravitreal injections had an improvement in BCVA from 1.81 (20/1,200) pre-operatively to 0.91 (20/160) post-operatively, p = 0.006. There was no difference between tamponade agents when comparing mean change in BCVA, p = 0.944.

Conclusions. There was a relationship between intravitreal injection treatment history and a large improvement in BCVA, and a similar association between combined laser and injection treatment history and improvement in BCVA. These relationships, however, were not present when controlling for confounders in multivariate analysis. There were likely other factors in the patient's treatment history such as timing, quantity, and order of treatments that played a role in the bivariate association observed in this study. *Kans J Med* 2022;15:123-126

INTRODUCTION

Diabetic retinopathy is a pervasive complication of diabetes mellitus, with an estimated prevalence of 28.5% to 40.3% among U.S. adults 40 years or older with diabetes mellitus.^{1,2} Among this same population, the prevalence of vision-threatening retinopathy, defined as severe

non-proliferative retinopathy, proliferative diabetic retinopathy (PDR), or macular edema, is estimated to be 4.4% to 8.2%.^{1,2}

Although laser photocoagulation treatment for proliferative diabetic retinopathy is associated with favorable long-term visual acuity stability in most patients,³ tractional retinal detachment (TRD) remains a leading cause of severe, persistent vision loss in those with diabetic retinopathy.⁴ Despite better control of PDR with intravitreal injections as an adjunct to laser,⁵ and effective control of non-proliferative diabetic retinopathy (NPDR) with intravitreal injections alone,⁶ once a retinal detachment has developed, surgery is the only remaining intervention to prevent profound blindness. Pars plana vitrectomy (PPV) can be effective in improving anatomical and visual outcomes in patients with TRD.⁷ Newer 23 and 25 gauge vitrectomy systems and even hybrid techniques have shown non-inferior outcomes to older 20 gauge instruments while offering advantages such as shorter operating times, reduced pain and inflammation,⁷⁻¹¹ minimal induced astigmatism, and improved patient comfort.¹⁰

Significant research has been done to identify outcome predictors among patients undergoing PPV for diabetic complications, with focus on surgical technique or pre-existing conditions.^{7,9,12} For instance, the use of silicone oil as a tamponade agent has been associated with poorer outcomes when compared to C3F8 or SF6 gasses.^{7,9} Regardless of poor outcomes in certain cohorts, the overall success rate defined as final anatomical reattachment approaches 80% for all studied eyes.⁷ Although several studies and case reports have explored bevacizumab as a pre-surgical treatment,¹²⁻¹⁷ little research focus has been given to pre-surgical treatment history of intravitreal injections and laser photocoagulation as outcome predictors for surgical repair of diabetic TRD. The purpose of this study was to identify factors in treatment history associated with outcome measures (i.e., change in visual acuity and retinal re-attachment rate) among patients who underwent surgical repair of diabetic tractional retinal detachments.

METHODS

Participants. A retrospective chart review was performed at a single ophthalmology group practice for patients seen between January 1, 2011 and June 15, 2018 inclusive. Eligible patients were 18 years or older who underwent surgical repair of diabetic TRD. Patients who had fewer than 30 days of post-operative follow up were excluded.

Instrument. A list of eligible patients was compiled by filtering International Classification of Disease (ICD) and Current Procedural Terminology (CPT) codes for patients with diabetic retinopathy who underwent surgical repair of either vitreous hemorrhage or retinal lesion. A list of 445 patients was generated, from which patients who met the inclusion criteria were selected by co-investigators. Data were abstracted into REDCap®.¹⁸ Data collected included patient demographics, pre-operative baseline measurements [e.g., treatment history, best corrected visual acuity (BCVA), intraocular pressure (IOP), and macula involvement], operating surgeon, surgical instruments and materials (e.g., instrument gauge, tamponade agent), post-operative

measurements (e.g., peak BCVA, IOP, anatomical success), intra- and post-operative complications, hypertensive status, hemoglobin A1C, and renal status (i.e., dialysis).

If an eye received treatment in the three months prior to surgery, all treatment history for diabetic retinopathy was recorded regardless of date of administration. A remote history of treatment outside of the three months prior to surgery also was recorded, but these eyes were considered treatment-naïve for the purpose of this study, as three months has been used previously as a washout period when studying intravitreal bevacizumab.¹⁹ All visual acuity measurements were converted to log of the minimum angle of resolution (logMAR) notation for analysis.²⁰

Procedures. This study was approved by the University of Kansas School of Medicine-Wichita's Human Subjects Committee and the ophthalmology practice's privacy officer. All work was compliant with the Health Insurance Portability and Accountability Act of 1996, and the research adhered to the tenants of the declaration of Helsinki. A retrospective chart review was performed, data were abstracted, de-identified, and analyzed in SAS (Version 9.4) software (SAS® Int. Inc., Cary, NC).

Statistical Analysis. Descriptive statistics for nominal, categorical, and continuous variables were conducted using PROC FREQ and PROC UNIVARIATE in SAS. Shapiro-Wilk was used for the test of normality of continuous variables. Bivariate analysis was conducted using treatment type, surgeon, tamponade agent, and pre-operative characteristics [e.g., rhegmatogenous retinal detachment (RRD), macula involvement, and dialysis] by pre-operative to post-operative change in BCVA. Retinal re-attachment rate was not included as an outcome measure for statistical analysis due to all but one eye achieving anatomical re-attachment. In case of non-normal distribution with appropriate transformation operations, the rank transform approach to nonparametric methods was used as combination of PROC RANK and PROC GLM in SAS to enable use of covariates in the models tested for change in BCVA. Several longstanding nonparametric tests including Kruskal-Wallis are either exactly equivalent to rank transform tests or are nearly equivalent to them. Covariates-adjusted least-squares means (to estimate the marginal means over a balanced population) were used for pairwise comparisons of groups by Tukey test using Kramer adjustment. All statistical tests at $p \leq 0.05$ were significant.

RESULTS

A total of 64 eyes from 53 patients were included in the study (Table 1). Eyes that had pre-or post-operative acuities of light perception (LP) or no light perception (NLP) could not be converted to LogMAR.²⁰ Two eyes improved from LP to count fingers (CF), three eyes improved from LP to hand motion (HM), and one eye improved from NLP to HM. One eye developed neovascular glaucoma and worsened from 20/400 to NLP.

Table 1. Patient characteristics.

Variable	
Number of eyes	64
Number of patients	53
Number (percent) of eyes in males	26 (41%)
Number (percent) of eyes in females	38 (59%)
Mean age at surgery (years)	49
Mean pre-operative IOP (mm Hg)	15
Mean post-operative day 1 IOP (mm Hg)	17
Number (percent) hypertensive patients	46 (72%)
Number (percent) dialysis patients	13 (20%)
Number (percent) type I DM	14 (22%)
Number (percent) type II DM	50 (78%)

Of all eyes, 56% (n = 36) had received treatment for proliferative diabetic retinopathy in the three months prior to surgery. Among those treated, 50% (n = 18) of eyes had both laser and bevacizumab treatments, 44% (n = 16) had only bevacizumab injections, one eye had only laser photocoagulation, and one eye had only ranibizumab injections. Seventeen percent (n = 11) of all studied eyes had received remote treatment longer than three months prior to surgery, and 27% (n = 17) of all studied eyes had no recorded treatment.

Three surgeons operated and used 25G instruments on all procedures except one, which used 20G instruments. Thirty-five percent (n = 25) of eyes were tamponaded with silicone oil, 13% (n = 8) with C3F8, 14% (n = 9) with SF6, and 14% (n = 9) with air. Sixteen percent (n = 10) of eyes had a combined tractional and rhegmatogenous retinal detachment, and 31% (n = 20) had macula involvement.

The most common complications were post-operative vitreous hemorrhage (38%, n = 24) and re-detachment (9%, n = 6). No intra-operative complications were reported. Of note, one eye did not achieve final anatomical success but BCVA did not change from CF pre-operatively. Among all eyes, mean post-operative IOP was 17 mm Hg (range: 5 - 38 mm Hg), and 22% (n = 14) of eyes had an IOP greater than 21 mmHg at the one-day post-operative visit.

Average BCVA for all eyes improved from 1.68 (20/1000, SD 1.07) pre-operatively to 1.34 (20/400, SD 1.05) post-operatively, $p = 0.0017$ (Figure 1).

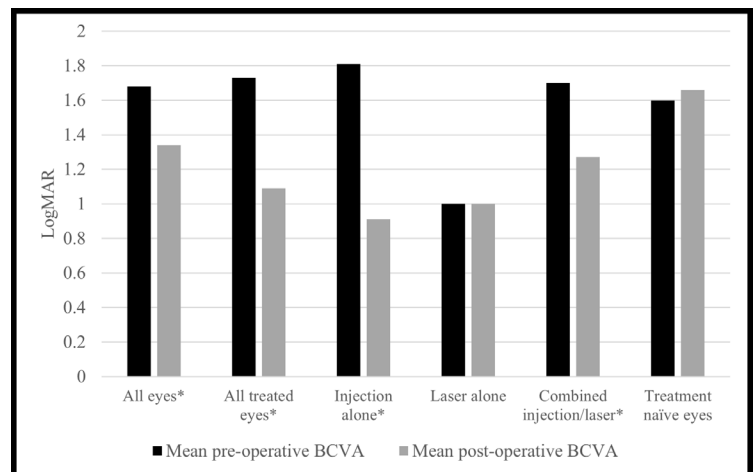


Figure 1. Difference in pre- and post-operative means among treatment types. * $p < 0.05$ when comparing pre-operative to post-operative BCVA

When comparing average change of pre-operative to post-operative BCVA between treatment types, eyes with treatment history of only injections changed 1.031 LogMAR, which was better than 0.091 LogMAR for treatment-naïve eyes, $p = 0.031$. Mean change of pre-operative to post-operative BCVA for eyes with treatment history of combined laser and injections was 0.529 LogMAR and was not different from any other treatment types, including no treatment. There was no difference between tamponade agents when comparing mean change in BCVA, $p = 0.944$. When comparing post-operative BCVA between tamponade agents, silicone oil (1.77 LogMAR, 20/1,200 snellen) and no tamponade (1.73 LogMAR, 20/1,000) were worse than air (0.66 LogMAR, 20/90) and SF6 (0.43 LogMAR, 20/50), $p = 0.001$. C3F8 (1.163 LogMAR, 20/300) was not different from any other agent.

One surgeon's (A) cases had an average BCVA improvement from pre-operative to post-operative of 1.125, $p = 0.002$, and the other two surgeons' (B, C) mean changes in BCVA pre-operatively to post-operatively were not different than zero (0.217, $p = 0.286$ and 0.282, $p = 0.086$). The improvement by 1.125 for surgeon A was greater than the improvements by 0.217 and 0.282 for surgeons B and C respectively, $p = 0.021$. Of note, surgeons A and C had fewer treatment-naïve eyes, and surgeon B had the largest number of cases (Table 2).

Table 2. Number of cases by surgeon.

Surgeon	A	B	C
Total number of cases	18	35	11
Treatment-naïve	2	24	1
Any treatment	16	11	9
Laser photocoagulation only	0	0	1
Laser plus injection	8	4	6
Injection only	8	7	2
One injection	7	4	1
Two injections	0	1	0
Three or more injections	1	2	1

Presence of a rhegmatogenous component ($p = 0.166$) or macular involvement ($p = 0.273$) did not have an association with change in visual acuity. Final reattachment was achieved on 98% ($n = 63$) of eyes. Six eyes re-detached, and five were reattached successfully with seven more surgeries total. Treatment type ($p = 0.158$), tamponade agent ($p = 0.620$), or surgeon ($p = 0.059$) were not associated with a change in the pre-operative to post-operative BCVA when analyzed in ANOVA ($p = 0.092$).

DISCUSSION

This study suggested that all eyes with any treatment history, treatment history of injection only, and treatment history of both injection and laser had pre-operative to post-operative improvements in visual acuity. Nearly half of all eyes (44%, $n = 28$) in this study had not received any form of treatment for their retinopathy in the three months prior to the date of surgery. This differed from a prior study that reported only 15% had untreated eyes.⁷ By excluding remote treatments beyond three months, the current study may have elevated this proportion artificially. Instrumentation gauge in this study reflected trends of surgeons' increased use of 25G instruments,⁸⁻¹¹ and a re-detachment rate of nine

percent and no reported intra-operative complications in this study were consistent with similar literature reports.²¹

There appeared to be no consensus for method of reporting visual acuity as an outcome of interest, with some studies using categorical data to report outcomes,^{3,7,21} whereas others reported means of pre- and/or post-operative acuities.^{8,9,12,22} The current study averaged the delta of the pre- and post-operative BCVA for bivariate and multivariate analysis. While there was no Snellen conversion for a change in LogMAR, this method has the advantage of utilizing continuous data for the eye's pre-operative acuity and may better account for the severity of the disease prior to surgical intervention. While this method may overestimate the surgical results of eyes with pre-surgical poor acuity due to dense vitreous hemorrhage or other media opacities but an intact neurosensory macula, the potential value of controlling a confounding factor was worth considering. For example, when analyzing tamponade agent by post-operative BCVA, the current study found similar results to prior research,^{7,8} suggesting silicone oil was associated with poorer visual outcomes. When using change in pre- to post-operative BCVA, however, the current study suggested no difference in results between tamponade agents.

In bivariate analysis, treatment type and operating surgeon were associated with a change in BCVA. A prior study that retrospectively evaluated intravitreal bevacizumab within one month of surgery found BCVA improvements in all analysis groups, even those not receiving a pre-operative injection.¹⁶ The current study expanded on that finding in that eyes with a three month or more history of intravitreal injection treatment were associated with a large improvement in pre-operative to post-operative BCVA. Where this study differed was the suggestion that vision in treatment-naïve eyes did not improve pre- to post-operative. The visual improvement in injected eyes may be a result of the better proliferative diabetic retinopathy control physicians are achieving with injections,²³ or an improvement in vitrectomy technique, as others have suggested.^{13,16}

The surgeon (A) with a significant difference between pre- and post-operative acuities had a low proportion of treatment-naïve eyes and a high proportion of eyes with a history of single bevacizumab injections. This suggested the surgeon may be using bevacizumab as a pre-treatment for a higher proportion of their surgical cases, and this usage pattern certainly fit previous studies' definition of bevacizumab pre-treatment.^{16,17} However, caution must be exercised with bevacizumab pre-treatment as there have been reports of rapid progression of TRD following intravitreal bevacizumab.^{14,15}

Regardless, when the variables of operating surgeon, treatment type, and tamponade agent were all controlled for in multivariate analysis, none of these variables were associated with a change in BCVA from pre- to post-operation. This lack of association may be due to other factors in the treatment history, such as timing, quantity, or order of treatments. While the number of eyes analyzed in the current study was like other studies evaluating diabetic TRD outcomes,^{8,17,22} the relative

infrequency of this diabetic complication made it challenging to power a study with so many potential confounding factors.

Limitations. Although the study was to include the collection of information regarding patients' control of diabetes and hypertension, these data were not readily available in all patients' charts. Of the 46 patients who were reportedly hypertensive, blood pressure measurements were not available, although all were documented to be on an oral antihypertensive. The length of diabetes prior to surgery and hemoglobin A1C also was missing from most charts. These missing data prevented this study from controlling for possible systemic confounders of hypertension and diabetes control, which have not been established to be associated with poor visual outcome, but have been theorized to be significant with a larger sample size.²² Another limitation of this study was the lack of control for media opacities, specifically dense vitreous hemorrhage and timing of cataract extraction, if performed. This limitation potentially overestimated an association with acuity change, but if included, these extra variables likely would diminish the statistical power of the analysis further.

REFERENCES

- 1 Zhang X, Saaddine JB, Chou CF, et al. Prevalence of diabetic retinopathy in the United States, 2005-2008. *JAMA* 2010; 304(6):649-656. PMID: 20633456.
- 2 Kempen JH, O'Colmain BJ, Leske MC, et al. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol* 2004; 122(4):552-563. PMID: 15078674.
- 3 Chew EY, Ferris FL, Csaky KG, et al. The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy. *Ophthalmology* 2003; 110(9):1683-1689. PMID: 13129862.
- 4 Fong DS, Ferris FL 3rd, Davis MD, Chew EY. Causes of severe visual loss in the early treatment diabetic retinopathy study: ETDRS report no. 24. *Am J Ophthalmol* 1999; 127(2):137-141. PMID: 10030553.
- 5 Figueira J, Fletcher E, Massin P, et al. Ranibizumab plus panretinal photocoagulation versus panretinal photocoagulation alone for high-risk proliferative diabetic retinopathy (PROTEUS study). *Ophthalmology* 2018; 125(5):691-700. PMID: 29395119.
- 6 Bressler SB, Liu D, Glassman AR, et al. Change in diabetic retinopathy through 2 years: Secondary analysis of a randomized clinical trial comparing aflibercept, bevacizumab, and ranibizumab. *JAMA Ophthalmol* 2017; 135(6):558-568. PMID: 28448655.
- 7 Storey PP, Ter-Zakarian A, Philander SA, et al. Visual and anatomical outcomes after diabetic traction and traction - Rhegmatogenous retinal detachment repair. *Retina* 2018; 38(10):1913-1919. PMID: 28796149.
- 8 Dikopf MS, Patel KH, Setlur VJ, Lim JI. Surgical outcomes of 25-gauge pars plana vitrectomy for diabetic tractional retinal detachment. *Eye (Lond)* 2015; 29(9):1213-1219. PMID: 26183284.
- 9 Lakhpanal RR, Humayun MS, de Juan E Jr, et al. Outcomes of 140 consecutive cases of 25-gauge transconjunctival surgery for posterior segment disease. *Ophthalmology* 2005; 112(5):817-824. PMID: 15878061.
- 10 Thompson JT. Advantages and limitations of small gauge vitrectomy. *Surv Ophthalmol* 2011; 56(2):162-172. PMID: 21236459.
- 11 Kumar A, Duraipandi K, Gogia V, Sehra SV, Gupta S, Midha N. Comparative evaluation of 23- and 25-gauge microincision vitrectomy surgery in management of diabetic macular traction retinal detachment. *Eur J Ophthalmol* 2014; 24(1):107-113. PMID: 23709329.
- 12 Lo WR, Kim SJ, Aaberg TM Sr, et al. Visual outcomes and incidence of recurrent vitreous hemorrhage after vitrectomy in diabetic eyes pretreated with bevacizumab (avastin). *Retina* 2009; 29(7):926-931. PMID: 19584650.
- 13 Chen E, Park CH. Use of intravitreal bevacizumab as a preoperative adjunct for tractional retinal detachment repair in severe proliferative diabetic retinopathy. *Retina* 2006; 26(6):699-700. PMID: 16829817.
- 14 Arevalo JF, Maia M, Flynn HW, et al. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. *Br J Ophthalmol* 2008; 92(2):213-216. PMID: 17965108.
- 15 Jonas JB, Schmidbauer M, Rensch F. Progression of tractional retinal detachment following intravitreal bevacizumab. *Acta Ophthalmol* 2009; 87(5):571-572. PMID: 18631336.
- 16 Pokroy R, Desai UR, Du E, Li Y, Edwards P. Bevacizumab prior to vitrectomy for diabetic traction retinal detachment. *Eye (Lond)* 2011; 25(8):989-997. PMID: 21738230.
- 17 Oshima Y, Shima C, Wakabayashi T, et al. Microincision vitrectomy surgery and intravitreal bevacizumab as a surgical adjunct to treat diabetic traction retinal detachment. *Ophthalmology* 2009; 116(5):927-938. PMID: 19269033.
- 18 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42(2):377-381. PMID: 18929686.
- 19 Chalam KV, Grover S, Sambhav K, Balaiya S, Murthy RK. Aqueous interleukin-6 levels are superior to vascular endothelial growth factor in predicting therapeutic response to bevacizumab in age-related macular degeneration. *J Ophthalmol* 2014; 2014:502174. PMID: 25110587.
- 20 Holladay JT. Visual acuity measurements. *J Cataract Refract Surg* 2004; 30(2):287-290. PMID: 15030802.
- 21 Abunajma MA, Al-Dhibi H, Abboud EB, et al. The outcomes and prognostic factors of vitrectomy in chronic diabetic traction macular detachment. *Clin Ophthalmol* 2016; 10:1653-1661. PMID: 27616879.
- 22 La Heij EC, Tecim S, Kessels AGH, Liem ATA, Japing WJ, Hendrikse F. Clinical variables and their relation to visual outcome after vitrectomy in eyes with diabetic retinal traction detachment. *Graefes Arch Clin Exp Ophthalmol* 2004; 242(3):210-217. PMID: 14663594.
- 23 Ip MS, Domalpally A, Hopkins JJ, Wong P, Ehrlich JS. Long-term effects of ranibizumab on diabetic retinopathy severity and progression. *Arch Ophthalmol* 2012; 130(9):1145-1152. PMID: 22965590.

Keywords: diabetic retinopathy, bevacizumab, retinal diseases, visual acuity, retrospective studies