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Factors Associated with Visual Acuity Outcomes after Vitrectomy for Diabetic Macular Edema

Diabetic Retinopathy Clinical Research Network*

Abstract

Purpose—To evaluate factors associated with favorable outcomes after vitrectomy for diabetic macular edema (DME).

Methods—Data were collected prospectively on 241 eyes undergoing vitrectomy for DME. Multivariate models were used to evaluate associations of 20 preoperative and intraoperative factors with 6-month outcomes of visual acuity and retinal thickness.

Results—Median central subfield thickness decreased from 412 μm to 278 μm at 6 months, but median visual acuity remained unchanged (20/80, Snellen equivalent). Greater visual acuity improvement occurred in eyes with worse baseline acuity ($P<0.001$) and in eyes in which an epiretinal membrane was removed ($P = 0.006$). Greater reduction in central subfield thickness occurred with worse baseline visual acuity ($P<0.001$), greater preoperative retinal thickness ($P = 0.001$), removal of internal limiting membrane ($P = 0.003$), and with optical coherence tomography evidence of vitreoretinal abnormalities ($P = 0.006$). No associations with clinician's preoperative assessments of the posterior vitreous were identified.

Conclusion—These results suggest that removal of epiretinal membranes may favorably affect visual outcome after vitrectomy. Pre-operative presence of vitreoretinal abnormalities appeared to be associated with somewhat greater reductions in retinal thickness but not with visual acuity outcome. These results may be useful for future studies evaluating vitrectomy for DME.

Summary Statement—In 241 eyes undergoing vitrectomy for diabetic macular edema, greater improvement in retinal thickening was independently associated with both greater thickening and worse visual acuity preoperatively, but greater improvement in visual acuity only with worse preoperative visual acuity, in both cases likely reflecting, at least in part, ceiling effects.

Keywords

Diabetic Macular Edema; Retinal Thickness; Visual Acuity; Vitrectomy

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Introduction

Macular edema is a major cause of central vision loss in patients with diabetic retinopathy. While vitrectomy has been performed as a treatment for diabetic macular edema (DME), information on the precise benefits and risks has been limited by the lack of substantial prospective data. The Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a prospective, observational study involving 241 eyes to evaluate visual and anatomic outcomes following vitrectomy performed to treat DME. We previously reported the outcome from the primary cohort of this study, specifically the 87 eyes with DME, preoperative visual acuity of 20/63 to 20/400 (Snellen Equivalent), and optical coherence tomography (OCT) central subfield thickness >300 μm that underwent vitrectomy, without concomitant cataract extraction. Within the primary cohort the indication for vitrectomy was the presence of vitreomacular traction (based on investigator assessment).[1] Although 6 months following vitrectomy the mean central retinal thickness decreased in most eyes within this primary cohort, a minority of eyes had improved visual acuity at this same time point. No strong correlation was found between vision and OCT outcomes. This subsequent report describes analyses from all 241 eyes enrolled in this study to try to identify if there were any pre-operative or intra-operative factors associated with visual acuity or OCT outcomes 6 months following vitrectomy.

Methods

The study was conducted by the DRCR.net at 50 clinical sites throughout the United States. The protocol and Health Insurance Portability and Accountability Act-compliant informed consent forms were approved by multiple institutional review boards. Each study participant gave written informed consent to participate in the study. Details of the protocol have been reported previously and the full protocol is available on the DRCR.net website (www.drcr.net, (Accessed April 13, 2010)). The study is listed on www.clinicaltrials.gov, (Accessed April 13, 2010) under identifier NCT00709319.

This study included individuals who were undergoing vitrectomy as treatment for DME. Eligible participants had to be at least 18 years old with type 1 or type 2 diabetes, and have blood pressure ≤ 180/110. The eye having vitrectomy had to meet the following criteria: 1) retinal thickening involving the center of the macula due to DME based on clinical exam, 2) presence of vitreomacular traction related to the edema, or in the absence of traction the edema is judged to persist despite previous non-surgical treatment and considered by the investigator unlikely to respond to further macular photocoagulation, and 3) best corrected visual acuity ≥20/800 (Snellen equivalent). Major study eye exclusion criteria included the following: 1) a history of macular photocoagulation, intravitreal corticosteroids, or other treatment for DME within 3.5 months prior to vitrectomy (a period judged to be sufficient to realize the effects of these interventions), 2) peripheral scatter (panretinal) photocoagulation within 4 months prior to vitrectomy, 3) prior pars plana vitrectomy, 4) other major ocular surgery (such as cataract extraction, scleral buckle, or any other intraocular surgery) within 6 months prior to or anticipated within the next 6 months following vitrectomy, or 5) YAG capsulotomy performed within 2 months prior to vitrectomy. A study participant could have only one study eye.

A standard pars plana vitrectomy, including the use of intraoperative dyes and drugs, was performed according to the investigator's usual routine. Postoperatively, injectable medications, focal/grid photocoagulation, or other treatments for DME were to be deferred until completion of the primary outcome assessment at the 6-month visit. Panretinal photocoagulation could be given at any time following surgery if judged medically necessary. Details describing the surgical procedure and the data collected postoperatively have been reported.[1] Follow-up visits were performed at 3, 6, and 12 months. Prior to surgery and at each

follow-up visit, a standardized refraction was performed and best-corrected visual acuity was measured at 3 meters by a certified visual acuity examiner using the Electronic- Early Treatment Diabetic Retinopathy Study Visual Acuity Tester (E-ETDRS Visual Acuity Test©). A letter score comparable to Early Treatment Diabetic Retinopathy Study chart testing was generated. OCT images were obtained at each of these visits through a dilated pupil by a certified operator using the Zeiss Stratus OCT (OCT3, Carl Zeiss Meditec Inc., Dublin, California). Seven field stereoscopic color fundus photographs were performed by certified photographers at the baseline visit. Photographs and OCT images were graded centrally (Fundus Photograph Reading Center; University of Wisconsin-Madison, Madison, WI).

Statistical Methods

Separate regression models were used to evaluate the association of preoperative and intraoperative variables (see Table 1 for listing of variables evaluated) with changes in visual acuity or OCT measured central subfield (CSF) thickness from baseline to 6 months after vitrectomy. Continuous values of these factors were evaluated in the models, wherever possible. Models for visual acuity change used ranks of the visual acuity letter scores transformed to have normal distributions using van der Waerden[2] scores and models for change in retinal thickness used a logarithmic transformation of CSF thickness ("logOCT").[3] Change in logOCT was calculated by taking the log (base 10) of the CSF thickness measurements divided by 200 (an approximation of normal CSF thickness with Stratus OCT3 instrument), and then subtracting the baseline logOCT from the 6-month logOCT and rounding to the nearest hundredth. LogOCT values were used to describe improvement or worsening in retinal thickness by ≥0.1, which represents approximately a 20% change in CSF thickness and is referred to as a one-step change. This amount of change is about double the error of measurement which is approximately 11% irrespective of the magnitude of thickness.[4] The association between change in visual acuity from baseline to 6 months and change in CSF thickness was evaluated with a Spearman correlation coefficient.

For visual acuity and CSF thickness outcomes, factors with a *P* value <0.10 in univariate models were included in multivariate models, with a final model consisting of factors with a *P* value <0.01 following a backwards selection process. In the multivariate models, missing values of covariates were handled by treating missing as a separate category for discrete covariates and adding a missing indicator variable for continuous covariates.

Study participants who did not complete a 6-month examination were excluded from all analyses. Similar results were obtained when the analyses were replicated using 2 methods to account for missing outcome data: last-observation-carried-forward and Rubin's multiple imputation.[5] All reported *P* values are 2-sided, unadjusted for multiple comparisons. In view of the large number of variables evaluated, only associations with *P* values <0.01 were considered unlikely to be due to chance. Statistical analyses were conducted utilizing SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

Results

The study included 241 eyes (of 241 study participants) that had a vitrectomy performed by 74 surgeons as treatment for DME between 2005 and 2008. Average age of the participants was 65 ± 10 years; 121 (50%) were women and 183 (76%) were white. Median visual acuity prior to surgery was a letter score of 57 (20/80 Snellen equivalent) with an interquartile range of 45 to 66 (20/50 to 20/125). Median CSF thickness was 412 μm (interquartile range 337 to 540). Over half (55%) had evidence of proliferative diabetic retinopathy (defined as neovascularization, fibrous proliferations or prior scatter (panretinal) photocoagulation lesions based on the grading of fundus photographs) at the time of vitrectomy and 72% had received prior treatment for DME. The clinician's primary reason for vitrectomy was vitreomacular

interface abnormality or traction in 170 (71%) eyes. Surgeons reported peeling an epiretinal membrane (ERM) in 146 eyes (61%) and removing internal limiting membrane (ILM) in 154 (64%). Removal of ERM and ILM was concordant in 141 eyes (in 100 both were peeled and in 41 neither were peeled) and discordant in 100 (approximately half in each direction). Various agents were commonly used (66%) to enhance visualization during surgery and at the close of the procedure corticosteroids, in some form, were administered in the majority (68%). Distributions of these and other clinical and surgical characteristics are listed in Table 1.

Six-month follow up was completed for 228 (95%) of the eyes. Six study participants died prior to 6 months, 4 dropped out of the study prior to 6 months, and 3 missed the 6 month visit. At 6 months, the median visual acuity letter score (Snellen equivalent) remained 57 (20/80) with an interquartile range of 44 to 69 (20/40 to 20/125). Median CSF thickness improved to 278 μm (interquartile range 216 to 371 μm). Visual acuity and OCT outcomes 3 and 12 months after vitrectomy were similar to the 6-month outcomes (data not shown).

Factors Associated with Visual Acuity Outcome

Visual acuity improved from baseline to month 6 by ≥10 letters in 26% (95% confidence interval(CI) 20% to 32%) of eyes and worsened by ≥10 letters in 22% (95% CI 17% to 27%). In the multivariate model (Table 2), among 20 factors evaluated (listed in Table 1 and supplemental Table 3 available at www.retinajournal.com), only the following 2 factors were associated with greater mean visual acuity improvement from baseline to month 6 (based on a *P* value <0.01): worse baseline visual acuity ($P \leq 0.001$) and ERM removal during surgery ($P = 0.006$).

The correlation between change in visual acuity from baseline to the 6-month visit and change in CSF thickness was −0.25. Visual acuity outcomes in categories stratified by both preoperative visual acuity and CSF thickness are shown in Table 4. The association of greater baseline CSF thickness with greater mean visual acuity improvement was of borderline significance in a univariate model (P=0.03, Table 2) but was dropped from the multivariate model that included baseline visual acuity.

In a multivariate model limited to eyes that were pseudophakic at the 6-month visit, baseline visual acuity ($P = 0.002$) was still associated with greater mean improvement in visual acuity from baseline to the 6-month visit; removal of an ERM was not as strongly associated with superior visual acuity in this subgroup ($P = 0.12$). Visual acuity outcomes appeared similar when the preoperative clinical impression was that vitreoretinal traction was present and when traction was not present ($P = 0.41$).

Factors Associated with Retinal Thickness Outcomes

A ≥1 logOCT step reduction in thickness from baseline to the 6-month visit occurred in 57% (95% CI 51% to 64%) of eyes and a ≥1 logOCT step increase in thickness occurred in 4% (95% CI 1% to 7%). In the univariate model, OCT outcomes were similar when the preoperative clinical impression was that vitreoretinal traction was present and when traction was not present ($P = 0.89$). In the multivariate model (Table 5), among the 20 variables evaluated (Supplemental Table 6, www.retinajournal.com), 4 were associated ($P<0.01$) with greater mean reduction in CSF thickness from baseline to the 6-month visit: greater baseline CSF thickness ($P = 0.001$), worse baseline visual acuity ($P<0.001$), removal of the ILM at surgery ($P = 0.003$), and reading center identification of definite or questionable vitreoretinal abnormalities on OCT ($P = 0.006$).

Impact of Lens Changes on the Results

One hundred and eleven (49%) eyes were pseudophakic prior to vitrectomy, cataract extraction was performed at the time of vitrectomy in 16 (7%) eyes and after vitrectomy but before the 6-month examination in 14 (6%) eyes, and 87 (38%) eyes remained phakic through the 6-month visit (Table 1). Eyes remaining phakic at the 6-month visit appeared more likely to have a decrease in visual acuity from the pre-operative to the 6-month visit measurement than eyes that were pseudophakic at the pre-operative exam (Table 2), but there was no difference in the change in CSF thickness comparing phakic and pseudophakic eyes (Supplemental Table 6, www.retinajournal.com).

Among the 87 eyes that remained phakic through the 6-month visit, 66 were clinically assessed at baseline to have either no lens opacity or an opacity that was less apparent than each of the standard photographs illustrating nuclear opacity, cortical opacity, and posterior subcapsular opacity. Twenty five of these eyes (38%) were clinically graded to have progressed at 6 months to an opacity greater than at least 1 of the 3 standard photographs. The remaining 21 phakic eyes had an opacity greater than at least one of the 3 standard images at baseline. The clinician's grade of lens opacity at the 6-month visit was downgraded in 4 eyes and unchanged in 17.

Discussion

We analyzed 20 preoperative and intraoperative variables to identify factors potentially associated with either a better visual acuity or better OCT outcome following vitrectomy for management of DME. The specific indications for vitrectomy varied, many different surgeons were involved, and there was diversity within the surgical procedures performed. The results are remarkable for the lack of significant associations such that relatively few factors were found to have any substantial impact on surgical outcomes. Importantly, although retinal thickness tended to improve as visual acuity improved, the correlation between change in each of these variables was fairly weak. With respect to preoperative factors, greater visual acuity improvement and larger reduction in CSF thickness were more likely to occur in eyes with lower levels of visual acuity. Although eyes with the largest amount of pre-operative retinal thickening manifested the greatest reduction in thickening, these results failed to demonstrate conclusively that baseline retinal thickness is independently associated with visual acuity outcome. These relationships likely reflect, in part, a ceiling effect on improvement when visual acuity reduction or retinal thickening or both at baseline are relatively minimal.

Removal of an ERM at the time of vitrectomy was associated with somewhat better visual acuity outcome but no association was found with degree of retinal thickness reduction, potentially reflecting resolution of distorted vision from the ERM rather than resolution of DME. Removal of the ILM at time of vitrectomy and pre-operative presence of other vitreoretinal abnormalities on OCT, were associated with somewhat greater reductions in retinal thickness but no association was found with visual acuity improvement. How surgeons distinguish removal of ERM from removal of ILM may not be standardized, although one would expect with indocyanine green staining of the ILM the ILM should be readily identifiable during surgery so that there should be little doubt when ILM was removed. There was enough discordance between ERM peeling and ILM removal within an eye to conclude that reporting of either procedure was not acting as a surrogate for the other. Visual acuity improvement was associated with lens status (as seen in the univariate analysis), being greater in eyes that were pseudophakic either entering vitrectomy or at the close of the procedure as compared to eyes that remained phakic through the first 6-month post-operative period. However, as no association was identified between lens status and change in retinal thickness, this association appears to be related to development or progression of lens opacity after surgery rather than there being a more favorable effect of vitrectomy on DME in pseudophakic eyes. Progression

of cataract following vitrectomy in eyes that remain phakic may confound follow-up visual acuity observations in any published series evaluating vitrectomy for these eyes.

Nasrallah and Hikichi[6, 7] hypothesized that vitreous detachment may promote resolution of DME since they reported higher prevalence rates of DME in eyes without a posterior vitreous detachment (PVD) when compared to eyes with PVD as well as higher rates of DME resolution in eyes that developed spontaneous PVD during follow-up. Our data are consistent with the theory that the vitreous plays a role in the pathogenesis of DME in that the majority of study eyes were suspected of having at least partial vitreous attachment at the pre-operative visit. However, assuming that all vitreous attachments are severed at the time of vitrectomy, our failure to find a favorable association between the clinician's assessment of an adherent posterior vitreous at baseline and month 6 visual acuity or OCT outcome would contradict this theory. This debate is further complicated by questionable validity and reproducibility of the clinician's ability to assess the status of the posterior vitreous pre-operatively, even if intraoperative assessment of posterior hyaloid attachment should be fairly reliable.

Few previous reports in the literature have evaluated factors associated with visual acuity or anatomic outcomes after vitrectomy for DME. In a retrospective study of 486 eyes that underwent vitrectomy and lensectomy (if phakic at the time of the procedure) for "diffuse nontractional DME" that had nearly complete (98%) follow-up at the 1-year examination, Kumagai et al [8] found that visual outcomes with ILM peeling were better than those associated with preservation of the ILM in a univariate analysis. Preoperative visual acuity was positively associated with final vision whereas age, hemoglobin A1C, previous panretinal and macular photocoagulation, and subfoveal lipid were negatively correlated. No relationship remained between ILM peeling and longer-term follow-up in the multivariate model. In addition, this is an unusual cohort as only 4% had received laser treatment for DME prior to surgery and OCT was not evaluated.

Song et al performed a retrospective review of 55 eyes all of whom were at least 6 months status post vitrectomy for DME that persisted following prior laser photocoagulation or intravitreal triamcinolone. In multivariate linear regression analysis eyes that underwent simultaneous cataract surgery (62% of the cohort) were more apt to have improved vision benefits relative to those that were pseudophakic at the time of vitrectomy (24%). Therefore, the vision outcomes in this study may be greatly affected by removal of lens opacity rather than the vitrectomy affects on the macular status. No association between ILM removal and vision outcomes was identified. An association between better pre-operative visual acuity and better post-operative vision was found. The authors suggest that permanent photoreceptor dysfunction from chronic edema may have led to this result.[9]

A few prospective series of a limited number of eyes undergoing vitrectomy also have been reported. Shah et al evaluated one year outcomes among 33 eyes undergoing vitrectomy with ILM peel for DME that persisted following one or more laser treatments. No significant correlation was found between baseline visual acuity and change in vision, nor between change in central macular thickness and change in vision. In multivariate regression analysis, baseline presence of clinical or OCT macular traction and absence of subretinal fluid appeared to favorably affect visual outcome; whereas no predictors of OCT outcomes were identified.[10] Several other prospective trials and small randomized controlled trials, as summarized by Laidlaw,[11] have reported variable visual acuity benefits from pars plana vitrectomy in eyes with DME, but these studies have not focused on factors associated with vision improvement in the setting of vitrectomy.

The role of vitrectomy compared with other approaches in the management of DME remains uncertain as the potential benefits and risks have not been clearly defined in the context of

long-term, adequately sized randomized clinical trials. The relatively large prospective series by the DRCR.net attempted to identify pre-operative or intraoperative variables that might predict eyes more apt to benefit from this intervention. In view of the large number of variables evaluated and the exploratory nature of the analyses in this study, no definite conclusions can be drawn. However, it appears that relatively few factors were found to have any relationship with vision or anatomic outcomes 6 months after vitrectomy. The results of this study may be useful for generating hypotheses that might be evaluated in future studies of vitrectomy in the setting of DME. However, with respect to patient management at present, the findings should be viewed with caution since it is unknown how these eyes would have fared in the absence of vitrectomy or with other treatment modalities.

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Table 1

Baseline and Surgery Characteristics (N= 241)

Age (years)	
Mean (Standard Deviation)	65 (10)
[Range]	[28, 88]
Gender- *n (%)*	
Woman	121 (50%)
Race- *n (%)*	
White	183 (76%)
Black/African American	23 (10%)
Hispanic or Latino	21 (9%)
Other	14 (6%)
Diabetes Related	
Diabetes Type - *n (%)*	
Type 1	35 (15%)
Type 2	206 (85%)
Duration of Diabetes (years)	
Median (25^{th}, 75^{th} percentile)	20 (13, 26)
[Range]	[<1, 68]
HbA1c* **(%)**	
Median (25^{th}, 75^{th} percentile)	7.3 (6.6, 8.1)
[Range]	[4.5, 13.3]
Ocular Characteristics	
Prior Treatment for Diabetic Macular Edema† - *n (%)*	173 (72%)
Focal/grid photocoagulation	148 (61%)
Intravitreal corticosteroids	85 (35%)
Peribulbar corticosteroids	7 (3%)
Intravitreal bevacizumab	11 (5%)
Retinopathy Severity □* - *n (%)*	
Microaneurysms only	2 (<1%)
Mild/moderate nonproliferative retinopathy	28 (13%)
Moderately severe nonproliferative retinopathy	55 (25%)
Severe nonproliferative retinopathy	14 (6%)
Proliferative retinopathy, including evidence of PRP	119 (55%)
Lens Status §- *n (%)*	
Phakic at time of 6 month exam	87 (38%)
Pseudophakic/Aphakic prior to vitrectomy	111 (49%)
Lens removed during vitrectomy	16 (7%)
Lens removed after vitrectomy prior to 6 month exam	14 (6%)
Status of Vitreous‡- *n (%)*	
Attached	138 (57%)
Partially attached	51 (21%)

Detached	31 (13%)
Uncertain	21 (9%)
Reasons for Vitrectomy† - *n (%)*	
Vitreomacular interface abnormality/traction	170 (71%)
Persistent edema after other treatment for DME	115 (48%)
Edema without prior DME treatment	2 (<1%)
Baseline Visual Acuity (letter score)	
Median (25th, 75th percentile)	57 (45, 66)
Approximate Snellen Equivalent	20/80 (20/50, 20/125)
Baseline OCT Central Subfield Thickness (μm)	
Median (25th, 75th percentile)	412 (337, 540)
Baseline OCT Vitreoretinal Abnormalities, as graded by reading center graders *	
No Evidence	61 (26%)
Questionable or Definite	177 (74%)
Surgical Characteristics	
Posterior Hyaloid Removed	237 (98%)
Epiretinal Membrane Peeled - *n (%)*	146 (61%)
Internal Limiting Membrane Removed - *n (%)*	154 (64%)
Agents Used to Improve Visualization† - *n (%)*	158 (66%)
Triamcinolone acetonide	82 (34%)
Indocyanine Green	75 (31%)
Trypan Blue	13 (5%)
Laser Performed (as described by surgeon) † - *n (%)*	130 (54%)
Focal to break(s)	31 (13%)
PRP	86 (36%)
Focal macular	12 (5%)
Barrier laser**	16 (7%)
Corticosteroids Used at Close of Vitrectomy † - *n (%)*	164 (68%)
Intravitreal	103 (43%)
Peribulbar	17 (7%)
Subtenon's	28 (12%)
Subconjunctival	54 (22%)

*Missing/non-gradable data not included for HbA1c (22), retinopathy severity (23), and vitreoretinal abnormalities (3)

†Same subjects could be listed for multiple categories

□From reading center grading of fundus photographs.

§13 subjects who did not complete the 6 month exam were excluded

‡From investigator's assessment prior to surgery

**Barrier laser on case report form is laser applied to peripheral retina in attempt to decrease risk of extension of peripheral retinal tear or detachment into center of retina.

HbA1c=Hemoglobin A1c, PRP=Panretinal Photocoagulation

Table 2

Multivariate Analyses for Change in Visual Acuity from Baseline to the 6-Month Study Visit (N=227*)

	N	Baseline Visual Acuity Median Letter Score	Median Change in Visual Acuity from Baseline (letters) (25th, 75th quartiles)	Visual Acuity Improvement ≥10 Letters	Visual Acuity Worsen ≥10 Letters	Univariate Analysis *P* value**	Final Multivariate Model‡ *P* Value**
Lens Status						**0.01**	
Phakic at time of 6-month examination	87	58	−4 (−12 to +7)	18 (21%)	29 (33%)		
Pseudophakic/Aphakic prior to vitrectomy	110	57	+3 (−4 to +11)	33 (30%)	14 (13%)		
Lens removed during vitrectomy	16	56	+7 (−5 to +11)	5 (31%)	3 (19%)		
Lens removed after vitrectomy prior to 6 -month examination	14	60	−2 (−21 to +7)	3 (21%)	4 (29%)		
Status of vitreous prior to surgery according to investigators§						**0.08**	
Attached	130	58	−1 (−9 to +7)	26 (20%)	30 (23%)		
Partially attached	48	57	+7 (−4 to +12)	18 (38%)	6 (13%)		
Detached	29	56	+3 (− 12 to +11)	10 (34%)	8 (28%)		
Baseline Visual Acuity(Snellen Equivalent)§						**<0.001**	**<0.001**
≥ 20/40	38	74	−2 (−9 to +2)	2 (5%)	9 (24%)		
< 20/40-20/80	99	62	+1 (−8 to +9)	23 (23%)	24 (24%)		
< 20/80	90	42	+4 (−6 to +13)	34 (38%)	17 (19%)		
Baseline OCT CSF Thickness§						**0.03**	
< 300	28	60	−4 (−18 to +6)	3 (11%)	9 (32%)		
300 – <400	77	62	+1 (−6 to +10)	20 (26%)	14 (18%)		
≥ 400	119	55	+3 (−8 to +11)	36 (30%)	26 (22%)		
Epiretinal Membrane Peeled						**0.02**	**0.006**
No	85	54	−2 (−12 to +9)	17 (20%)	24 (28%)		
Yes	142	58	+3 (−5 to +11)	42 (30%)	26 (18%)		

*13 study participants who missed the 6 month visit and 1 who did not have visual acuity recorded are not included

‡The *P* values for the full multivariate model (which includes all factors with $P<0.10$ in the univariate models) were as follows: lens status=0.02, status of vitreous=0.18, baseline visual acuity <0.001, baseline OCT CSF = 0.28, epiretinal membrane peeled = 0.02. The final multivariate model, as shown in the table, includes factors that remained in the multivariate model after a backward selection process using $P<0.01$ to stay in the model.

** *P* values are from regression models obtained based on ranks of visual acuity scores (van der Waerden scores). For factors with missing, non-gradable, and uncertain data (status of vitreous [20], OCT CSF thickness [3]), an indicator for missing data was added to the model.

§ Continuous/ordinal version of variable used in regression model to obtain *P*-value

OCT= Optical coherence tomography, CSF= Central Subfield

Table 3

Univariate Analysis for Change in Visual Acuity from Baseline to the 6-Month Study Visit (N=227*) - Supplemental table for website

		Baseline Visual Acuity Letter Score	Change in Visual Acuity from Baseline (letters)	Visual Acuity Improvement ≥ 10 letters	Visual Acuity Worsen ≥ 10 letters	
	N	Median	Median (quartiles)	N (%)	N (%)	P Value‡
Demographic Characteristics						
Age†						0.35
<65	94	58	+3 (−9 to +11)	27 (29%)	21 (22%)	
≥65	133	57	0 (−7 to +9)	32 (24%)	29 (22%)	
Gender						0.50
Woman	114	56	−1 (−10 to +11)	31 (27%)	30 (26%)	
Man	113	58	+2 (−6 to +9)	28 (25%)	20 (18%)	
Race						0.50
White	172	57	+1 (−8 to +11)	48 (28%)	38 (22%)	
Non-White	55	59	+2 (−7 to +9)	11 (20%)	12 (22%)	
Diabetes Related						
Diabetes Type						0.48
Type 1	32	58	+2 (−11 to +10)	8 (25%)	9 (28%)	
Type 2	195	57	+1 (−8 to +10)	51 (26%)	41 (21%)	
Diabetes duration†						0.43
<10	32	53	0 (−9 to +12)	12 (38%)	7 (22%)	
10-<20	70	56	+1 (−9 to +9)	15 (21%)	17 (24%)	
≥20	125	58	+2 (−7 to +10)	32 (26%)	26 (21%)	
HbA1c†						0.12
<7%	89	57	+2 (−8 to +11)	25 (28%)	18 (20%)	
7-<9%	90	57	+3 (−8 to +10)	24 (27%)	21 (23%)	
≥9%	32	63	−1 (−9 to +6)	6 (19%)	8 (25%)	
Ocular Characteristics						
Prior Focal/Grid Photocoagulation						0.76
No	87	57	+1 (−8 to +11)	24 (28%)	18 (21%)	
Yes	140	57	+1 (−8 to +10)	35 (25%)	32 (23%)	

		Baseline Visual Acuity Letter Score	Change in Visual Acuity from Baseline (letters)	Visual Acuity Improvement ≥ 10 letters	Visual Acuity Worsen ≥ 10 letters	
	N	Median	Median (quartiles)	N (%)	N (%)	P Value‡
Baseline Retinopathy Severity †						0.88
Nonproliferative retinopathy	93	57	0 (−8 to +7)	21 (23%)	22 (24%)	
Proliferative retinopathy, including evidence of PRP	113	56	+3 (−8 to +11)	32 (28%)	23 (20%)	
Lens Status						0.01
Phakic at time of 6-month examination	87	58	−4 (−12 to +7)	18 (21%)	29 (33%)	
Pseudophakic/Aphakic prior to vitrectomy	110	57	+3 (−4 to +11)	33 (30%)	14 (13%)	
Lens removed during vitrectomy	16	56	+7 (−5 to +11)	5 (31%)	3 (19%)	
Lens removed after vitrectomy prior to 6-month examination	14	60	−2 (−21 to +7)	3 (21%)	4 (29%)	
Status of Vitreous†						0.08
Attached	130	58	−1 (−9 to +7)	26 (20%)	30 (23%)	
Partially attached	48	57	+7 (−4 to +12)	18 (38%)	6 (13%)	
Detached	29	56	+3 (− 12 to +11)	10 (34%)	8 (28%)	
Reason for Vitrectomy: Vitreomacular Interface Abnormality/Traction						0.41
No	67	54	0 (−10 to +9)	15 (22%)	17 (25%)	
Yes	160	59	+2 (−7 to +11)	44 (28%)	33 (21%)	
Baseline Visual Acuity†						<0.001
≥20/40	38	74	−2 (−9 to +2)	2 (5%)	9 (24%)	
<20/40-20/80	99	62	+1 (−8 to +9)	23 (23%)	24 (24%)	
<20/80	90	42	+4 (−6 to +13)	34 (38%)	17 (19%)	
Baseline OCT CSF Thickness †						0.03
<300	28	60	−4 (−18 to +6)	3 (11%)	9 (32%)	
300-<400	77	62	+1 (−6 to +10)	20 (26%)	14 (18%)	
≥400	119	55	+3 (−8 to +11)	36 (30%)	26 (22%)	
Baseline OCT Vitreoretinal Abnormalities, as graded by reading center						0.78
No Evidence	60	57	−1 (−8 to +9)	12 (20%)	13 (22%)	
Questionable or Definite	164	57	+2 (−8 to +11)	45 (27%)	37 (23%)	
Surgical Characteristics						
Posterior Hyaloid Removed						0.68

		Baseline Visual Acuity Letter Score	Change in Visual Acuity from Baseline (letters)	Visual Acuity Improvement ≥ 10 letters	Visual Acuity Worsen ≥ 10 letters	
	N	Median	Median (quartiles)	N (%)	N (%)	P Value‡
No	4	72	+4 (+2 to +6)	0 (0%)	0 (0%)	
Yes	223	57	+1 (−8 to +10)	59 (26%)	50 (22%)	
Epiretinal Membrane Peeled						0.02
No	85	54	−2 (−12 to +9)	17 (20%)	24 (28%)	
Yes	142	58	+3 (−5 to +11)	42 (30%)	26 (18%)	
Internal Limiting Membrane Removed						0.15
No	80	57	−1 (−9 to +9)	17 (21%)	18 (23%)	
Yes	147	57	+2 (−6 to +11)	42 (29%)	32 (22%)	
Agents used to improve visualization						0.61
No	78	58	0 (−9 to +10)	20 (26%)	19 (24%)	
Yes§	149	57	+2 (−7 to +10)	39 (26%)	31 (21%)	
Photocoagulation (all types)						0.36
No	106	57	+1 (−6 to +11)	28 (26%)	21 (20%)	
Yes	121	57	0 (−9 to +10)	31 (26%)	29 (24%)	
Corticosteroids used at close						0.90
No	72	57	+1 (−10 to +11)	19 (26%)	18 (25%)	
Yes	155	57	+1 (−8 to +10)	40 (26%)	32 (21%)	

*13 study participants who missed the 6-month visit and 1 who did not have visual acuity recorded are not included

†Continuous/ordinal version of variable used in regression model to obtain *P*-value.

‡Unadjusted *P*-values from regression models obtained based on ranks of visual acuity scores (van der Waerden scores); missing, non-gradable, and uncertain values were not included in models (HbA1c (16), retinopathy severity (21), status of vitreous(20), OCT CSF thickness (3), vitreoretinal abnormalities (3))

§Further stratifying this group results in the following: N=68 receiving triamcinolone only had median (quartiles) change in visual acuity of 0 (−7, +9); N=62 receiving indocyanine green only had median (quartiles) change in visual acuity of +2 (−6, +11)

PRP=panretinal photocoagulation, HbA1c= hemoglobin A1c, OCT=optical coherence tomography, CSF= central subfield.

Table 4

Six Month Study Visit Outcomes According to Preoperative Visual Acuity and Central Subfield Thickness*

			Change in Visual Acuity from Baseline (letters)	Visual Acuity Improvement ≥ 10 letters	Visual Acuity Worsen ≥ 10 letters		Change in CSF Thickness from Baseline (um)	Change in logOCT from Baseline	Central Subfield Reduction ≥1 log step	Central Subfield Increase ≥1 log step
		N†	Median (quartiles)	N (%)	N (%)	N†	Median (quartiles)	Mean (Standard Deviation)	N (%)	N (%)
Baseline Visual Acuity	**Baseline CSF Thickness**									
≥20/40	**<300**	8	−3 (−17 to 0)	0	2 (25%)	8	−8 (−35 to +36)	−0.01 (0.09)	2 (25%)	2 (25%)
	300-<400	23	−1 (−12 to +3)	2 (9%)	7 (30%)	23	−58 (−88 to −35)	−0.09 (0.09)	8 (35%)	0
	≥400	7	−2 (−4 to +1)	0	0	7	−160 (−165 to −101)	−0.15 (0.07)	5 (71%)	0
<20/40-20/80	**<300**	11	−4 (−56 to +7)	0	4 (36%)	11	+2 (−64 to +108)	0.00 (0.14)	4 (36%)	3 (27%)
	300-<400	32	+7 (−4 to +11)	11 (34%)	5 (16%)	31	−73 (−116 to −10)	−0.11 (0.09)	15 (48%)	0
	≥400	55	−1 (−10 to +9)	12 (22%)	14 (25%)	52	−149 (−260 to −68)	−0.18 (0.18)	32 (62%)	2 (4%)
<20/80	**<300**	9	−2 (−14 to +10)	3 (33%)	3 (33%)	9	+3 (−32 to +39)	0.00 (0.11)	1 (11%)	1 (11%)
	300-<400	22	+1 (−5 to +14)	7 (32%)	2 (9%)	21	−119 (−149 to −89)	−0.18 (0.13)	17 (81%)	1 (5%)
	≥400	57	+7 (−5 to +13)	24 (42%)	12 (21%)	57	−231 (−349 to −112)	−0.26 (0.20)	41 (72%)	0

*The Spearman correlation coefficient of visual acuity and central subfield thickness was −0.35 preoperatively, −0.03 at 6 months, and −0.25 for the change from baseline to 6 months

†Of the N=228 subjects who completed a 6-month visit, the following data were missing: visual acuity at 6 months (1), central subfield thickness at baseline (3), central subfield thickness at 6 months (6)

CSF=central subfield thickness

Table 5

Multivariate Analyses for Change in Optical Coherence Tomography Central Subfield from Baseline to the 6-Month Study Visit (N=219*)

	N	Baseline Central Subfield Median (um)	Change in Central Subfield from Baseline Median (um, quartiles)	Change in logOCT from Baseline Mean (Standard Deviation)	Central Subfield Reduction ≥1 log step N (%)	Central Subfield Increase ≥1 log step N (%)	Univariate Analysis *P* value**	Full† and Final‡ Multivariate Analysis *P* value**
Baseline CSF Thickness§							**<0.001**	**0.001**
<300	**28**	246	−2 (−52 to +46)	**0 (0.12)**	7 (25%)	6 (21%)		
300-<400	**75**	343	−84 (−128 to −38)	**−0.12 (0.11)**	40 (53%)	1 (1%)		
≥400	**116**	525	−182 (−304 to −84)	**−0.22 (0.19)**	78 (67%)	2 (2%)		
Baseline Visual Acuity (Snellen Equivalent)§							**<0.001**	**<0.001**
≥20/40	**38**	352	−58 (−101 to −19)	**−0.08 (0.10)**	15 (39%)	2 (5%)		
<20/40-20/80	**94**	412	−90 (−167 to −34)	**−0.14 (0.16)**	51 (54%)	5 (5%)		
<20/80	**87**	495	−159 (−293 to −68)	**−0.21 (0.19)**	59 (68%)	2 (2%)		
Internal Limiting Membrane Removed							**0.02**	**0.003**
No	**75**	401	−88 (−167 to +2)	**−0.12 (0.18)**	36 (48%)	5 (7%)		
Yes	**144**	413	−106 (−231 to −51)	**−0.18 (0.17)**	89 (62%)	4 (3%)		
Baseline OCT Vitreoretinal Abnormalities, as graded by reading center							**0.03**	**0.006**
No Evidence	**60**	417	−85 (−167 to +1)	**−0.11 (0.17)**	28 (47%)	6 (10%)		
Questionable or Definite	**156**	398	−104 (−201 to −39)	**−0.17 (0.17)**	95 (61%)	3 (2%)		

*13 study participants who missed the 6-month visit, 3 missing central subfield measurement at baseline, and 6 missing central subfield measurement at 6 months are not included

**_P_ values are from regression models obtained based on logarithmic transformation of central subfield thickness ("logOCT").

†Includes all factors that were $P<0.10$ in the univariate models.

‡Includes factors that remained in the multivariate model after a backward selection process using $P<0.01$ to stay in the model. (For this analysis, all factors in the full model remained in the final model.)

§Continuous/ordinal version of variable used in regression model to obtain *P*-value

OCT= optical coherence tomography, CSF=central subfield thickness

Table 6

Univariate Analysis for Change in Optical Coherence Tomography Central Subfield from Baseline to the 6-Month Study Visit (N=219[*]) - Supplemental table for website

	N	Baseline CSF Thickness (um) Median	Change in CSF Thickness from Baseline (um) Median (quartiles)	Change in logOCT from Baseline Mean (Standard Deviation)	Central Subfield Reduction ≥1 log step N (%)	Central Subfield Increase ≥1 log step N (%)	*P* Value[‡]
Demographic Characteristics							
Age							0.36
<65	89	418	−116 (−217 to − 40)	−0.18 (0.18)	52 (58%)	3 (3%)	
≥65	130	405	−92 (−171 to −19)	−0.14 (0.17)	73 (56%)	6 (5%)	
Gender							0.24
Women	109	420	−113 (−217 to − 40)	−0.17 (0.18)	65 (60%)	4 (4%)	
Men	110	402	−90 (−171 to −31)	−0.14 (0.17)	60(55%)	5 (5%)	
Race							0.76
White	167	405	−104 (−196 to − 38)	−0.16 (0.17)	96 (57%)	6 (4%)	
Non-White	52	417	−88 (−212 to −20)	−0.15 (0.18)	29 (56%)	3 (6%)	
Diabetes Related							
Diabetes Type							0.94
Type 1	31	395	−99 (−167 to −40)	−0.15 (0.18)	16 (52%)	2 (6%)	
Type 2	188	413	−99 (−201 to −33)	−0.16 (0.17)	109 (58%)	7 (4%)	
Diabetes Duration[†]							0.69
<10	32	487	−171 (−303 to − 60)	−0.18 (0.19)	18 (56%)	3 (9%)	
10-<20	64	413	−95 (−191 to −35)	−0.15 (0.16)	36 (56%)	3 (5%)	
≥20	123	390	−91 (−172 to −19)	−0.15 (0.17)	71 (58%)	3 (2%)	
HbA1c[†]							0.81
A)<7%	87	407	−95 (−174 to −39)	−0.16 (0.17)	45 (52%)	2 (2%)	
B)7-<9%	87	405	−101 (−189 to − 32)	−0.14 (0.16)	52 (60%)	4 (5%)	
C)>=9%	30	408	−100 (−240 to − 19)	−0.17 (0.17)	18 (60%)	2 (7%)	
Ocular Characteristics							
Prior Focal/Grid Photocoagulation							0.74
No	83	383	−88 (−204 to −20)	−0.15 (0.19)	42 (51%)	4 (5%)	
Yes	136	427	−110 (−191 to − 47)	−0.16 (0.16)	83 (61%)	5 (4%)	

	N	Baseline CSF Thickness (um) Median	Change in CSF Thickness from Baseline (um) Median (quartiles)	Change in logOCT from Baseline Mean (Standard Deviation)	Central Subfield Reduction ≥1 log step N (%)	Central Subfield Increase ≥1 log step N (%)	*P* Value‡
Baseline Retinopathy Severity†							0.15
Nonproliferative retinopathy	91	407	−86 (−149 to −10)	−0.13 (0.15)	46 (51%)	4 (4%)	
Proliferative retinopathy, including evidence of PRP	109	412	−121 (−217 to − 50)	−0.18 (0.18)	68 (62%)	4 (4%)	
Lens Status							0.68
Phakic at time of 6-month examination	83	421	−97 (−202 to −40)	−0.16 (0.16)	47 (57%)	2 (2%)	
Pseudophakic/Aphakic prior to vitrectomy	108	409	−105 (−209 to − 33)	−0.17 (0.18)	64 (59%)	4 (4%)	
Lens removed during vitrectomy	15	359	−93 (−176 to −9)	−0.13 (0.19)	6 (40%)	1 (7%)	
Lens removed after vitrectomybut prior to 6-month examination	13	404	−89 (−159 to −68)	−0.11 (0.15)	8 (62%)	2 (15%)	
Status of Vitreous†							0.38
Attached	125	402	−88 (−172 to −10)	−0.14(0.18)	64 (51%)	8 (6%)	
Partially attached	46	448	−155 (−204 to − 77)	−0.20 (0.17)	34 (74%)	1 (2%)	
Detached	29	382	−91 (−159 to −51)	−0.15 (0.13)	16 (55%)	0	
Reason for Vitrectomy: Vitreomacular Interface Abnormality/Traction							0.89
No	68	438	−94 (−188 to −37)	−0.15 (0.17)	35 (51%)	1 (1%)	
Yes	151	395	−101 (−200 to − 35)	−0.16 (0.17)	90(60%)	8 (5%)	
Baseline Visual Acuity†							<0.001
≥20/40	38	352	−58 (−101 to −19)	−0.08 (0.10)	15 (39%)	2 (5%)	
<20/40 -20/80	94	412	−90 (−167 to −34)	−0.14 (0.16)	51 (54%)	5 (5%)	
<20/80	87	495	−159 (−293 to − 68)	−0.21 (0.19)	59 (68%)	2 (2%)	
Baseline OCT CSF thickness†							<0.001
<300	28	246	−2 (−52 to +46)	0 (0.12)	7 (25%)	6 (21%)	
300-<400	75	343	−84 (−128 to −38)	−0.12 (0.11)	40 (53%)	1 (1%)	
≥400	116	525	−182 (−304 to − 84)	−0.22 (0.19)	78 (67%)	2 (2%)	
Baseline OCT Vitreoretinal Abnormalities, as graded by reading center							0.03
No Evidence	60	417	−85 (−167 to +1)	−0.11 (0.17)	28 (47%)	6 (10%)	
Questionable or Definite	156	398	−104 (−201 to − 39)	−0.17 (0.17)	95 (61%)	3 (2%)	
Surgical Characteristics							
Posterior Hyaloid Removed							0.97

	N	Baseline CSF Thickness (um) Median	Change in CSF Thickness from Baseline (um) Median (quartiles)	Change in logOCT from Baseline Mean (Standard Deviation)	Central Subfield Reduction ≥1 log step N (%)	Central Subfield Increase ≥1 log step N (%)	*P* Value‡
No	4	456	−102 (−273 to − 39)	−0.16 (0.16)	2 (50%)	0 (0%)	
Yes	215	411	−99 (−200 to −34)	−0.16 (0.17)	123 (57%)	9 (4%)	
Epiretinal Membrane Peeled							0.12
No	82	423	−90 (−190 to −10)	−0.13 (0.17)	44 (54%)	4 (5%)	
Yes	137	398	−106 (−202 to − 40)	−0.17 (0.18)	81 (59%)	5 (4%)	
Internal Limiting Membrane Removed							0.02
No	75	401	−88 (−167 to +2)	−0.12 (0.18)	36 (48%)	5 (7%)	
Yes	144	413	−106 (−231 to − 51)	−0.18 (0.17)	89 (62%)	4 (3%)	
Agents used to improve visualization							0.73
No	74	417	−98 (−232 to −31)	−0.16 (0.19)	39 (53%)	4 (5%)	
Yes§	145	404	−99 (−176 to −40)	−0.15 (0.16)	86 (59%)	5 (3%)	
Photocoagulation (any type)							0.62
No	103	412	−101 (−186 to − 34)	−0.15 (0.16)	56 (54%)	3 (3%)	
Yes	116	411	−98 (−212 to −40)	−0.16 (0.18)	69 (59%)	6 (5%)	
Corticosteroids used at close							0.52
No	68	411	−109 (−183 to − 32)	−0.15 (0.16)	36 (53%)	3 (4%)	
Yes	151	411	−97 (−204 to −36)	−0.16 (0.18)	89 (59%)	6 (4%)	

*13 study participants who missed the 6-month visit, 3 missing CSF measurement at baseline, and 6 missing CSF measurement at 6 months are not included

†Continuous/ordinal version of variable used in regression model to obtain *P*-value.

‡Unadjusted *P*-values from regression models obtained based on logarithmic transformation of CSF thickness ("logOCT"); missing, non-gradable, and uncertain values are excluded from models (HbA1c (15), retinopathy severity (19), status of vitreous (19), vitreoretinal abnormalities (3)

§Further stratifying this group results in the following: N=66 receiving triamcinolone only had median (quartiles) change in CSF thickness of −96 (−167, −50); N=60 receiving indocyanine green only had median (quartiles) change in CSF thickness of −92 (−200, −14)

CSF=central subfield, HbA1c= hemoglobin A1c, OCT= optical coherence tomography, PRP=panretinal photocoagulation.