Graefe's Archive for Clinical and Experimental Ophthalmology (2021) 259:363–368
https://doi.org/10.1007/s00417-020-04898-z

RETINAL DISORDERS

Surgical outcomes of vitrectomy for intractable diabetic macular edema

Ryo Mukai[1] · Hidetaka Matsumoto[1] · Hideo Akiyama[1]

Received: 9 June 2020 / Revised: 6 August 2020 / Accepted: 16 August 2020 / Published online: 20 August 2020

Abstract

Purpose To investigate clinical outcomes of vitrectomy for intractable diabetic macular edema (DME) in which anti-vascular endothelial growth factor (anti-VEGF) agents or periocular steroid were not effective.

Methods This retrospective study examined 27 eyes of 25 cases. The main measurements included changes in visual acuity (VA) and retinal morphology. Vitrectomies were performed using the Constellation System 25G.

Results Prior to undergoing vitrectomy, patients were treated with anti-VEGF agents or periocular injection of triamcinolone acetonide. The average number of anti-VEGF agent injections was 3.1 ± 2.8. Triamcinolone was used in 15 eyes. There was no significant change in the mean logMAR best-corrected visual acuity (BCVA) between baseline and posttreatment, with values of 0.49 ± 0.29 and 0.55 ± 0.33, respectively ($P = 0.31$). Compared with preoperative BCVA, postoperative BCVA improved by more than two lines in 4 eyes (14%), remained the same in 17 eyes (63%), and decreased in 6 eyes (23%). Morphologically, retinal thickness improved by more than 50 μm in 16 eyes (59%), remained unchanged in 7 eyes (26%), and increased in 5 eyes (18%). Retinal edema resolved in all of the cases in which macular epiretinal membrane (ERM) or vitreomacular traction (VMT) was detected by optical coherence tomography during pretreatment.

Conclusions Vitrectomy can potentially stabilize the retinal morphology in intractable DME and is likely more effective in DME cases accompanied by ERM or VMT.

Keywords DME · Vitrectomy · Anti-VEGF · Triamcinolone

Introduction

Diabetes is a major disease worldwide, with the International Diabetes Federation reporting that 463 million people suffer from diabetes globally [1]. In Japan, the prevalence of diabetic retinopathy has been estimated to be 10% in all patients with diabetes, with hemoglobin A1c (HbA1c) levels over 6.5% [2]. Diabetic macular edema (DME) is one of the major complications seen in diabetic retinopathy. As DME is a vision-threatening condition, various treatments have been attempted in patients with DME. Recently, anti-vascular endothelial growth factor (anti-VEGF) has become the major treatment for these patients, based on the results of the RISE and RIDE [3], VIVID [4], DRCR-net [5], and Protocol-T studies [6]. Vitrectomies have been performed as a treatment for naïve patients with DME since 1992 [7], because initially the patients were reported to have a thickened and taut premacular posterior hyaloid membrane [7], which was thought to contribute to the development of DME. Subsequently, vitrectomy was used to treat DME without traction on the vitreoretinal interface [8, 9] according to the idea that removal of the vitreous or internal limiting membrane might lead to rapid absorption of DME [10]. In contrast, long-term management of patients with DME has revealed that some become refractory to anti-VEGF agents or periocular steroid therapies. Although these therapies have greatly contributed to improvements in visual function and retinal morphology, there are still cases that continue to have impaired visual outcomes or lingering retinal edema after treatment with anti-VEGF or periocular steroid. Thus, it remains unclear whether vitrectomy is actually beneficial in patients with intractable DME, specifically in patients who were previously treated with anti-VEGF therapy. To clarify this, the present study evaluated and analyzed the surgical outcomes for patients with intractable DME.

✉ Ryo Mukai
rmukai@gunma-u.ac.jp

[1] Department of Ophthalmology, Gunma University Graduate School of Medicine, 3-35-15 Showa-cho, Maebashi, Gunma 371-8511, Japan

Key messages

- Many patients with diabetic macular edema (DME) respond poorlyto anti-VEGF or local steroid treatment during their clinical course.
- Vitrectomy for intractable DME can potentially stabilize the retinal anatomy and visual function at least for 1 year, specifically for DME with vitreoretinal traction or epiretinal membrane.

Methods

This retrospective study was designed to evaluate the efficacy of vitrectomy in participants with intractable DME. The study protocol was approved by our Institutional Review Board and complied with the ethical standards defined by the Declaration of Helsinki. The study plan was disclosed to all participants prior to their enrollment in the study.

Participants included in the study had to be 20 years of age or older with DME due to diabetes, which was primarily evaluated based on the HbA1c blood concentration. In addition, all participants with DME had to have been treated with anti-VEGF (bevacizumab, ranibizumab, or aflibercept) or periocular triamcinolone acetonide prior to participating in the study. This included participants with DME that failed to resolve even though they had previously undergone these treatments. Furthermore, the participant's eye had to exhibit subretinal fluid (SRF) and/or intraretinal fluid (IRF) on swept-source optical coherence tomography (SS-OCT; Topcon DRI Triton, Tokyo) imaging. Vitrectomies, including posterior vitreous detachment and internal limiting membrane peeling, were performed by 11 surgeons using the Constellation 25G system (*Alcon* Laboratories, Inc., USA). Cataract surgery was simultaneously performed in 9 eyes.

The primary measurements analyzed included changes in visual acuity (VA) and retinal morphology. Best-corrected visual acuity (BCVA) of each eye included in study was examined at baseline and at 3, 6, and 12 months postoperatively. Retinal morphological changes were evaluated based on the SS-OCT images at baseline and at 3, 6, and 12 months posttreatment. All cases were followed up for at least 3 months, with a total of 13 eyes (48%) evaluated throughout the entire follow-up period.

One-way analysis of variance was used to analyze whether there was improvement in the VA and a reduction of the retinal thickness after the surgery. Data were analyzed using GraphPad Prism Version 7 software (GraphPad Software, La Jolla, CA, USA). All data are presented as mean ± standard error.

Results

Based on fundus examinations, optical coherence tomography angiography, or fluorescein angiography, 20 eyes were diagnosed with proliferative diabetic retinopathy (PDR), 5 eyes with pre-PDR, and 1 eye with simple diabetic retinopathy.

Prior to surgery, 25 eyes had been treated with anti-VEGF, with a mean of 3.1 ± 2.8 injections. Periocular triamcinolone acetonide was injected into 15 eyes. The average period before entering the study was 21.0 ± 15.0 months (range, 4–61 months). Table 1 summarizes the preoperative demographic characteristics of the patients.

Best-corrected logMAR visual acuities before and at 3, 6, and 12 months postoperatively were 0.49 ± 0.06, 0.55 ± 0.06, 0.40 ± 0.08, and 0.38 ± 0.08, respectively (Fig. 1). Although there was a tendency for the VA to decrease, there was no significant improvement after surgery. Compared with the preoperative BCVA, the postoperative BCVA improved by more than two lines in 4 eyes (14%), remained the same in 17 eyes (63%), and decreased in 6 eyes (23%) at 3 months postoperatively. Improvements in BCVA at 6 and 12 months were seen in 18% and 23% of cases respectively, with the values increasing during the follow-up (Fig. 2). The central retinal thickness (CRT) values before and at 3, 6, and 12 months postoperatively were 550 ± 24, 472 ± 44, 391 ± 41, and 415 ± 50 μm, respectively. There was a significant decrease ($P < 0.05$) in the CRT at 6 months compared with that observed at baseline (Fig. 3).

Table 1 Preoperative demographic characteristics: *HbA1c* Hemoglobin A1c, *Cr* creatine, *VEGF* vascular endothelial growth factor, *PEA* phacoemulsification, *IOL* intraocular lens. The data was presented as mean ± standard error

$N = 27$ eyes	
Mean age (years)	64.6 ± 2.2 (34–80)
Gender(male/female)	19/6
HbA1c (%)	7.0 ± 0.2
Cr (mg/dl)	1.73 ± 0.46
Averaged number of anti-VEGF (injections)	3.1 ± 0.5
The number of cases with local steroid (eyes)	15
Accompanied with PEA + IOL (eyes)	16

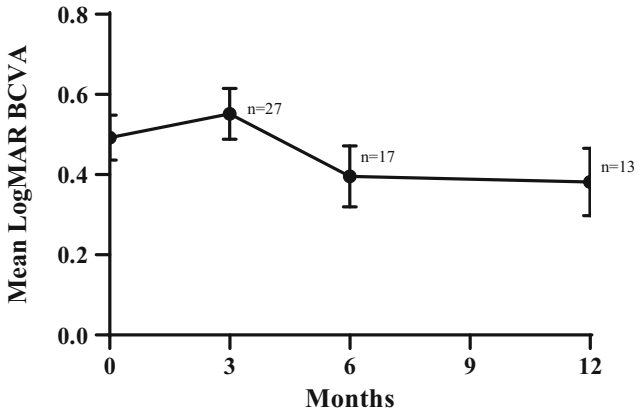

Fig. 1 Change in mean best-corrected visual acuity (BCVA) before and at 3, 6, and 12 months postoperatively

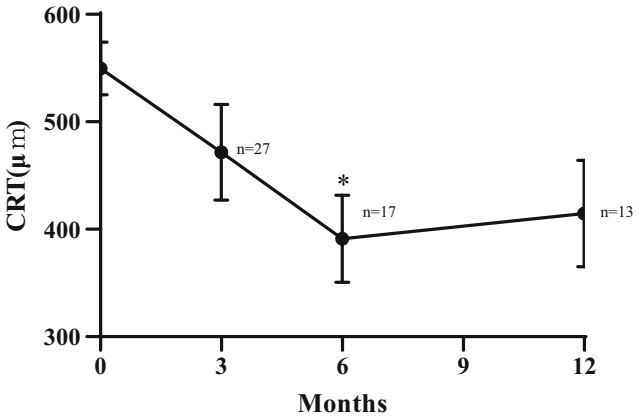

Fig. 3 Change in central retinal thickness (CRT) before and at 3, 6, and 12 months postoperatively. CRT was significantly reduced at 6 months postoperatively (*$P < 0.05$)

Nine of the 27 eyes had vitreomacular traction (VMT) or epiretinal membrane (ERM) prior to surgery. The best-corrected logMAR improved from 0.56 ± 0.12 at baseline to 0.54 ± 0.10, 0.21 ± 0.09, and 0.14 ± 0.07 at 3, 6, and 12 months postoperatively, with a significant improvement ($P < 0.05$) found at 12 months after the surgery. In addition, CRT values before and at 3, 6, and 12 months postoperatively were 485 ± 35, 306 ± 41, 361 ± 44, and 331 ± 55 μm, respectively. There was a significant decrease ($P < 0.01$) in the CRT at 3 months compared to that observed at baseline (Figs. 4 and 5).

Discussion

The results of this retrospective study suggest that vitrectomy is effective in patients with intractable DME. The retinal anatomy in 78% of the patients had stabilized by 12 months postoperatively. However, there was no significant improvement in BCVA after the surgery.

Since the 1990s, vitrectomy has been performed in patients with DME based on the observation that the attached posterior vitreous might be highly associated with the formation of DME [7]. Similarly, Sebag and Balazs reported finding cases in which the remaining vitreous cortex on the macula resulted in persistent macular edema [11]. Subsequently, Yamaguchi et al. reported cases in which the vitreofoveal separation potentially led to resolution of the DME [12]. Based on these reports, the beneficial effect of using vitrectomy for DME was widely evaluated. Otani and Kishi reported on the visual outcomes of vitrectomy for treatment naïve DME. In their study, patients were followed up for 5 months after the surgery. Although there was no significant improvement in the mean VA after surgery, improvement in VA of more than two lines

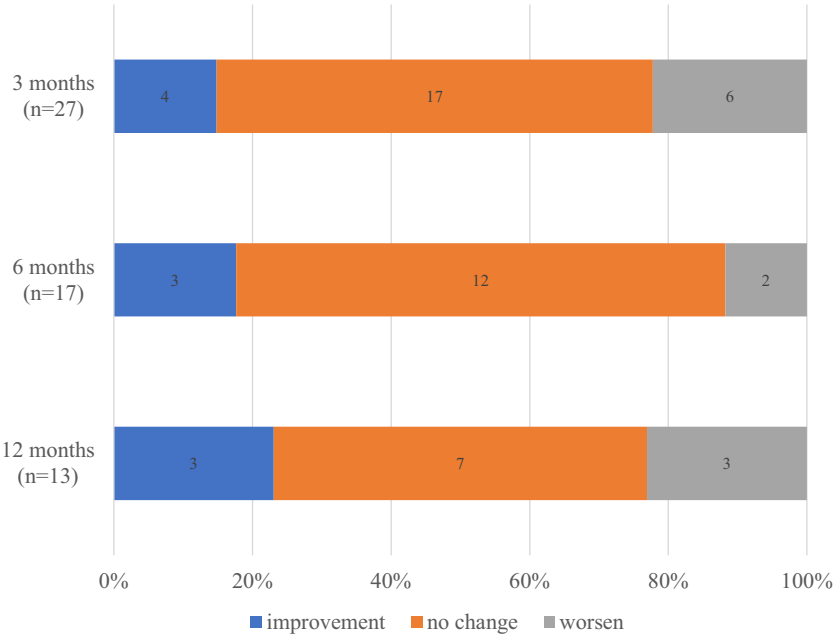

Fig. 2 The proportion of patients with changes in best-corrected visual acuity of 0.2 logMAR vision or more at 3, 6, and 12 months postoperatively

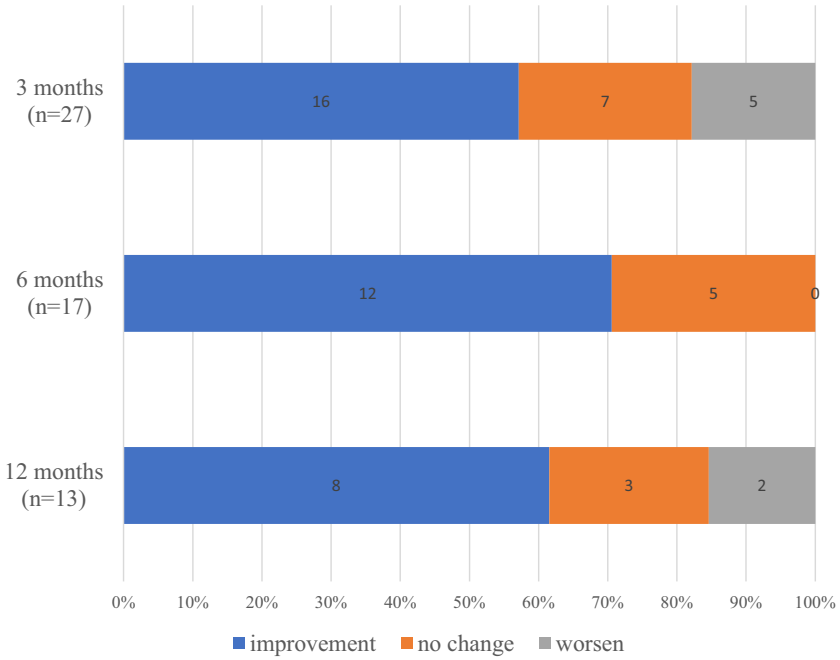

Fig. 4 The proportion of patients with changes in central retinal thickness (CRT) of 50 μm or more at 3, 6, and 12 months postoperatively

was achieved in 57% of the patients. Anatomically, they reported that the CRT decreased from 617 to 546 μm [13]. Heij et al. followed up 19 patients with DME for a median of 11 months postvitrectomy and demonstrated that there was significant improvement in BCVA, with 71% of the eyes showing an improvement in VA of one line or more. Additionally, the macular edema resolved in 95% of the patients at the final visit [14]. Notably, the patients included in this study did not have evident VMT. It has been reported in previous studies that patients attained anatomical improvement after undergoing vitrectomy [14]. In contrast, the postoperative BCVA and the frequencies of the improvement in BCVA were limited in the present study. This suggested that chronic DME, as seen in patients in the present study, might affect preoperative macular function, even though there were some patients that sustained a moderate BCVA from beginning of the study. This speculation is based on the pathogenesis of DME, in which multiple factors such as ischemia of the retina, accumulation of hard exudate, and other general conditions have been shown to affect macular function [15].

In 9 of 27 eyes with VMT or ERM that were examined in our study, BCVA was significantly improved at 12 months postoperatively. This result is consistent with the findings reported by a previous study [16]. Moreover, our results showed that the good VA was maintained even at 12 months. It should be noted that in cases with DME associated with VMT or ERM, we observed recurrence of DME postoperatively during the 12 months of follow-up. It was necessary to treat these patients with additional anti-VEGF or periocular corticosteroid. However, the average number of additional postoperative treatments between patients with VMT or ERM and those without tractions was 0.56 ± 0.73 and 2.44 ± 2.85, respectively, even though the follow-up period after the surgery differed

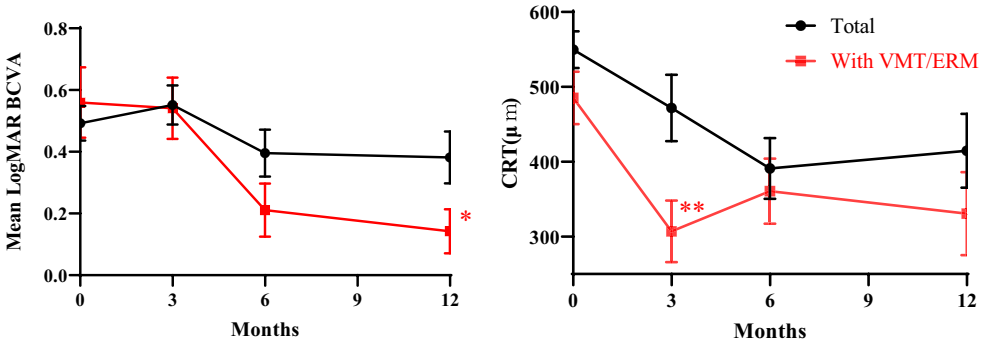

Fig. 5 Change in mean best-corrected visual acuity (BCVA) and central retinal thickness (CRT) in all cases and in patients with vitreomacular traction (VMT) or epiretinal membrane (ERM) (9/27 eyes) before and at 3, 6, and 12 months postoperatively. A significant improvement in VA at 12 months postoperatively ($P < 0.05$), and a significant decrease in CRT at 3 months postoperatively ($P < 0.01$) were seen in patients with VMT or ERM

between the two groups (7.3 ± 4.5 months versus 8.0 ± 4.2 months, respectively).

The pharmacokinetic properties of anti-VEGF [17] likely mean it has a shorter half-life in the vitrectomized eyes. Consequently, administration of periocular steroid will potentially be a more beneficial strategy when taking into consideration the longer management that patients with DME must undergo.

Based on the findings of previous reports, we removed the internal limiting membranes (ILMs) in all cases in the present study. Gandorfer et al. were the first to demonstrate the efficacy of ILM removal, with 11 of 12 eyes showing improvement in VA by at least two lines during the follow-up period (mean 4 months) [17]. Subsequently, several other institutions have reported similar good results [18–21]. One of the beneficial advantages of removing the ILM is that it not only can prevent the postoperative formation of the epimacular membrane [17] but it also can potentially lead to a complete release of the tractional force from the vitreous and rapid resolution of diffuse macular edema [7]. Recently, Imai et al. reported that en bloc removal of a cystoid lesion combined with vitrectomy can lead to a sustained VA and a stabilized retinal thickness postoperatively [22]. In addition, these authors showed that the encapsulated fibrinogen consisted of a cystoid lesion. In the present study, several patients exhibited a recurrence of DME after the initial surgery, so this new technique might be effective in these types of patients.

The limitations of the present study included its retrospective design and the inclusion of only a small number of subjects in a single-arm modality of treatment. In the future, a prospective comparative study will need to be conducted to definitively clarify the present findings.

In conclusion, vitrectomy for intractable DME can sustain and stabilize both visual function and retinal morphology, and may be specifically beneficial for DME patients with VMT and ERM.

Contributions All authors contributed to the study conception and design. Material preparation, data collection, and analyses were performed by Ryo Mukai. The first draft of the manuscript was written by Ryo Mukai, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent to review their medical records was obtained from all individual participants included in this study.

References

1. Inter national Diabetes Federation (2020) IDF Diabetes Atlas Ninth Edition 2019, Brussels
2. Fukushima S, Nakagami T, Suto C, Hirose A, Uchigata Y (2013) Prevalence of retinopathy and its risk factors in a Japanese population. J Diabetes Investig 4:349–354. https://doi.org/10.1111/jdi.12044
3. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, Gibson A, Sy J, Rundle AC, Hopkins JJ, Rubio RG, Ehrlich JS, Rise, Group RR (2012) Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 119:789–801. https://doi.org/10.1016/j.ophtha.2011.12.039
4. Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS, Midena E, Kaiser PK, Terasaki H, Marcus DM, Nguyen QD, Jaffe GJ, Slakter JS, Simader C, Soo Y, Schmelter T, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Zeitz O, Metzig C, Brown DM (2014) Intravitreal aflibercept for diabetic macular edema. Ophthalmology 121:2247–2254. https://doi.org/10.1016/j.ophtha.2014.05.006
5. Diabetic Retinopathy Clinical Research Network; Writing Committee; Aiello LP, Beck RW, Bressler NM, Browning DJ, Chalam KV, Davis M, Ferris FL, 3rd, Glassman AR, Maturi RK, Stockdale CR, Topping TM (2011) Rationale for the diabetic retinopathy clinical research network treatment protocol for center-involved diabetic macular edema. Ophthalmology 118: e5–14. DOI: https://doi.org/10.1016/j.ophtha.2011.09.058
6. Bressler NM, Beaulieu WT, Glassman AR, Blinder KJ, Bressler SB, Jampol LM, Melia M, Wells JA 3rd, Diabetic Retinopathy Clinical Research Network (2018) Persistent macular thickening following intravitreous aflibercept, bevacizumab, or ranibizumab for central-involved diabetic macular edema with vision impairment: a secondary analysis of a randomized clinical trial. JAMA Ophthalmol 136:257–269. https://doi.org/10.1001/jamaophthalmol.2017.6565
7. Lewis H, Abrams GW, Blumenkranz MS, Campo RV (1992) Vitrectomy for diabetic macular traction and edema associated with posterior hyaloidal traction. Ophthalmology 99:753–759. https://doi.org/10.1016/s0161-6420(92)31901-3
8. Kadonosono K, Itoh N, Ohno S (2000) Perifoveal microcirculation before and after vitrectomy for diabetic cystoid macular edema. Am J Ophthalmol 130:740–744. https://doi.org/10.1016/s0002-9394(00)00575-4
9. Park JH, Woo SJ, Ha YJ, Yu HG (2009) Effect of vitrectomy on macular microcirculation in patients with diffuse diabetic macular edema. Graefes Arch Clin Exp Ophthalmol 247:1009–1017. https://doi.org/10.1007/s00417-009-1062-1
10. Bhagat N, Grigorian RA, Tutela A, Zarbin MA (2009) Diabetic macular edema: pathogenesis and treatment. Surv Ophthalmol 54:1–32. https://doi.org/10.1016/j.survophthal.2008.10.001
11. Sebag J, Balazs EA (1984) Pathogenesis of cystoid macular edema: an anatomic consideration of vitreoretinal adhesions. Surv Ophthalmol 28(Suppl):493–498. https://doi.org/10.1016/0039-6257(84)90231-5
12. Yamaguchi Y, Otani T, Kishi S (2003) Resolution of diabetic cystoid macular edema associated with spontaneous vitreofoveal separation. Am J Ophthalmol 135:116–118. https://doi.org/10.1016/s0002-9394(02)01855-x
13. Otani T, Kishi S (2002) A controlled study of vitrectomy for diabetic macular edema. Am J Ophthalmol 134:214–219. https://doi.org/10.1016/s0002-9394(02)01548-9
14. La Heij EC, Hendrikse F, Kessels AG, Derhaag PJ (2001) Vitrectomy results in diabetic macular oedema without evident

vitreomacular traction. Graefes Arch Clin Exp Ophthalmol 239: 264–270. https://doi.org/10.1007/s004170000251

15. Ip MS, Domalpally A, Sun JK, Ehrlich JS (2015) Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. Ophthalmol 122: 367–374. https://doi.org/10.1016/j.ophtha.2014.08.048
16. Flaxel CJ, Edwards AR, Aiello LP, Arrigg PG, Beck RW, Bressler NM, Bressler SB, Ferris FL 3rd, Gupta SK, Haller JA, Lazarus HS, Qin H (2010) Factors associated with visual acuity outcomes after vitrectomy for diabetic macular edema: diabetic retinopathy clinical research network. Retina 30:1488–1495. https://doi.org/10.1097/IAE.0b013e3181e7974f
17. Gandorfer A, Messmer EM, Ulbig MW, Kampik A (2000) Resolution of diabetic macular edema after surgical removal of the posterior hyaloid and the inner limiting membrane. Retina 20: 126–133
18. Bahadir M, Ertan A, Mertoglu O (2005) Visual acuity comparison of vitrectomy with and without internal limiting membrane removal in the treatment of diabetic macular edema. Int Ophthalmol 26:3–8. https://doi.org/10.1007/s10792-006-0008-4
19. Yamamoto T, Hitani K, Tsukahara I, Yamamoto S, Kawasaki R, Yamashita H, Takeuchi S (2003) Early postoperative retinal thickness changes and complications after vitrectomy for diabetic macular edema. Am J Ophthalmol 135:14–19. https://doi.org/10.1016/s0002-9394(02)01819-6
20. Stolba U, Binder S, Gruber D, Krebs I, Aggermann T, Neumaier B (2005) Vitrectomy for persistent diffuse diabetic macular edema. Am J Ophthalmol 140:295–301. https://doi.org/10.1016/j.ajo.2005.03.045
21. Kumagai K, Furukawa M, Ogino N, Larson E, Iwaki M, Tachi N (2009) Long-term follow-up of vitrectomy for diffuse nontractional diabetic macular edema. Retina 29:464–472. https://doi.org/10.1097/IAE.0b013e31819c632f
22. Imai H, Otsuka K, Tetsumoto A, Miki A, Nakamura M (2020) Effectiveness of en bloc removal of fibrinogen-rich component of cystoid lesion for the treatment of cystoid macular edema. Retina 40:154–159. https://doi.org/10.1097/IAE.0000000000002359