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Vitrectomy for Diabetic Cystoid Macular Edema

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Purpose: We evaluated visual outcomes following vitrectomy for diabetic cystoid macular edema.

Methods: Visual outcomes and factors possibly influencing final visual acuity were assessed and documented retrospectively in 45 eyes of 40 patients, all of whom were followed up for at least 6 months postoperatively.

Results: Compared with the preoperative logarithm of the minimum angle of resolution (logMAR) visual acuity, final logMAR visual acuity improved 0.2 or more in 51% of the eyes, was unchanged in 47%, and decreased 0.2 or more in 2%. A final postoperative visual acuity of 0.5 or better was achieved in 38%. Preoperative visual acuity and the extent of the cystoid space on fluorescein angiography were significantly related to final visual acuity. A final postoperative visual acuity of 0.5 or better was noted in 8% of eyes with a preoperative visual acuity below 0.1, in 50% of eyes with a preoperative visual acuity of 0.1 or better, in 71% of eyes with a cystoid space smaller than 5 disc areas, and in 20% of eyes with a cystoid space of 5 disc areas or more. The state of the posterior vitreous membrane did not influence final visual acuity. There were no complications that decreased visual acuity.

Conclusions: We conclude that diabetic cystoid macular edema is a good indication for vitrectomy, regardless of the state of the posterior vitreous membrane. A preoperative visual acuity of 0.1 or better and/or a cystoid space smaller than 5 disc areas may be indications for surgery aimed at achieving a final postoperative visual acuity of 0.5 or better. **Jpn J Ophthalmol 2002;46:315–322** © 2002 Japanese Ophthalmological Society

Key Words: Diabetic cystoid macular edema, factors influencing final visual acuity, state of posterior vitreous membrane, visual outcome, vitrectomy.

Introduction

The results of vitrectomy for diabetic macular edema were first reported in cases with a thickened and taut posterior vitreous membrane.[1] Subsequent studies evaluated vitrectomy results in cases with neither a thickened posterior vitreous membrane nor posterior vitreous detachment,[2] and recently, in cases associated with posterior vitreous detachment.[3,4] However, there have been only a few detailed studies on the association of systemic and ocular factors with visual outcomes and no studies on the association between the above three states of the posterior vitreous membrane and visual outcomes. In this study, we evaluated visual outcomes after vitrectomy, including associations with systemic and ocular factors in cystoid macular edema (CME) cases among those of diffuse macular edema. In addition, the associations between the above three posterior vitreous membrane states and postoperative visual acuity were evaluated retrospectively.

Materials and Methods

The subjects were 40 patients (45 eyes) who underwent vitrectomy at our department between June 1994 and October 1999, and were followed up for 6 to 49 months (mean ± SD = 18.7 ± 11.7 months). There were 24 men (28 eyes) and 16 women (17 eyes), and patient age at the time of surgery ranged

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from 25 to 71 years. Eyes showing localized fluorescein leakage or no definite CME on fluorescein angiography (FA) were excluded from vitrectomy. Eyes that had undergone cataract surgery and showed an improvement of two lines or more within 1 week postoperatively were also excluded because the cataract was considered to have a significant influence on visual outcome.

The items evaluated were visual outcome, the associations of visual outcome with five systemic factors and seven ocular factors, and intraoperative and postoperative complications. The five systemic factors and seven ocular factors are shown in Table 1.

Among the ocular factors, the degree of hard macular exudate deposition was classified into three grades using the standard photographs shown in Figure 1. The extent of the cystoid space on FA images was analyzed in terms of the cystoid space area divided by the disc area on angiograms obtained 10 minutes after intravenous injection of fluorescein using an IMAGEnet image analysis system (Topcon, Tokyo), as shown in Figure 2. The degree of obstruction of the perifoveal capillary network was evaluated using a 3-grade system[5] (ie, grades 1 to 3, shown in Figure 3). No grade 4 eyes were observed in this study.

The CME eyes were classified according to the state of the posterior vitreous membrane into three groups: with a thickened and taut posterior vitreous membrane (group I), with neither a thickened posterior vitreous membrane nor posterior vitreous detachment (group II), and with posterior vitreous detachment (group III).

As to the surgical procedure, after removal of the vitreous gel, the presence or absence of posterior vitreous detachment was determined using a Glizzard needle. If there was no posterior vitreous detachment, it was artificially produced. When membrane-like tissue was observed in the macula, it was removed using a micro-hooked needle,[6] but the internal limiting membrane was not intentionally removed. In patients with proliferative retinopathy, endophotocoagulation involving an area as peripheral as possible was added, and when definite cataract was observed, phacoemulsification was performed in combination with intraocular lens implantation. Macular photocoagulation for residual macular edema was not performed to assess the effects of vitrectomy.

Statistical analysis was performed using the χ^2 test, the Fisher direct probability method, the Wilcoxon signed-rank test, the Kruskal-Wallis test, and multiple regression analysis. $P < .05$ was considered significant.

Results

Visual Outcomes

Compared with the preoperative visual acuity in the logarithm of the minimum angle of resolution (logMAR), final logMAR visual acuity improved more than 0.2 in 23 (51%) of the 45 eyes, was unchanged in 21 (47%), and decreased more than 0.2 in 1 (2%). The final visual acuity was ≧0.5 in 17 eyes (38%) (Table 2, Figure 4).

In 30 eyes, visual acuity at 6 months postoperatively could be compared with that 12 months after surgery. The logMAR visual acuities were 0.64 ± 0.36 and 0.52 ± 0.34, six and 12 months after the operation, respectively, being significantly better at 12 months ($P < .01$, Wilcoxon signed-rank test, Table 3).

Intraoperative and Postoperative Complications

Intraoperatively, iatrogenic retinal tears developed in 10 (33%) of the 30 eyes in which posterior vitreous detachment was created intentionally, but there was no postoperative retinal detachment.

Postoperatively, vitreous hemorrhage requiring washout occurred in 2 (4%) of the 45 eyes, neovascular glaucoma in 1 (2%), and glaucoma not accompanied by iris and/or angle neovascularization in 2 (4%). However, none of the eyes with these complications showed a decrease in visual acuity of two lines or more as compared with the preoperative value (Table 4).

Table 1. Association of Visual Outcomes with Systemic and Ocular Factors

Systemic Factors	Ocular Factors
Age	Stage of retinopathy (preproliferative vs proliferative)
Duration of diabetes mellitus	Interval between decreased visual acuity and surgery
Hemoglobin A_{1c} value	Presence or absence of history of macular photocoagulation
Presence or absence of hypertension	Degree of macular hard exudates
Presence or absence of nephropathy	Extent of the cystoid space by fluorescein angiography
	Degree of perifoveal capillary network obstruction
	Preoperative visual acuity

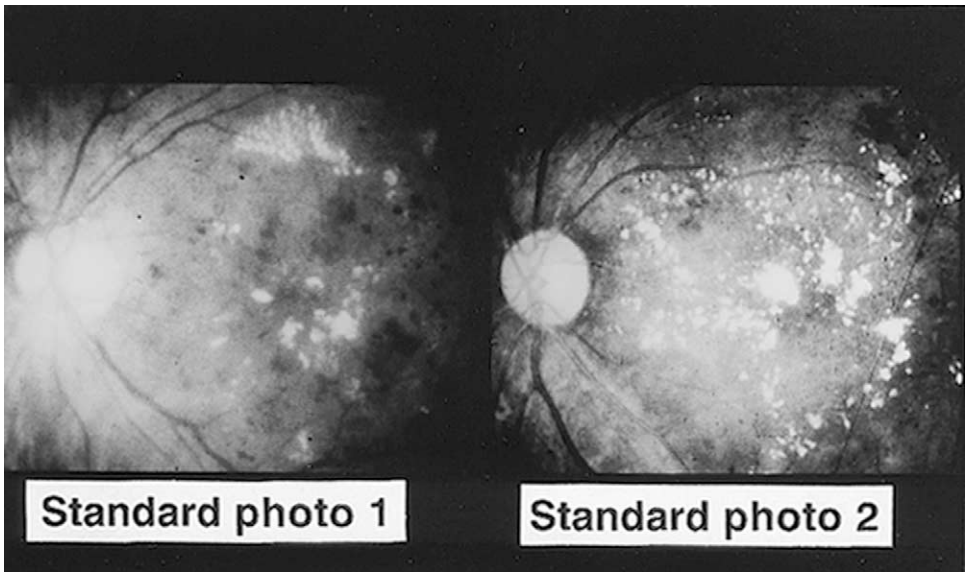

Figure 1. Standard photos used to determine the degree of hard exudate deposition in the macula.

Associations Between Systemic/Ocular Factors and Final Visual Acuity

As to the five systemic factors, patient age was 56.7 ± 11.3 years, the duration of diabetes mellitus was 9.5 ± 7.1 years. The hemoglobin A_{1c} value was 7.0 ± 1.2%, hypertension was present in 17 patients and absent in 23, and nephropathy was present in 16 patients and absent in 24.

Figure 2. Evaluation of the extent of the cystoid space by fluorescein angiography. An IMAGEnet image analysis system (Topcon, Tokyo) was used. The extent of the cystoid space on fluorescein angiography images was analyzed in terms of the cystoid space area divided by the disc area.

Among the ocular factors, preproliferative retinopathy was observed in 13 eyes and proliferative retinopathy in 32. The interval between the reported onset of visual loss and surgery was 5.9 ± 3.1 months. Eight eyes had a history of macular photocoagulation, 37 did not. The degree of hard exudate deposition in the macula was less than in Standard photo 1 in 30 eyes, comparable to or more marked than that in Standard photo 1 but less than that in Standard photo 2 in 9 eyes, and comparable to or more marked than that in Standard photo 2 in 6 eyes (Figure 1). On FA images, the cystoid space was 7.8 ± 4.3 disc areas. Grade 1 perifoveal capillary network obstruction was observed in 5 eyes, grade 2 in 27, and grade 3 in 11; grading was impossible in 2 eyes, and no grade 4 obstruction was observed. The preoperative logMAR visual acuity was 0.83 ± 0.35.

Multiple regression analysis was performed, and the associations between the postoperative logMAR visual acuity and the five systemic and seven ocular factors were evaluated. The postoperative logMAR visual acuity was significantly associated only with the preoperative logMAR visual acuity and the cystoid space area on FA ($P < .0001$, $R^2 = 0.48$).

Association Between Preoperative Visual Acuity and a Final Visual Acuity ≧0.5

The above evaluation confirmed a significant relationship between postoperative and preoperative visual acuities. Therefore, the association between preoperative visual acuity and a final visual acuity ≧0.5, adequate for reading, was evaluated.

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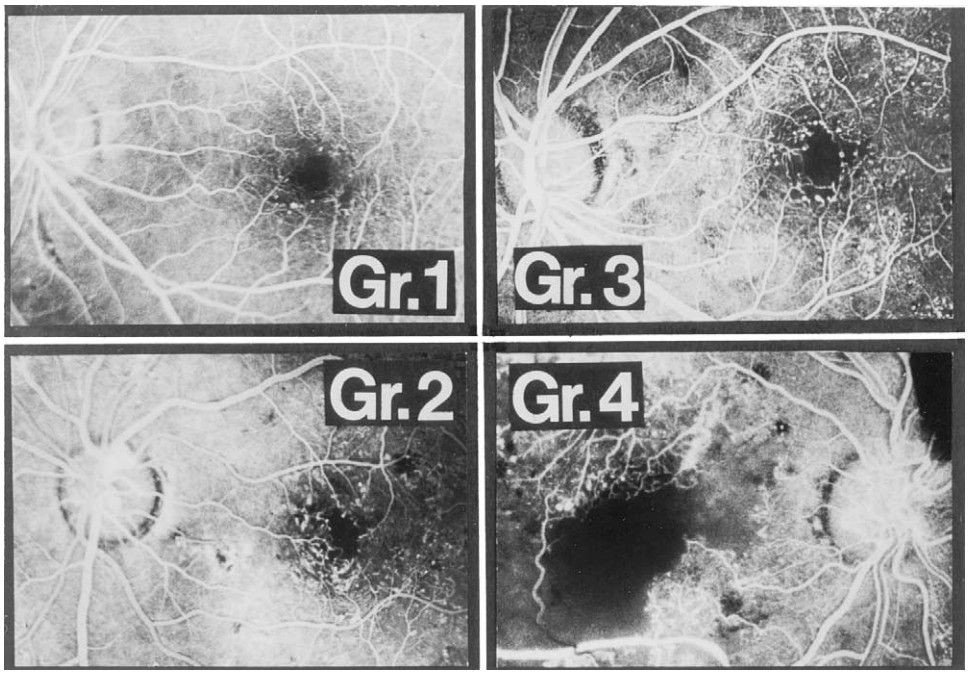

Figure 3. Evaluation of the degree of obstruction of the perifoveal capillary network using a 3-grade system (grades 1 to 3). No grade 4 eyes were observed in this study.

The final visual acuity was ≧0.5 in only one (8%) of the 13 eyes with a preoperative visual acuity <0.1, but in 16 (50%) of 32 eyes with a preoperative visual acuity ≧0.1, showing a significant difference ($P < .008$, Fisher direct probability calculation method, Table 5).

Association Between the Extent of the Cystoid Space and a Final Visual Acuity ≧0.5

Similarly, the association between the extent of the cystoid space on FA images, which was also confirmed to be related to postoperative visual acuity, and a final visual acuity ≧0.5 was evaluated. Analysis was performed in 42 eyes because angiograms 10 minutes after intravenous injection of fluorescein were inappropriate for image processing in 3 eyes.

The final visual acuity was ≧0.5 in 12 (71%) of 17 eyes with a cystoid space <5 disc areas but in only 5 (20%) of 25 with a cystoid space ≧5 disc areas, showing a significant difference ($P < .04$, Fisher direct probability calculation method, Table 6).

Table 2. Visual Outcomes (45 Eyes)

Visual Outcome	No. of Eyes*
Improvement	23 (51)
No change	21 (47)
Decrease	1 (2)
Final visual acuity ≧ 0.5	17 (38)

*Values in parentheses are percentages.

Association Between the Preoperative Visual Acuity/Cystoid Space Extent on FA Images and a Final Visual Acuity ≧0.5

The incidence of a final visual acuity ≧0.5 was evaluated in eyes showing both a preoperative visual acuity ≧0.1 and a cystoid space <5 disc areas. The final visual acuity was ≧0.5 in 11 (79%) of the 14 eyes meeting those two conditions but in none of the 8 eyes that fulfilled neither.

Association Between the State of the Posterior Vitreous Membrane and Final Visual Acuity

The relationships of the state of the posterior vitreous membrane to the preoperative logMAR visual acuity, final logMAR visual acuity, and a final visual acuity ≧0.5 were evaluated. According to the state of the posterior vitreous membrane, 3 eyes were classified as group I, 27 as group II, and 15 as group III.

In group I, the preoperative logMAR visual acuity was 0.84 ± 0.28, the final logMAR visual acuity was 0.62 ± 0.43, and the final visual acuity was ≧0.5 in one (33%) of the 3 eyes. In group II, the preoperative logMAR visual acuity was 0.85 ± 0.36, the final logMAR visual acuity was 0.59 ± 0.35, and the final

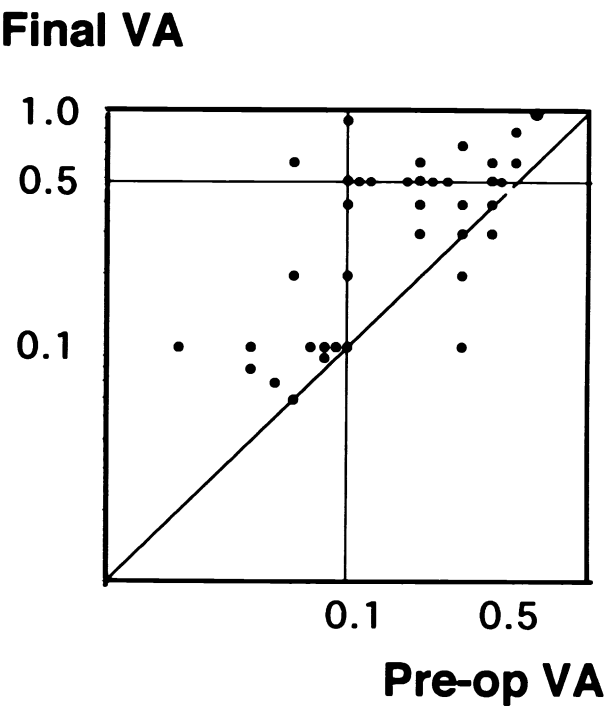

Figure 4. Visual outcomes (45 eyes). Pre-op VA: preoperative visual acuity; final VA: final visual acuity.

visual acuity was ≧0.5 in 9 (33%) of the 27 eyes. In group III, the preoperative logMAR visual acuity was 0.80 ± 0.35, the final logMAR visual acuity was 0.49 ± 0.35, and the final visual acuity was ≧0.5 in 7 (47%) of the 15 eyes.

The preoperative logMAR visual acuity did not differ significantly among the 3 groups ($P > .9$, Kruskal-Wallis test). Both the final logMAR visual acuity and the final visual acuity (≧0.5) were good in group III, but no significant differences were observed in the final logMAR visual acuity ($P = .5$, Kruskal-Wallis test) or the final visual acuity ≧0.5 ($P = .5$, χ^2 analysis) among the three groups (Table 7).

Discussion

In vitrectomy for diabetic macular edema, various systemic[7] and ocular factors[8–11] have been reported to affect postoperative visual acuity. In this study, multiple regression analysis was performed to assess 5 systemic factors and 7 ocular factors (total, 12 factors) including previously reported factors. Postoperative visual acuity was significantly related only to preoperative logMAR visual acuity and the extent of the cystoid space on FA.

In addition, the association between preoperative visual acuity, the extent of the cystoid space and a final visual acuity ≧0.5, adequate for reading, was evaluated. The final visual acuity was ≧0.5 in less than 10% of the eyes with a preoperative visual acuity <0.1 but in 50% of those with a preoperative visual acuity ≧0.1, and in about 70% of eyes with a cystoid space <5 disc areas but in only 20% of those with a cystoid space ≧5 disc areas. Of the eyes with both a preoperative visual acuity ≧0.1 and a cystoid space <5 disc areas, about 80% showed a final visual acuity ≧0.5.

Therefore, when attention is paid to these preoperative conditions, a final visual acuity ≧0.5, ie, adequate acuity for reading, may be achieved in a relatively high percentage of eyes.

Preoperatively, it must de explained to patients that improved visual acuity may require a long period of time. In this study, visual acuity 12 months after the operation was significantly improved as compared with that at 6 months postoperatively. Representative FA results are shown in Figure 5. Twelve months after surgery, fluorescein dye leakage and pooling in the macula were further decreased as compared with the state 6

Table 3. Comparison Between Visual Acuities 6 and 12 Months Postoperatively (30 Eyes)

Time of Visual Acuity Measurement	LogMAR Visual Acuity*
6 months after surgery	0.64 ± 0.36
12 months after surgery	0.52 ± 0.34
P value	<.01

*LogMAR: logarithm of the minimum angle of resolution.

Table 4. Intraoperative and Postoperative Complications

Complication	No. of Eyes*
Intraoperative	
Iatrogenic retinal tears	10/30 (33)
Postoperative	
Vitreous hemorrhage	2/45 (4)
Neovascular glaucoma	1/45 (2)
Other types of glaucoma	2/45 (4)

*Values in parentheses are percentages.

Table 5. Association Between Preoperative Visual Acuity and Final Visual Acuity ≧ 0.5

Preoperative Visual Acuity	No. of Eyes with Final Visual Acuity ≧ 0.5*
<0.1	1/13 (8)
≧0.1	16/32 (50)
P value	<.008

*Values in parentheses are percentages.

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Table 6. Association Between the Extent of the Cystoid Space by Fluoroscein Angiography and Final Visual Acuity ≧ 0.5

Extent of Cystoid Space (Disc Areas)	No. of Eyes with Final Visual Acuity ≥ 0.5*
<5	12/17 (71)
≧5	5/25 (20)
P value	<.04

*Values in parentheses are percentages.

months after the operation, and visual acuity had increased from 0.6 to 1.0.

Lewis et al[1] were the first to report the results of vitrectomy for diabetic macular edema in 10 eyes with a thickened and taut posterior vitreous membrane in the posterior pole. After artificial posterior vitreous detachment, macular edema disappeared or decreased in all eyes, and improved final visual acuity was achieved in 8 eyes. Tachi and Ogino[2] performed vitrectomy in 33 eyes with neither a thick posterior vitreous membrane nor posterior vitreous detachment. After intentional detachment of the posterior vitreous membrane, they observed disappearance of or a reduction in edema in all eyes and improved vision in 39%. Yamamoto et al[3] and Ikeda et al[4] reported the results of vitrectomy not involving retinal surface manipulation in eyes with diffuse macular edema showing definite posterior vitreous detachment. Visual acuity improvement was observed in 50% by Yamamoto et al[3] and in 80% by Ikeda et al.[4]

This study included eyes with all three of the above-mentioned pathological states of the posterior vitreous membrane. To our knowledge, there have been no studies comparing postoperative visual acuities among these three posterior vitreous membrane states. In this study, no significant difference was observed in the mean preoperative or postoperative logMAR visual acuity or the percentage of eyes with a final visual acuity ≧0.5 among the three groups classified according to the state of the posterior vitreous membrane. Our results suggest that these three groups have similar chances for vision improvement and for achieving a visual acuity adequate for reading. Herein, 7% of eyes were classified as group I with a thickened and taut posterior vitreous membrane, 60% as group II with an attached posterior vitreous but not a thickened posterior vitreous membrane, and 33% as group III with posterior vitreous detachment. Though the percentage classified as group I was low, Lewis et al[1] described their subjects with this condition as a small subset of patients with diabetic macular edema. Harbour et al,[8] who treated eyes with conditions similar to those in the Lewis et al study, also described this pathologic condition as "an uncommon cause of diabetic macular edema." Therefore, eyes classifiable as group I appear to be relatively rare. On the other hand, there may be many eyes classifiable as group II or III. The results of this study suggest that all three groups have good indications for vitrectomy.

Table 7. Association Between the Pathologic State of the Posterior Vitreous Membrane and Visual Outcome

State of PVM*	Preoperative logMAR†	Final logMAR VA‡	Final VA ≧0.5 (%)
Group I	0.84 ± 0.28	0.62 ± 0.43	33
Group II	0.85 ± 0.36	0.59 ± 0.35	33
Group III	0.80 ± 0.35	0.49 ± 0.35	47
P value	>.9	=.5	=.5

*PVM: posterior vitreous membrane.
†LogMAR: logarithm of the minimum angle of resolution.
‡VA: visual acuity.

In this study, only eyes with CME were evaluated. Lee et al[12] reported long-term results of grid pattern photocoagulation for diffuse macular edema and observed poorer visual outcomes after 2, as well as 3, years in the group with CME than in the group without CME. Thus, we considered it appropriate to perform vitrectomy in eyes with CME which have a relatively poor prognosis after photocoagulation.

The mechanism by which vitrectomy reduces macular edema has been discussed. As to the pathogenesis of macular edema due to traction of the posterior vitreous membrane, Lewis et al[1] suggested that vitreous membrane traction damages both internal and external blood-retinal barriers resulting in shallow foveal retinal detachment similar to that observed with impending macular holes. On the other hand, Tachi[13] speculated that vitreous membrane traction reduces extravascular hydrostatic pressure in the retina, inducing marked extravascular leakage, and that surgical removal of the posterior vitreous membrane changes the hydrostatic pressure gradient, rapidly reducing extravascular leakage and edema.

As to the mechanism by which vitrectomy reduces macular edema, Yamamoto et al[3] suggested that vitrectomy in eyes with posterior vitreous detachment enhances intraocular circulation of oxygen released by the ciliary body, which increases intraocular oxygen pressure and removes substances enhancing vascular permeability to substances such as cytokine. Ikeda et al[4] proposed a similar mechanism.

Among these hypotheses, the presence of foveal retinal detachment has been evaluated by optical coherence tomography.[14] In the future, measurement

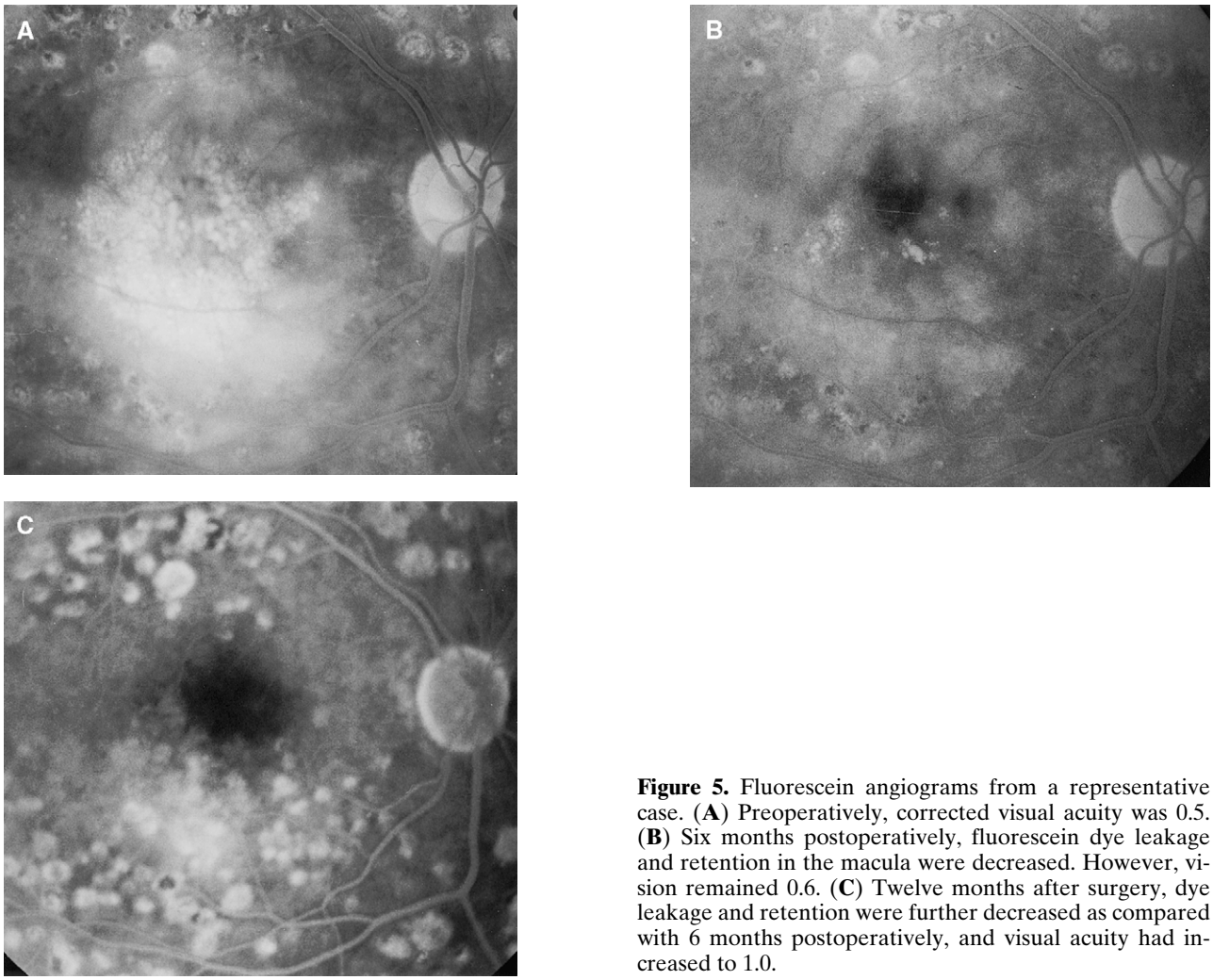

Figure 5. Fluorescein angiograms from a representative case. (**A**) Preoperatively, corrected visual acuity was 0.5. (**B**) Six months postoperatively, fluorescein dye leakage and retention in the macula were decreased. However, vision remained 0.6. (**C**) Twelve months after surgery, dye leakage and retention were further decreased as compared with 6 months postoperatively, and visual acuity had increased to 1.0.

of intraocular oxygen pressure and determination of the cytokine concentration in intraocular fluid at the time of surgery will be necessary.

Complications are possible. Iatrogenic retinal tears were observed frequently during creation of a posterior vitreous detachment, but no postoperative retinal detachment occurred. Neovascular glaucoma developed in one eye, but ocular pressure could be controlled, so that there was no decrease in visual acuity. When previous studies involving 20 or more eyes were reviewed, the incidence of iatrogenic retinal tears was 8–21%,[15,16] that of neovascular glaucoma 1–5%,[15–17] and that of postoperative retinal detachment 2–5%.[15,16] Because the incidences of neovascular glaucoma and retinal detachment capable of severely affecting visual outcomes were low, vitrectomy for this disease appears to be relatively safe.

We have described here the outcomes of vitrectomy for eyes with CME. If attention is paid to preoperative conditions, useful postoperative visual acuity may be achieved by vitrectomy in a high percentage of cases regardless of the pathological state of the posterior vitreous membrane. However, only a small number of retrospective cases were evaluated in this study. To establish surgical indications, prospective randomized clinical trials including comparison with grid pattern photocoagulation, are necessary.

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References

1. Lewis H, Abrams GW, Blumenkranz MS, Campo RV. Vitrectomy for diabetic macular traction and edema associated with posterior hyaloid traction. Ophthalmology 1992;99:753–759.
2. Tachi N, Ogino N. Vitrectomy for diffuse macular edema as-

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sociated with diabetic retinopathy. Atarashii Ganka (J Eye) 1994;11:1077–1081.

3. Yamamoto T, Yamamoto S, Takeuchi S. Pars plana vitrectomy for diabetic macular edema with posterior vitreous detachment. Atarashii Ganka (J Eye) 2000;17:133–138.
4. Ikeda T, Sato K, Katano T, Hayashi Y. Improved visual acuity following pars plana vitrectomy for diabetic cystoid macular edema and detached posterior hyaloid. Retina 2000; 20:220–222.
5. Sato Y, Ohkuma K, Kamata A, Matsui M. Clinical studies on macular changes in diabetic retinopathy, Part 3. Studies on pathologies of retinal capillary beds in and around the macula in diabetic retinopathy. Nippon Ganka Gakkai Zasshi (Acta Soc Ophthalmol Jpn) 1984;88:1084–1092.
6. Tano Y. Micro-hooked needle. Ganka Shujutsu (J Jpn Soc Ophthalmic Surg) 1988;1:313–315.
7. Maruiwa F, Nao-i N. The limitations of vitrectomy for diabetic macular edema. Ganka Shujutsu (J Jpn Soc Ophthalmic Surg) 1999;12:505–508.
8. Harbour JW, Smiddy WE, Flynn HW Jr, Rubsamen PE. Vitrectomy for diabetic macular edema associated with a thickened and taut posterior hyaloid membrane. Am J Ophthalmol 1996;121:405–413.
9. Tachi N, Ogino N. Long-term follow-up of vitrectomy for diffuse macular edema associated with diabetic retinopathy. Nihon Ganka Kiyo (Folia Ophthalmol Jpn) 1996;47: 248–254.
10. Takenoshita Y, Nakano T, Naoi N, Yokogami K, Sawada A. Visual outcome following vitreous surgery for diabetic macular edema. Ganka Rinsho Iho (Jpn Rev Clin Ophthalmol) 1998;92:1287–1290.
11. Tachi N, Ogino N. Vitrectomy for diffuse macular edema associated with diabetic retinopathy. Ganka Shujutsu (J Jpn Soc Ophthalmic Surg) 1995;8:129–134.
12. Lee CM, Olk RJ. Modified grid laser photocoagulation for diffuse diabetic macular edema—Long-term visual results. Ophthalmology 1991;98:1594–1602.
13. Tachi N. Vitrectomy for macular edema. Ganka Shujutsu (J Jpn Soc Ophthalmic Surg) 1994;7:407–414.
14. Otani T, Kishi S, Maruyama Y. Patterns of diabetic macular edema with optical coherence tomography. Am J Ophthalmol 1999;127:688–693.
15. Takagi H, Torii Y, Yamauchi T, Shimizu E, Kiryu J, Ogura Y. Long-term results of vitrectomy for diabetic macular edema. Rinsho Ganka (Jpn J Clin Ophthalmol) 1997;51:977–980.
16. Tachi N, Ogino N. Vitrectomy for diffuse macular edema in cases of diabetic retinopathy. Am J Ophthalmol 1996;122: 258–260.
17. Ito S, Ando F, Kawai T, Toura K. Effect of vitrectomy for diabetic maculopathy. Nihon Ganka Kiyo (Folia Ophthalmol Jpn) 1999;50:682–686.