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Treatment of Full-Thickness Macular Holes With Autologous Serum

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Abstract: A total of 28 patients (29 eyes) with stage 2–4 idiopathic full-thickness macular holes were treated with the use of autologous serum. Autologous serum (20–30 μL) was placed over each macular hole followed by injection of 16% perfluoropropane gas. Postoperatively, 28 eyes (97%) had flattening of the macular hole, and the hole could not be detected in 27 eyes (93%). Twenty-two eyes (76%) showed visual acuity improvement by at least two lines or more. Preoperative factors such as good visual acuity, earlier stage, and younger age were correlated with postoperative good visual acuity. These results suggest that autologous serum is beneficial in the treatment of full-thickness macular holes. **Jpn J Ophthalmol 1997; 41:332–338** © 1997 Japanese Ophthalmological Society

Key Words: Autologous serum, macular hole, retinal perforations, treatments, vitrectomy.

Introduction

Idiopathic macular holes had been regarded as surgically untreatable until Kelly and Wendel[1] reported that visual recovery was attained by performing vitrectomies in eyes with idiopathic macular holes. Visual improvement after vitrectomy is usually associated with flattening of the surrounding rim of a neurosensory retinal detachment (fluid-cuff).[1–6] Using the method of Kelly and Wendel[1] (ie, vitrectomy alone with perfluorocarbon gas tamponade), anatomic success rates of 47–79% have been reported.[1–8] In attempts to improve anatomic success, surgeons have used various adjuvants such as transforming growth factor β2 (TGF-β2),[9–11] autologous serum,[12–14] and autologous platelet concentrates.[7] Of these adjuvants, a prospective randomized clinical trial has been performed only for the use of TGF-β2.[9] However, TGF-β2 is expensive and at present unavailable. In this study, we used autologous serum for the treatment of macular holes because autologous serum is inexpensive and easy to obtain.

Material and Methods

Twenty-nine eyes of 28 patients with idiopathic full-thickness macular holes were treated with vitrectomy (by SK or KS) with the use of autologous serum at Ehime University Hospital or Takanoko Hospital between December 1993 and October 1995. There were 19 women (20 eyes) and 9 men (9 eyes). The patients ranged in age from 34–80 years (average ± SD, 63.9 ± 10.7). Duration of symptoms ranged from 10 days to 15 years (median 60 days). All eyes were phakic. According to the criteria described by Johnson and Gass,[15] six eyes had stage 2, 13 eyes had stage 3, and 10 eyes had stage 4 macular holes. All the patients were followed for at least 3 months (3–24 months, average 14.1 months) postoperatively. Informed consent in written form was obtained from each patient.

All eyes underwent slit-lamp examinations, including biomicroscopy of the vitreous and retina. Best corrected visual acuities were measured preoperatively and 1, 3, 6, and 12 months postoperatively. Among these postoperative visual acuities, the best visual acuities were used for analysis. In addition, Amsler grid testing was performed to evaluate metamorphopsia preoperatively and postoperatively. A surgery was regarded as anatomically successful if flattening of the surrounding rim of the neurosen-

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Table 1. Patient Data

Case	Age	Sex	Stage of Macular Hole	Duration of Symptoms (mos)	Diameter of MH (DD)	Diameter of Fluid-Cuff (DD)	Cataract Surgery[a]	Preoperative Visual Acuity	Postoperative Visual Acuity	MH Closure	MH Disappearance	Follow-Up (mos)
1	58	F	2	0.3	0.2	0.4	—	0.2	1.0	Yes	Ycs	24
2	53	F	2	0.6	0.1	0.4	—	0.2	0.9	Yes	Yes	24
3	68	M	2	3	0.2	0.6	—	0.15	0.4	Yes	Yes	9
4	78	F	2	2	0.2	0.5	Yes	0.2	0.8	Yes	Yes	12
5	77	F	2	6	0.2	0.3	Yes	0.5	0.8	Yes	Yes	11
6-L	58	F	2	0.5	0.1	0.3	Yes	0.6	0.9	Yes	Yes	7
7	58	F	3	17	0.3	0.5	—	0.07	0.3	Yes	Yes	24
8	72	F	3	2	0.3	0.6	Yes	0.15	0.2	Yes	No	12
9	45	F	3	0.5	0.2	0.8	—	0.1	0.4	Yes	Yes	12
10	72	F	3	1	0.3	0.7	—	0.2	0.2	No→Yes[b]	No→Yes[b]	24
11	63	F	3	4	0.3	0.5	—	0.05	0.15	Yes	Yes	24
12	66	F	3	0.6	0.2	0.3	Yes	0.15	0.7	Yes	Yes	14
13	34	M	3	1	0.5	0.7	—	0.3	0.6	Yes	Yes	6
14	44	F	3	8	0.2	0.5	—	0.05	0.3	Yes	Yes	7
15	69	F	3	5	0.3	0.6	Yes	0.1	0.4	No→Yes[b]	No→Yes[b]	12
16	66	F	3	1	0.2	0.6	Yes	0.09	0.1	Yes	Yes	12
17	63	F	3	1	0.2	0.4	Yes	0.07	0.2	Yes	Yes	7
18	62	F	3	3	0.2	0.5	—	0.3	0.3	No→Yes[b]	No→Yes[b]	18
19	71	F	3	0.5	0.2	0.4	Yes	0.06	0.15	Yes	Yes	18
20	62	M	4	0.5	0.3	0.5	—	0.2	0.6	Yes	Yes	11
21	62	M	4	1.6	0.4	0.9	Yes	0.1	0.3	Yes	Yes	23
22	68	M	4	4	0.3	0.7	—	0.07	0.15	Yes	Yes	24
23	62	F	4	1.3	0.4	0.7	Yes	0.2	0.2	No→No[c]	No→No[c]	20
24	80	M	4	1.5	0.3	0.4	Yes	0.05	0.1	Yes	Yes	7
25	59	F	4	8	0.5	1.3	Yes	0.05	0.2	Yes	Yes	12
26	73	M	4	49	0.3	0.6	Yes	0.04	0.08	Yes	Yes	12
27	68	M	4	13	0.6	1.0	Yes	0.1	0.3	Yes	Yes	12
28	79	M	4	183	0.4	0.5	Yes	0.1	0.2	Yes	Yes	3
6-R	58	F	4	36	0.3	0.5	—	0.15	0.15	Yes	Yes	7

DD: disk diameter. 6-L: case 6, left eye. 6-R: case 6, right eye.
[a]Phacoemulsification and aspiration with intraocular lens implantation.
[b]Macular hole closed or disappeared after second operation.
[c]Macular hole neither closed nor disappeared after second operation.

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sory retinal detachment occurred (macular hole closure), or if the edge of the macular hole could not be detected (macular hole disappearance). In addition, the relation between postoperative visual acuities and preoperative factors that had been reported to be correlated with postoperative visual acuity (ie, age, stage of macular holes, diameter of macular holes, diameter of fluid-cuff, duration of symptoms, and preoperative visual acuity) were investigated. The diameter of the macular holes and fluid-cuffs were compared with the vertical diameter of the disc using fundus photographs.

Pars plana vitrectomy was performed in each eye. Except in eyes with stage 4 macular holes, the posterior vitreous was separated from the retina using a vitrectomy instrument under active pressure aspiration. Epiretinal membranes were detected using the extrusion needle or a micro-hooked 20-gauge disposable needle.[16] When the epiretinal membrane was engaged, it was gently peeled off using the needle and/or tissue forceps. A fluid/gas exchange was then performed. A flexible canula was used to drain intravitreal fluid over the optic disc and from the macular hole. Careful attention was paid to avoid contact with the retinal pigment epithelium. After 10 minutes had elapsed with the sclerotomy sites plugged, the remaining fluid was usually observed to be present over the vascular arcade. Fluid drainage was repeated in the same manner. Two or three drops (20–30 μL) of autologous serum were then placed over the macular hole from a 1 mL syringe with a 27-gauge needle. The injection of the serum was performed slowly to allow precise dose control. More than 25 mL of 16% perfluoropropane (C_3F_8) gas was injected while gas and air were allowed to escape from the open sclerotomy site. Postoperatively, face-down position was assumed by the patient soon after returning to an inpatient room (approximately 10–20 minutes after surgery ended).

Combined cataract surgeries were performed in 14 eyes with mild lens opacification. In each of these cases, a cataract was removed by phacoemulsification prior to pars plana vitrectomy, and an intraocular lens implantation preceded fluid/air exchange.

Repeat pars plana vitrectomies were performed from 2 to 26 weeks in four eyes in which the macular holes had not resolved.

At the beginning of each surgery, venous blood was drawn from the patient. The blood was allowed to clot for 10 minutes, then centrifuged at 3000 rpm for 15 minutes. The supernatant was drawn with a 1 mL syringe. All procedures were performed under sterile conditions.

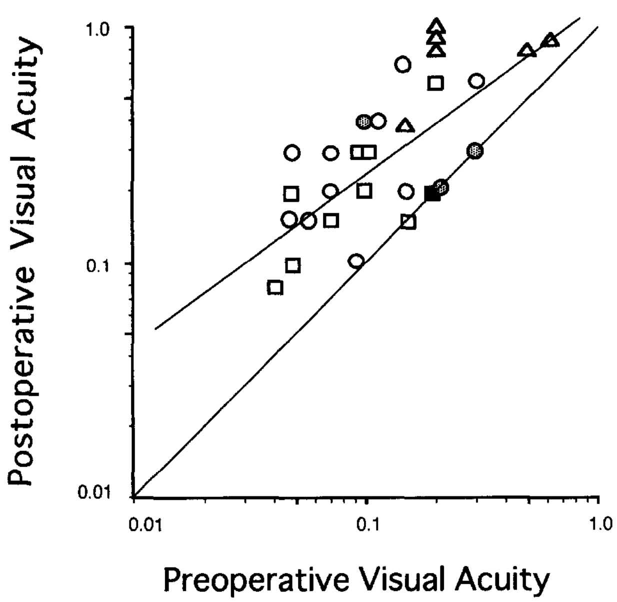

Figure 1. Comparison of preoperative versus postoperative visual acuities. △: Stage 2. ○: Stage 3. □: Stage 4 macular hole. ●: Anatomic success after second vitrectomy. ■: Anatomic failure after second vitrectomy.

Results

Clinical data on the 29 eyes are summarized in Table 1. Twenty-five of 29 eyes (86%) had flattening of the surrounding rim of the neurosensory retinal detachment after the initial vitrectomies. In 24 of 29 eyes (83%), the edge of the macular hole could not be detected. Reoperations were performed for four eyes in which the fluid-cuff had remained after the initial vitrectomies. In three of these four eyes, the edge of the macular hole could not be seen after the reoperations. Eventually, 28 of the 29 eyes (97%) had flattening of the edge of the macular holes; and in 27 of the 29 eyes, the macular holes resolved.

Preoperative fluorescein angiograms showed that all 29 eyes had hyperfluorescence in the base of the macular holes. Postoperative fluorescein angiograms were performed in 25 eyes. Of these 25 eyes, there was resolution of the fluid-cuff in 23. Of these 23 eyes, the hyperfluorescence was no longer present in 12 eyes and was significantly reduced in the remaining 11 eyes. In an eye with a remaining fluid-cuff, the hyperfluorescence did not change postoperatively. In contrast, hyperfluorescence decreased in an eye that had a visible edge of the macular hole despite resolution of the fluid-cuff.

Metamorphopsia, evaluated by Amsler grid testing, improved in 28 eyes. In one eye, although the

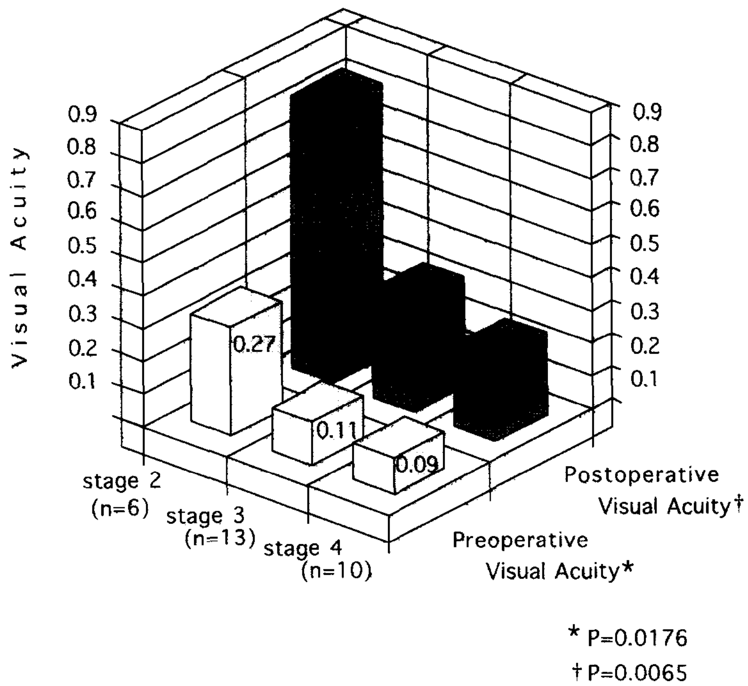

Figure 2. Relationship between visual acuity changes and stage of macular hole. Statistically significant differences in preoperative and postoperative visual acuities were observed among stages (Kruskal-Wallis test).

metamorphopsia did not change, the macular hole disappeared and visual acuity improved (case 15).

Postoperative visual acuity was 0.3 or more in 16 eyes (55%), 0.5 or more in eight eyes (28%). Visual acuity improved by at least two lines in 22 of the 29 eyes (76%). Visual acuity changes were within 1 line in 7 of the 29 eyes. Mean logarithmic visual acuity statistically improved from 0.12 to 0.30 (Wilcoxon signed rank test, $P < 0.0001$). Postoperative visual acuity can be expressed by

$$y = 0.27 + 0.85x \ (r = 0.71, P < 0.001)$$

where y and x are the logarithm of postoperative and preoperative visual acuity, respectively (Figure 1). Visual acuity improved in six of six eyes with stage 2 macular holes, in 9 of 13 eyes with stage 3 macular

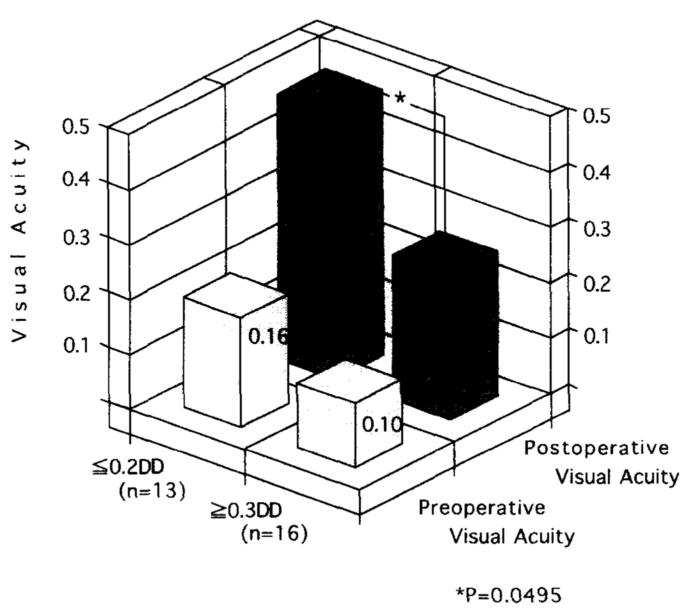

Figure 3. Relationship between visual acuity changes and diameter of macular holes. Postoperative visual acuities are statistically better in eyes with macular holes equal to or smaller than 0.2 DD than in eyes with macular holes larger than 0.2 DD (Mann-Whitney U-test).

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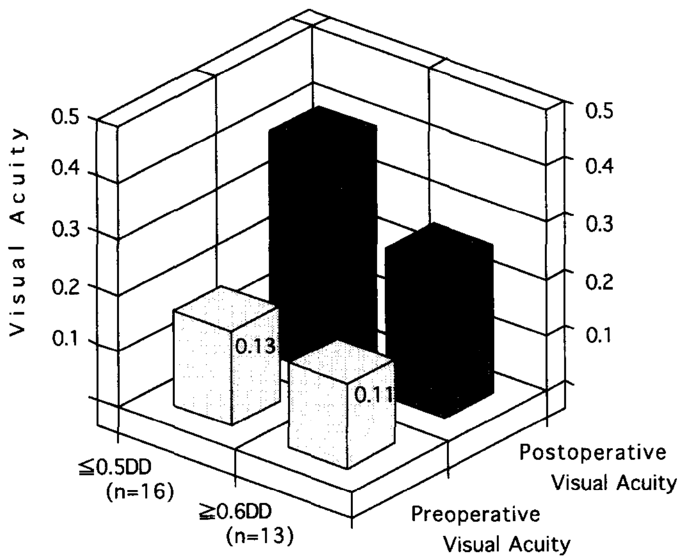

Figure 4. Relationship between visual acuity changes and diameter of fluid-cuff. Eyes with equal to or smaller than 0.5 DD show better preoperative and postoperative mean visual acuity, although no statistical differences are observed.

holes, and in 7 of 10 eyes with stage 4 macular holes. There were statistically significant differences among stages between preoperative (Kruskal-Wallis test, $P = 0.0176$) and postoperative (Kruskal-Wallis test, $P = 0.0065$) visual acuities (Figure 2).

Visual acuity improved in 11 of 13 eyes (85%) with macular holes of 0.2 or smaller disk diameter (DD). In contrast, visual acuity improved in 11 of 16 eyes (69%) with macular holes of 0.3 or larger DD. The mean logarithm of postoperative visual acuity of eyes with 0.2 or smaller DD macular holes was significantly better than the mean logarithm of postoperative visual acuity of eyes with 0.3 or larger DD macular holes (Mann-Whitney U-test, $P = 0.0495$) (Figure 3).

Visual acuity improved in 13 of 16 eyes (81%) with fluid-cuff of 0.5 or smaller DD. In contrast, visual acuity improved in 9 of 13 eyes (69%) with fluid-cuff of 0.6 or larger DD. Although the visual improvement rate and mean logarithm of postoperative visual acuity were better in eyes with 0.5 or smaller DD fluid-cuff, no statistical difference was observed (Figure 4).

For all 29 eyes, the logarithm of preoperative visual acuity ($r = 0.71$, $P < 0.001$), stage of macular hole ($r = 0.539$, $P = 0.0026$) (Figure 5), and age of patient ($r = 0.388$, $P = 0.0373$) were correlated, using linear regression, with the logarithm of postoperative visual acuity. Other factors, such as diameter of macular hole ($r = 0.298$, $P = 0.1169$), or diameter of fluid-cuff ($r = 0.269$, $P = 0.1589$) were not statistically correlated with the logarithm of postoperative visual acuity. There was little correlation between duration of symptoms and the logarithm of postoperative visual acuity, perhaps because for many patients onset was uncertain.

Postoperatively, retinal detachment occurred in three (10%) eyes. Retinal breaks in these eyes included horse-shoe tears at the inferior equator (cases 11 and 27) and an atrophic hole in the lattice degeneration at the temporal equator (case 14). The retinas of these eyes were reattached after scleral buckling procedures. In 7 of 13 phakic eyes, lens opacities progressed after the vitrectomies. Cataract surgery was performed in six of these seven eyes. Neither fibrin formation nor macular puckers were observed in any patient during follow-up.

Discussion

Kelly and Wendel[1] reported that, in a total of 52 eyes, flattening of the rim surrounding retinal detachment and visual improvement of at least two lines were seen in 32 eyes (58%) and 22 eyes (42%), respec-

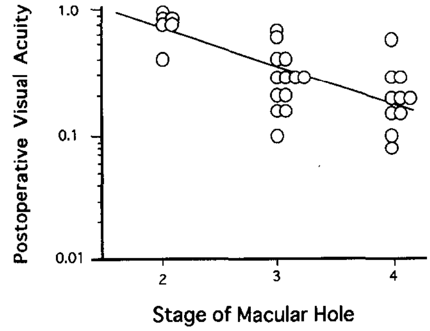

Figure 5. Relationship between stage and postoperative visual acuity.

tively. Three years later, their surgical results showed improvement (ie, anatomic success rate and visual improvement rate were reported to be 74% [125 of 170 eyes] and 56% [95 of 170 eyes], respectively.[6] The surgical technique Kelly and Wendel[1] used was pars plana vitrectomy with removal of epiretinal membrane followed by sulfur hexafluoride gas tamponade.[1,6] Using similar techniques, Ogino[4] reported that overall anatomic success rate, including reoperations, was 67% (50 of 75 eyes). In addition, Maeno et al[8] reported that anatomic success rate and visual improvement rate using these same techniques were 71% (36 of 51 eyes) and 65% (33 of 51 eyes), respectively. It seems likely that anatomic success rate and visual improvement rate without using adjuvants are about 60–80% and 40–70%, respectively.

In an attempt to improve surgical results, Glaser et al[9] reported that anatomic success rate and visual improvement rate were 100% (11 of 11 eyes) and 91% (10 of 11 eyes), respectively, with use of 1330 ng TGF-β2. Liggett et al[12] reported that both anatomic success rate and visual improvement rate were 100% (11 of 11 eyes) with use of autologous serum.

Overall anatomic success rate and visual improvement rate of our patients were 97% (28 of 29 eyes) and 76% (22 of 29 eyes), respectively. However, to compare our results precisely, factors known to influence surgical results should be considered. Compared with the rate of macular hole closure achieved by Ogino[4] and Maeno et al,[8] our results are better, especially for eyes with poor preoperative conditions (ie, stage 4 or diameter of macular holes equal to or larger than 0.4 DD). Our data suggest that autologous serum may be beneficial in the treatment of full-thickness macular holes, especially when poorer preoperative conditions exist.

Histopathological study of successfully treated eyes with macular holes revealed that the retinal glia played an important role in the healing process.[17,18] The apparent beneficial effect of serum may be due to the presence of various kinds of growth factors, such as platelet-derived growth factor, epidermal growth factor, and insulin-like growth factor-1. Furthermore, serum has been shown to be chemotactic for glial cells[19] and retinal pigment epithelial cells[20] in vitro. Also, it has been shown in vivo that serum stimulates proliferation of glial cells, retinal pigment epithelial cells and fibroblasts at the edges of retinal breaks in the rabbit retina.[21] These experimental data suggest the possibility that autologous serum is likely to stimulate glial cell migration and proliferation, which may lead to closure or disappearance of macular holes.

Fibrin formation has been reported as a complication related to the use of serum.[13,14] However, we have observed no patients with this complication. In previous reports,[13,14] the amount of serum used was more than 0.1 mL: we used (20–30 μL). This dose difference may account for the lack of fibrin complications in our patients. However, this complication should be studied further.

Although our study is not a randomized clinical trial, the results suggest the efficacy of autologous serum in the treatment of full-thickness macular holes. A randomized clinical trial will be necessary to confirm that autologous serum is beneficial in the treatment of full-thickness macular holes.

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