The Effect of Autologous Serum on Vitrectomy with Internal Limiting Membrane Peeling for Idiopathic Macular Hole

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Abstract

Purpose: We sought to evaluate the effects of intraoperative adjunctive autologous serum in idiopathic full-thickness macular hole surgeries, and to compare the surgical outcomes with a no-serum control group.

Methods: In this retrospective, case-control study, 38 consecutive eyes received vitrectomy with internal limiting membrane removal for idiopathic full-thickness macular holes. Two groups were created according to the use of autologous serum. Outcome measures were visual acuity (VA), closure of the macular hole confirmed by optical coherence tomography, and surgical complications.

Results: Anatomical closure of the macular hole was achieved in 18 of 19 eyes (94.7%) in the vitrectomy with the autologous serum group, and in 18 of 19 eyes (94.7%) in the control group. The closure rates did not differ significantly between 2 groups ($P=1.000$; the Fisher's exact test). At the final follow-up, the mean logMAR VA improved significantly in both groups (SD, standard deviation) [from 1.08 (0.21) to 0.47 (0.21) in vitrectomy with the serum group and from 1.01 (0.32) to 0.44 (0.30) in the control group (both $P<0.001$; 2 tailed, paired t test)]. There was no significant difference between these 2 groups in terms of visual outcomes ($P=0.738$; 2-tailed t test). There were no surgical complications, such as retinal detachment and endophthalmitis.

Conclusions: The outcome of macular hole surgery did not differ both anatomically and functionally regardless of the use of adjuvant autologous serum. There seemed to be no additive effect with autologous serum.

Introduction

MACULAR HOLE SURGERY involves a vitrectomy to remove the anteroposterior and tangential vitreomacular traction exerted by the posterior vitreous cortex at the fovea, followed by gas tamponade to flatten and reappose the hole edges.¹⁻³ Internal limiting membrane (ILM) removal can further relieve foveal traction from within the retinal surface and provide good anatomical and functional results with high closure and low reopening rates.^{4,5} Staining ILM with a dye can facilitate visualization of the ILM during surgery and help complete removal. Among different dyes, indocyanine green (ICG) was first used for ILM staining and remained the standard in some countries because the staining of ILM and the ease of ILM removal were optimum with ICG. However, ICG may have direct toxicity or indirect phototoxicity on retinal tissues, resulting in poorer visual outcomes.⁶⁻⁸

Autologous serum, an intraoperative adjunctive agent, used to be instilled over the macular hole following an air-fluid exchange to enhance anatomic success.⁹⁻¹¹ It was also found to help remove ICG dye used in surgery, significantly

shorten the period of residual retinal ICG staining, and probably reduce its toxicity.¹² Although autologous serum did not seem to enhance anatomic or visual results of macular hole surgery without ILM peeling,¹ there were few reports regarding the effect of autologous serum on ICG-assisted ILM peeling for idiopathic macular holes. In this study, we sought to evaluate the effects, both with and without autologous serum, on ICG-assisted ILM peeling and compare the surgical outcomes using optical coherence tomography (OCT).

Methods

The study was approved by the Hospital Institutional Review Board (IRB) committee and followed the tenets of the Declaration of Helsinki. From retrospectively reviewing the medical records, we consecutively recruited patients who received pars plana vitrectomy with ILM removal for the idiopathic macular hole by the same surgeon (T.T.W.) between October 2008 and December 2010. We excluded eyes with macular holes secondary to causes, such as trauma,

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TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS RECEIVING MACULAR HOLE SURGERY

	Vitrectomy group	Vitrectomy with serum group	P value
No.	19	19	
Eye (OD)	10 (52.6%)	7 (36.8%)	0.515
Female	13 (68.4%)	17 (89.5%)	0.232
Age (years)	60.79 (5.21)	63.89 (6.62)	0.117
Mean refractive errors (diopters)	+0.35 (1.36)	+0.16 (1.09)	0.643
Mean axial length (mm)	23.58 (0.96)	23.32 (0.77)	0.475
Mean preoperative logMAR VA	1.01 (0.32)	1.08 (0.21)	0.407
Phakic eyes	16 (84.2%)	15 (78.9%)	1.000
Stage of macular hole	0.100		
Stage 2	9 (47.4%)	3 (15.8%)	
Stage 3	4 (21.1%)	5 (26.3%)	
Stage 4	6 (31.6%)	11 (57.9%)	
Mean duration of symptoms (months)	3.92 (4.37)	4.32 (3.84)	0.769
Mean follow-up (months)	11.58 (7.34)	8.42 (6.06)	0.157

OD, right eye; VA, visual acuity.

diabetic retinopathy, uveitis, retinal detachment, and those with concomitant retinoschisis and previous vitreoretinal surgery. Eyes with high myopia might have affected the surgical results and were excluded in this study.^{13–15}

We performed detailed ophthalmologic examinations for every patient, including best-corrected visual acuity (VA), intraocular pressure, slit lamp biomicroscopy, indirect ophthalmoscopy, OCT, and fundus photographs (after dilation of the pupils with 10% phenylephrine and 1% tropicamide). Diagnosis and staging of macular holes were defined by findings from biomicroscopy and OCT (Stratus OCT, Carl Zeiss Meditec, Dublin, CA, or RTVue Scanner; Optovue, Inc., Fremont, CA).

Every patient underwent a standard 20-gauge or 23-gauge pars plana vitrectomy, followed by 0.05% ICG-assisted ILM peeling and tamponade with 16% perfluoropropane gas. From November 2009, we applied autologous serum as an adjunctive agent in macular hole surgeries. The serum was prepared from the blood drawn from the patient's antecubital vein after sterile preparation. Approximately 10 mL of blood was spun at 3,000 rpm for 10 min. Approximately 0.2 mL of the supernatant was applied over the macula after air drying, left for 3 min, and removed with a back-flush cannula before the air-gas exchange. All patients were instructed to maintain a face-down posture for 2 weeks postoperatively.

We recorded the following data for analysis: gender, age, refractive errors (diopters), axial length, lens status, duration of symptoms, preoperative and postoperative VA, OCT findings (including stages of the macular hole according to the Gass classification^{16,17} and closure of the macular hole after operation), use of autologous serum during surgery, further cataract surgery, complications, and follow-up time.

Two groups were sorted according to the use of autologous serum. Outcome measures were VA, closure of the macular hole, and surgical complications. Complete closure of the macular holes was determined by OCT, with reconnection of hole edges, intact retinal layers, and foveal depression at each scan view. Otherwise, the hole was classified as unclosed.

We used Snellen charts to measure VA, and VA was converted to logarithm of minimum angle of resolution (logMAR) for calculation. Data were analyzed using SPSS statistical software version 12.0 (SPSS, Inc., Chicago, IL). Differences in data between the groups were analyzed by the Chi-square test for categorical variables and the 2-tailed *t*-test

for continuous variables. The paired *t*-test was used to compare the VA before and after operation. A level of $P < 0.05$ was considered statistically significant.

Results

Between October 2008 and December 2010, 38 consecutive eyes with idiopathic macular holes met the criteria and underwent macular hole surgery by T.T.W. All eyes were further divided into 2 groups: 19 in the autologous serum group, and 19 in the control (no-serum) group.

For all, there were 30 (78.9%) females, but a nearly even distribution of right eyes and left eyes (44.7% right eyes). The mean age was 62.34 (SD) (6.08 years). The mean refractive error was +0.25 (1.22) diopters, and the mean axial length was 23.44 (0.85) mm. Table 1 summarizes the baseline characteristics of the 2 groups. There were no significant differences between these 2 groups in terms of the female percentage, mean age, mean spherical equivalent refraction, mean axial length, mean preoperative logMAR VA, percentage of phakic eyes, duration of symptoms, and mean follow-up duration. There was also no significant difference between the 2 groups in the staging of the macular hole.

Postoperative results are listed in Table 2. Overall, the macular hole closure rate was 94.7% (36/38), with 31 eyes (81.6%) achieving visual improvement of at least 2 Snellen lines and 19 eyes (50%) achieving Snellen acuity of 6/15 or better. In the vitrectomy with the autologous serum group, anatomical closure of the macular hole (defined by OCT) was achieved in 18 of 19 eyes (94.7%), compared with 18 of 19 eyes (94.7%) in the control group ($P = 1.000$; Fisher's exact test). The 2 groups achieved a comparable closure rate.

During follow-up, 6 eyes (31.6%) in the vitrectomy with the serum group received cataract surgery, while 8 eyes (42.1%) in the control group received cataract surgery. At the final follow-up, the mean logMAR VA had improved significantly in both groups; i.e., from 1.08 (SD) (0.21) [Snellen equivalent (SE), 6/72] to 0.47 (0.21) (SE, 6/18) in vitrectomy with the serum group and from 1.01 (0.32) (SE, 6/61) to 0.44 (0.30) (SE, 6/17) in the control group (both $P < 0.001$; the 2-tailed, paired *t*-test). There was no significant difference between these 2 groups in terms of visual outcomes ($P = 0.738$; the 2-tailed *t*-test). There were no observed surgical complications, such as retinal detachment and

TABLE 2. OUTCOMES OF MACULAR HOLE SURGERY

	<i>Vitrectomy group</i>	<i>Vitrectomy with serum group</i>	<i>P Value</i>
Mean final logMAR VA	0.44 (0.30)	0.47 (0.21)	0.738
Final VA of 6/15 or better	12 (63.2%)	7 (36.8%)	0.194
Complete closure of macular hole	18 (94.7%)	18 (94.7%)	1.000
Cataract surgery during follow-up	8 (42.1%)	6 (31.6%)	0.737
Complications	0	0	

VA, visual acuity.

endophthalmitis. During the follow-up visits, none of the closed holes had reopened.

Discussion

Idiopathic full-thickness macular hole causes central visual loss, frequently occurring in women over the sixth decade of life and at a younger age in myopic eyes.^{3,18} Theoretically, anteroposterior and tangential vitreomacular traction have been considered to be involved in the development of macular holes.^{2,3} In 1991, Kelly and Wendel first described the initial surgical attempt to treat idiopathic macular holes. They relieved the traction using pars plana vitrectomy and meticulous peeling of the posterior hyaloid and epiretinal membrane, followed by intraocular gas tamponade to flatten and approximate the edges of the macular hole. This technique resulted in an increased closure rate to 58%.¹⁹ Some studies also reported the use of intraoperative adjuncts, such as the transforming growth factor β 2, autologous serum, autologous platelets, and thrombin and fibrin mixtures, in an attempt to enhance macular hole repair, but the outcomes varied.^{9,20–22}

Autologous serum is readily available and easy to prepare during the perioperative period. Serum containing numerous growth factors can induce fibrocellular migration, adhesion, and proliferation.²³ Liggett et al.⁹ first used autologous serum as an adjuvant to increase the macular hole closure rate, and all 11 eyes (100%) had resolution of the surrounding subretinal fluid and flattening of the hole. Later, several case series also reported that autologous serum was beneficial in treating full-thickness macular holes and favorable in re-treating eyes with previous failed macular hole surgery.^{10,11,20}

However, a large case-control study by Banker et al.²¹ reported that using serum as an adjuvant to macular hole surgery had only a slight beneficial effect, and, if present, it might be limited to larger holes. The Moorfields Macular Hole Study Group carried out a randomized clinical trial to evaluate the outcome of macular hole surgery and found that autologous serum application did not enhance the results.¹ Nevertheless, both studies peeled the epiretinal membrane, but not the ILM, and the outcome of macular hole closure was not confirmed by OCT.^{1,21}

Later, peeling of the ILM was proposed in an attempt to further remove the tangential traction from within the retinal surface, bringing about increased anatomical and visual outcomes of surgery for macular holes. Several reports also indicated that experienced surgeons could achieve an anatomical closure rate of more than 90% after ILM peeling for macular holes.^{2–5} Although there are other dyes with greater safety, including trypan blue and brilliant blue G, ICG still remains the standard for staining transparent ILM by some surgeons in some countries due to its greater availability and its optimal, selective staining of ILM. However, the potential adverse

effects of ICG on retinal tissues remain a concern.^{6,7} Although ICG can help clear identification of ILM, facilitate complete peeling, and contribute to increased anatomic success of macular hole surgery, it may lead to poorer visual outcomes.^{8,24}

Possible explanations for poor visual outcomes suggested ICG might alter the cleavage plane to involve the innermost retinal layer, and it might also have phototoxicity or direct toxic effects on the exposed retinal pigment epithelium (RPE) at the base of the macular hole.^{6,7} It has been reported that ICG can remain in the eye for several months, and infrared hyperfluorescence from ICG may persist for up to 36 months after ICG-assisted ILM peeling.^{12,25} Consequently, the persistence of ICG may, in turn, cause prolonged adverse effects by promoting phototoxicity.²⁵

Possible solutions to minimize the adverse effects of ICG include brief intravitreal application of a small amount of ICG at a low concentration. Secondly, reducing the intensity and duration of endoillumination may lessen the possible phototoxicity. Moreover, the application of perfluorocarbon liquid, viscoelastic, whole blood, or serum over the exposed RPE area at the macular hole before injection of ICG dye may have protective effects from direct toxicity. Nakamura et al. also reported that autologous serum irrigation before completion of macular hole surgery could help remove residual ICG dye and reduce the persistence of dye, owing to ICG's high affinity and quick binding to lipoprotein in serum.¹²

In our study, we sought to evaluate if intraoperative autologous serum could affect the anatomic and functional outcomes of ICG-assisted macular hole surgery. At the baseline, there was no significant difference between vitrectomy with serum and without serum groups in demographic characteristics, such as the percentage of females, mean age, mean refractive errors, mean axial length, mean preoperative VA, lens status, staging of macular hole, duration of symptoms, and follow-up time. We observed that a complete anatomical closure of the macular hole was achieved in 18 (94.7%) of 19 eyes in both groups. Intraoperative autologous serum did not seem to further improve the anatomical closure rates, potentially because the small sample size was inadequate to detect any significant differences. Moreover, the advanced technique of ILM peeling by the surgeon has already increased the hole closure rate to a great extent, and autologous serum does not seem to have a distinct, additive effect.

With respect to functional outcomes, we did not observe any significant differences between the 2 groups in terms of final VA and visual improvement. At the final follow-up, the mean postoperative VA improved significantly from the baseline in both groups, and autologous serum did not have an additive effect on the visual outcome. The lack of difference between groups may be due to the absence of effect and small sample size. Besides, we used a small amount and a relatively low concentration of ICG (0.05%) for staining compared with

the usual dosage of 0.1% to 1% and washed the dye quickly and soon after instillation of ICG, it consequently might not give rise to significant toxic effects on retinal tissues and a worse VA under such circumstances. In addition, it may be difficult to completely remove the residual dye with serum, especially those that had entered the RPE cells, although serum can effectively remove free ICG dye over the retinal surface and shorten its period of residual retinal staining.¹² Since ICG toxicity on RPE may occur right after exposure to the dye, protection of the exposed RPE at the base of the macular hole may be an important issue, and other dyes with greater safety, such as brilliant blue G, may be a better choice.²⁴

In conclusion, ICG-assisted ILM peeling has anatomical and functional benefits for idiopathic full-thickness macular holes. Autologous serum did not further increase the hole closure rate. Although autologous serum might help remove the residual ICG from the retinal surface and thus reduce its potential toxicity, it did not seem to further improve the visual outcome. As a result, an alternative and a safer dye, such as brilliant blue G, may be a better choice for staining ILM.

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Author Disclosure Statement

No competing financial interests exist.

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