A Planned Foveal Detachment Technique for the Resolution of Diabetic Macular Edema Resistant to Anti-VEGF Therapy

Running title: Diabetic macular edema surgical method

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Summary statement

In conjunction with conventional vitrectomy and internal limiting membrane removal, we performed subretinal injection of balanced salt solution to treat diffuse diabetic macular edema resistant to anti-vascular endothelial growth factor therapy. This treatment was effective for a rapid resolution of diabetic macular edema and for improvement of visual acuity.

Abstract

Purpose: To evaluate the therapeutic efficacy of subretinal balanced salt solution (BSS) injections for treating diffuse diabetic macular edema (DME) resistant to anti-vascular endothelial growth factor (VEGF) therapy.

Methods: We performed subretinal injection of BSS in conjunction with vitrectomy and internal limiting membrane (ILM) removal for 14 eyes of 12 patients with DME resistant to anti-VEGF therapy. This injection of BSS was performed at the site where the ILM had been removed with a pressure of 4-6 psi. All patients were followed up for at least 1 year.

Results: The preoperative mean central retinal thickness (CRT) of 644.2 ± 150.5 μm significantly decreased to 262.8 ± 109.1 μm ($p < 0.01$) 1 week after surgery. This improvement in CRT was maintained to the final visit. The mean best-corrected visual acuity before surgery was 0.60 ± 0.48 and improved significantly to 0.31 ± 0.42 ($p < 0.01$) at the final visit. Macular edema recurred in 4 eyes (27%). No complications occurred during surgery or postoperatively in any of the patients.

Conclusion: A planned foveal detachment technique appears to be effective for rapid resolution of diffuse DME resistant to anti-VEGF therapy and for improvement of visual acuity.

Introduction

Diabetic macular edema (DME) is the most common cause of vision loss in people with diabetes.[1] In recent years, anti-vascular endothelial growth factor (VEGF) reagents have become the first-line treatment for DME based on numerous studies showing their beneficial effects.[2-7] However, macular edema is reported to persist in some patients despite multiple intravitreal anti-VEGF injections[8.] Additionally, patients with diabetes with other systemic diseases, such as cardiovascular disease, cannot tolerate multiple anti-VEGF injections over a long treatment period. In such cases, alternative treatments, including vitrectomy, are needed.

While vitrectomy does reduce retinal thickness, one of the major shortcomings of this procedure for the treatment of diffuse DME is that it does not consistently improve visual acuity.[9] One possible reason for this is that vitrectomy only has a weak impact on the pathophysiology of DME. Improvement of the condition of the retina after vitrectomy takes time, and during that time the photoreceptor cells may be damaged. Indeed, vitrectomy only reduces retinal thickness and improves edema gradually.[9-14] It has been shown that chronic macular edema leads to permanent photoreceptor dysfunction and poor visual prognosis.[15] Furthermore, recent optical coherence tomography (OCT) observations show that a shorter time period from the onset of DME to its resolution is the major factor affecting the integrity of the ellipsoid zone and a good visual outcome,[16-18] indicating the importance of a rapid resolution of DME after vitrectomy.

Takagi et al[19] published a procedure to remove foveal hard exudates in diabetic retinopathy by detaching the fovea and flushing out the hard exudates from the retina with a subretinally injected balanced salt solution (BSS). When we carried out this procedure, we encountered one case in which we were unable to remove the foveal hard exudates, but the macular edema resolved the day after surgery. We thus hypothesized that subretinal BSS injection might resolve macular edema, and we conducted a pilot study to evaluate the therapeutic efficacy of subretinal BSS injections in conjunction with conventional vitrectomy and ILM removal for treating diffuse DME.[20] We found that this surgical technique promoted a rapid resolution of diffuse DME and an improvement in visual acuity. However, at the time of that study anti-VEGF therapy for DME was not approved in Japan, so the clinical effect of this surgical procedure on DME resistant to anti-VEGF therapy was unclear.

In this study, we evaluated the therapeutic efficacy of subretinal BSS injections in conjunction with conventional vitrectomy for treating diffuse DME resistant to anti-VEGF therapy.

Materials and methods

Study design and patients

This study was a prospective, interventional case series. All investigations adhered to the tenets of the Declaration of Helsinki. Each patient was informed about the risks and benefits of the surgery, and consent was obtained in writing. The study was approved by the Institutional Review Boards at the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and at the Inoue Eye Clinic.

Fourteen eyes of 12 consecutive patients with DME resistant to anti-VEGF therapy were enrolled in this study and underwent pars plana vitrectomy with subretinal injection of BSS between June 2014 and December 2015, as described below. The inclusion criterion for eyes with diffuse DME was a central retinal thickness (CRT) of more than 275 μm despite undergoing anti-VEGF therapy at least 3 times. The exclusion criteria were as follows: (1) presence of apparent retinal pigment epithelium (RPE) atrophy; (2) presence of proliferative diabetic retinopathy; (3) presence of diabetic optic atrophy; (4) presence of neovascular glaucoma; and (5) presence of an apparent accumulation of hard exudates at the fovea. When leakage of contrast from microaneurysms (MA) was seen in preoperative fluorescein angiography, direct photocoagulation was performed for MA, and when nonperfusion areas (NPA) was seen, retinal photocoagulation was performed for the NPA.

All patients underwent comprehensive ophthalmological examinations. This included measurements of best-corrected visual acuity (BCVA) with refraction using the 5-m Landolt C acuity chart and indirect and contact lens slit-lamp biomicroscopy. Spectral domain (SD) or swept source OCT (Cirrus; Carl Zeiss Meditec, Inc., Dublin, CA, USA; Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany; DRI OCT-1 Atlantis, Topcon Medical Systems, Tokyo, Japan) was used to examine all eyes before surgery and 1 day, 1 week, 1 month, 3 months, 6 months, and final visit after surgery. CRT was defined as the distance between the inner surface of the RPE and the inner surface of the neurosensory retina at the macula. All patients were followed up for at least 1 year.

Surgical techniques

Supplemental Digital Content 1 is a video demonstrating the injection of BSS into the subretinal space. The surgery was carried out according to a previous report using a 25-gauge, transconjunctival, microincision vitrectomy system.[20] Cataract surgery was performed simultaneously in patients with cataract. After core vitrectomy, we stained the ILM with 0.25 mg/mL Coomassie brilliant blue G 250 solution (Sigma-Aldrich, St. Louis, MO) and removed the ILM (Figure 1B). We then injected 50–100 μl of BSS into the subretinal space to detach the fovea, ensuring that the foveal detachment covered the entire scope of the DME (Figure 1C). This injection of BSS was performed at the site where the ILM had been removed using a 38-gauge cannula (MedOne Surgical Inc., Sarasota, FL, USA) with a pressure of 4-6 psi (viscous fluid control system, Alcon Laboratories, Fort Worth, TX).[21] In a previous study, we confirmed that the injected BSS enters the subretinal space and causes foveal retinal detachment using real-time intraoperative SD-OCT.[20]

Endpoints

The primary endpoint for this study was the change in CRT at 6 months after surgery. The secondary endpoints were change in BCVA at the final visit after surgery, recurrence of DME, and surgical complications. We defined the recurrence of DME as an increase in CRT of more than 100 μm compared with the minimum CRT achieved during the follow-up period.

Data analysis

BCVA was recorded as decimal values and converted to logMAR units for statistical analysis. To evaluate surgical outcomes, CRT was compared before and after surgery using a one-way analysis of variance (ANOVA) with a Tukey-Kramer test. Pre- and postoperative BCVAs were compared using paired t-tests. A p value < 0.05 was considered significant. All statistical analyses were performed using SPSS for Mac, version 22.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation.

Results

The characteristics of the 14 eyes of 12 consecutive patients who were enrolled in this study are shown in Table 1. The mean age of the 8 male and 6 female patients was 61.2 ± 9.2 years (range 45–70 years). The mean follow-up period was 20.8 ± 5.3 months (range 12–30 months). The patterns of preoperative structural changes in diffuse DME were cystoid macular edema in 8 eyes (57%) and sponge-like retinal swelling in 6 eyes (43%). DME with serous retinal detachment was observed in 4 eyes (29%). A preoperative fundus examination and OCT revealed that none of the eyes had epiretinal membrane or thickening of the posterior hyaloid. Before this study, all eyes were treated with anti-VEGF drugs at least 3 times, and 5 eyes (36%) had been treated with sub-tenon injection of triamcinolone acetonide (STTA). Preoperatively, 7 eyes (50%) were pseudophakic and 7 were phakic. Cataract surgery was performed simultaneously with surgery for DME for all phakic eyes.

The mean CRT was 644.2 ± 150.5 μm before surgery. This value decreased significantly to 262.8 ± 109.1 μm ($p < 0.01$) 1 week after surgery. This improvement in CRT was maintained to the final visit (Figure 2). At the final visit, 13 eyes (93%) had a CRT of less than 275 μm.

The mean BCVA before surgery was 0.60 ± 0.48 (range: 0.30–1.40) and significantly improved to 0.31 ± 0.42 (range: -0.18 – 1.10; $p < 0.01$; Table 1 and Figure 3) at the final visit. Visual acuity improved by more than 10 ETDRS letters in 9 eyes (64%) and remained unchanged in 5 eyes (37%). There were no cases where the visual acuity worsened by more than 10 ETDRS letters (Table 1 and Figure 3).

OCT revealed that both the ellipsoid zone and the external limiting membrane (ELM) were intact in 7 eyes (50%) before surgery and at the final visit (Table 1). Macular edema recurred in 4 eyes (27%). To resolve the recurrence of macular edema, we treated these eyes with STTA. The mean number of STTA treatments was 2.3 ± 1.5 (Table 1). No complications occurred during surgery or postoperatively in any of these patients. A representative case is shown in Figure 4.

Discussion

In this study, we described a planned foveal detachment technique and demonstrated that it is effective for rapid resolution of diffuse DME resistant to anti-VEGF therapy and for improvement of visual acuity. Regarding the preoperative period, a shorter time interval between the onset of DME and vitrectomy has been associated with both an improved integrity of the external limiting membrane and the ellipsoid zone and with better visual outcomes.[16,22] Since this also applies to the postoperative period, we hypothesized that the speed at which edema resolves after vitrectomy is a key factor for a good visual prognosis. The Diabetic Retinopathy Clinical Research Network reported that 3 months after vitrectomy the decrement in CRT is only 160 μm (n = 87).[9] Furthermore, Yamamoto et al[12] found that CRT decreased by

140 μm by 1 week after surgery, but it took 4 months for CRT to drop below 300 μm (n = 65). In other studies, Stolba et al[13] and Yanyali et al[14] reported that 1 month after surgery CRT decreased by 62.2 and 112 μm, respectively, and thereafter it decreased gradually, by 80 μm after 6 months and by 188 μm after 12 months (n = 25 and 27, respectively). By contrast, the current study showed a rapid and significant decrease in CRT, by 356 μm after 1 week and 439 μm after 6 months (Figure 2). These results indicate that the planned foveal detachment technique acts with conventional vitrectomy to facilitate the resolution of DME.

BSS subretinal injection rapidly improved DME resistant to anti-VEGF therapy. This result indicates that this novel technique improves DME pathology by a mechanism different from that of anti-VEGF therapy.[23] A few mechanisms may be used to explain the rapid resolution of macular edema by this planned foveal detachment technique. First, injection of BSS into the subretinal space decreases the osmotic pressure and the viscosity of the subretinal fluid, and this may promote water transport from the subretinal space to the choroid via the RPE. As the subretinal fluid is absorbed, it allows the retina to re-contact with the RPE and so enables the resumption of the supply of nutrients and oxygen from the choroid to the retina. Second, injection of BSS into the subretinal space improves the environment surrounding the RPE by washing out inflammatory cytokines and migratory cells above the RPE.[24] These environmental changes might improve RPE function and result in the RPE pumping fluid from the retina to the choroid. Third, in terms of absorption of the edema within the retina, injection of BSS into the subretinal space might cause temporary damage to the ELM, which separates the environments of the sensory retina and subretina and restricts water movement.[25,26] This may facilitate absorption of the edema within the retina. In this study, continuity of the ELM had been preserved preoperatively in 7 out of 14 eyes, and it was preserved in all cases postoperatively. This suggests that ELM damage caused by BSS injection may be reversible. Interestingly, the edema improvement was maintained in the long-term in 10 out of 14 eyes. Based on the sustained surgical effect, in addition to improvement of oxygenation in the intraocular environment with vitreous surgery and ILM removal,[27-29] the aforementioned mechanisms of BSS subretinal injection may have interrupted the vicious cycle caused by DME, namely ischemia, chronic inflammation, and leakage.

In this study, DME recurred in 4 out of the 14 eyes, and steroids were administered as additional treatment for these eyes. The mean number of administrations was 2.3 ± 1.5 in a mean observation period of 18.3 months. In these cases, anti-VEGF therapy was administered preoperatively but did not have a sufficient effect, so steroids were selected for postoperative DME recurrence. Various methods for administering steroids are not approved in Japan, including dexamethasone intravitreal implant. Therefore, we used STTA in this study.

Five of the 14 eyes (36%) had preoperative visual acuity of 20/200 or lower, and all these cases had preoperative rupture of the ellipsoid zone and the ELM (Table 1). In each of these cases, there was improvement in the edema after BSS subretinal injection, but all these cases had poor postoperative visual acuity of 20/100 or lower, possibly because of preoperative damage to the photoreceptor cells. Further studies will be needed to determine whether this surgery is indicated for these kinds of cases.

We recently reported that we were able to inject t-PA subretinally with extremely low injection pressure by removing the ILM at the injection site in advance.[21] Furthermore, we also demonstrated that we were able to perform subretinal injection by placing the tip of the cannula in contact with the surface of the retinal nerve fiber layer without penetrating the retina. In this study, we performed the BSS injections using the same method as that described in previous reports, and we were able to perform injections safely using this low injection pressure of 4-6 psi.

This study has many limitations, including the lack of a control group, a small sample size, and a relatively short follow-up period. In addition, simultaneous cataract surgery was performed in all phakic eyes; therefore, the effect of cataract surgery may exaggerate the effect of vitrectomy on the improvement of visual acuity. Further randomized and controlled clinical studies involving a larger number of patients are needed to determine whether this technique could be beneficial to patients with DME resistant to anti-VEGF therapy.

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Figure legends

Fig. 1

Surgical method for the planned foveal detachment technique. **A.** Gray denotes the area of macular edema. Asterisk indicates the fovea. **B.** Schematic drawing showing an inner limiting membrane (ILM) removal. After core vitrectomy, we stained the ILM with 0.25 mg/mL Coomassie brilliant blue G 250 solution and removed the ILM. The dotted line denotes the area where the ILM was removed. **C-E.** Schematic drawings and surgical photograph showing subretinal injection of balanced salt solution (BSS). We injected 50–100 μl BSS into the subretinal space at the site where the ILM had been removed using a 38-gauge cannula. We placed the tip of the cannula in contact with the surface of the retinal nerve fiber layer without penetrating the retina (D). The injection pressure was monitored and controlled using a viscous fluid control system at 4-6 psi.

Fig. 2

Change in central retinal thickness. Graph showing the change in the central retinal thickness before and after surgery. Asterisk indicates $p < 0.01$

Fig. 3

Change in best-corrected visual acuities. Scatterplot comparing preoperative and postoperative best-corrected visual acuities for 14 eyes that underwent planned foveal detachment for diffuse diabetic macular edema resistant to anti-VEGF therapy. logMAR, logarithm of the minimal angle of resolution

Fig. 4.

Results of the planned foveal detachment technique in patient 3, a 47-year-old man with diffuse diabetic macular edema resistant to anti-VEGF therapy. **A.** Preoperative optical coherence tomography (OCT) showing cystoid macular edema with serous retinal detachment. Central retinal thickness (CRT) was 698 μm and best-corrected visual acuity (BCVA) was 20/29. **B.** OCT taken six hours after surgery showing a decreased macular edema. **C.** OCT taken one month after surgery showing resolution of macular edema. **D.** OCT taken 26 months after surgery showing resolution of macular edema. CRT was 145 μm and BCVA was 20/17.

Supplemental Digital Content 1

Video showing the subretinal injection of balanced salt solution after removal of the internal limiting membrane. (Figure 1)

List of Supplemental Digital Content:

Supplemental Digital Content 1 (mp4). Video that demonstrates the subretinal injection of balanced salt solution.