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Zofia Anna Nawrocka, MD, PhD (vel Zofia Michalewska), Prof., Jerzy Nawrocki, MD, PhD, Prof

PII: S2666-9145(22)00096-3
DOI: https://doi.org/10.1016/j.xops.2022.100207
Reference: XOPS 100207

To appear in: Ophthalmology Science

Received Date: 19 April 2022
Revised Date: 13 July 2022
Accepted Date: 15 July 2022

Please cite this article as: Nawrocka Z.A. & Nawrocki J., Vitrectomy in diabetic macular edema - A swept-source optical coherence tomography (OCT) angiography study, Ophthalmology Science (2022), doi: https://doi.org/10.1016/j.xops.2022.100207.

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Vitrectomy in diabetic macular edema - A swept-source optical coherence tomography angiography study

Zofia Anna Nawrocka, Prof. MD, PhD (vel Zofia Michalewska),¹ Jerzy Nawrocki, Prof., MD, PhD¹

¹Ophthalmic Clinic “Jasne Blonia”, Rojna 90, Lodz, Poland

Corresponding author: Zofia Anna Nawrocka, MD, PhD,
Ophthalmic Clinic “Jasne Blonia”, Rojna 90, Lodz, Poland,
Tel: +48 (0)42 636 82 82; E-mail: zosia_n@yahoo.com

Financial Support: None
No conflicting relationship exists for any author.

Running head: SS-OCT A in diabetic vitrectomy

Abstract Word Count: 259  Main Text Word Count: 2695

KEYWORDS
anti-VEGF injections, diabetic macular edema, DME, swept-source optical coherence tomography angiography, swept source OCT angiography, SS OCTA, vitrectomy.
ABSTRACT

Purpose

The foveal avascular zone (FAZ) has been reported to decrease after anti-VEGF injections in diabetic macular edema (DME) in the long term. This study aimed to present the changes in Swept-Source OCT Angiography (SS-OCTA) after vitrectomy in patients with DME.

Design

Retrospective interventional study.

Participants

35 eyes were included (mean age 62).

Methods

Patients were followed for 12 months after vitrectomy with ILM peeling for DME.

Main Outcome Measures

The following parameters were measured: central retinal thickness (CRT), central choroidal thickness (CCT), superficial FAZ (sFAZ), deep FAZ (dFAZ), vessel density in the superficial (sVD) and deep retinal layers (dVD).

Results

CRT and sFAZ significantly decreased after surgery (respectively: 401µm to 338µm; p < 0.00, 401 µm to 293 µm; p < 0.001). Initial visual acuity improved from 20/160 (0.97 LogMAR) to 20/80 (0.62 LogMAR), (p < 0.001). The sVD rate was 42.3% and decreased after surgery, reaching 41.6% at the end of the follow-up. The dVD rate 1 week after surgery was 28.9% and remained stable throughout the observation period. The most important prognostic factors for final visual acuity were preoperative visual acuity and preoperative CRT while dFAZ and dVD at the time of edema resolution also correlated with final visual acuity.

Conclusions
sFAZ decreases after vitrectomy, which might indicate that vitrectomy has a protective effect on diabetic macular edema, similar to anti-VEGF injections. Prognostic factors for better final functional results are better initial visual acuity and lower CRT before vitrectomy, in addition to a lower dFAZ diameter and a higher dVD at the moment of edema resolution.
Diabetic macular edema (DME) is the main cause of vision loss in diabetic patients,\(^1\) and about 40% of patients with diabetes mellitus (DM) develop DME during their lifetime. Due to the growing number of patients with DM, DME is expected to become an even more acute medical problem over the coming decades.

Although anti-VEGF injections remain the gold standard treatment for DME, several indications for vitrectomy exist, such as coexisting epiretinal membrane or traction.\(^2\)

Recalcitrant edema, which was earlier reported in 25%-64%\(^3\) of eyes, may also be an indication for vitrectomy. One recent study suggested that patients with subretinal fluid in diffuse DME might also benefit from vitrectomy.\(^4\) Anti-vascular endothelial growth factor (VEGF) injections must be repeated on a regular basis in most patients,\(^5\) which might be difficult due to factors such as travel limitations or comorbidities in some cases. Decreased compliance is usually associated with lower visual gains. Also of importance is the fact, that in some countries, access to continuous anti-VEGF injections is limited due to financial constraints.\(^6\) Moreover, anti-VEGF injections might be teratogenic and should be avoided in patients of child-bearing age.

Although vitrectomy yields good anatomic outcomes (reduced central retinal thickness [CRT]), the visual gains after the procedure were reported to be limited in some studies.\(^2\) One of the factors responsible for this might be the fact that surgeons usually decide to perform vitrectomy in long-standing, usually treatment-resistant cases, and persistent DME was previously reported to be usually associated with an increased risk of irreversible photoreceptor loss. However, we proved several years ago that ILM peeling performed in severe complications of diabetes, as vitreous haemorrhage or tractional retinal detachment reduces the rate of DME in the long-term.\(^7\) Our group had earlier presented good functional outcomes in patients operated on for treatment naïve DME, with a gain of over 1 logMAR line in 60% of eye.\(^8\)
Swept-source optical coherence tomography angiography (SS-OCTA) is a novel technique that enables noninvasive visualization of the retinal and choroidal vessels. The size of the foveal avascular zone (FAZ) has been shown to be correlated with advancement of diabetic retinopathy (DR). Anti-VEGF treatment, besides its beneficial influence on visual acuity, was also reported to decrease FAZ in patients treated for DME. This was more significantly in the long-term, especially at the level of deep retinal layers. Some changes in SS-OCTA parameters have also discussed in eyes vitrectomized for different indications. Although vitrectomy is not a routine surgery in DME, it not only relieves traction, but also increases oxygen concentration and lowers VEGF levels near the fovea. Thus, some changes in SS-OCTA findings might be expected in these eyes.

Recently, vitrectomy with subfoveal Balanced Salt Solution (BSS) was proposed in DME. The suggested mechanisms of action would be decrease of osmotic pressure and viscosity of subfoveal fluid, promoting water transport from the subretinal space to the choroid through RPE and washing out cytokines and migratory cells.

Here, we present the results of vitrectomy with subretinal BSS injection in treatment-naïve patients and in patients previously treated with anti-VEGF agents. We have also discussed the influence of changes in SS-OCTA images on the final functional outcome.

METHODS

This retrospective interventional study was approved by the Local Ethics Committee at Ophthalmic Clinic Jasne Blonia and followed the tenets of the Declaration of Helsinki. All patients signed an informed consent form. We included consecutive diabetic patients (type 1 or 2 diabetes) with confirmed DME on OCT. None of the patients had previously undergone laser photocoagulation in the macula. Patients who had received anti-VEGF injections earlier were allowed for inclusion in this study if the time since the last injection exceeded at least three months before surgery. These patients had refused further anti-VEGF treatment due to
planned pregnancy (4 patients) or financial or logistical reasons. None of them were anti-
VEGF non-responders. A thorough discussion with all patients, informing them about the
risks and benefits of such a decision, was performed.

All patients underwent a complete ophthalmic examination before and then 1 week and 1, 3,
6, and 12 months after surgery. Additionally, spectral-domain OCT (SD-OCT; Spectralis,
Heidelberg Engineering, Heidelberg, Germany) and SS-OCTA (Triton, Topcon, Tokyo, Japan)
were performed during each follow-up. The following parameters were measured: central
retinal thickness (CRT), central choroidal thickness (CCT), diameter of the superficial foveal
avascular zone (sFAZ), deep foveal avascular zone (dFAZ), vessel density in the superficial
retinal layers (sVD), and vessel density in the deep retinal layers (dVD).

The fovea avascular zone was defined as the area around the central fovea with no demarcated
vessels seen on SS-OCTA. The FAZ was evaluated using 3x3 angiograms. OCT A images
were automatically segmented at the levels of superficial and deep vasculature, at the
avascular zone and choriocapillaris. An experienced examiner monitored all images in course
to correct eventual segmentation errors. The FAZ area (mm²) was manually measured, both at
the level of SCP and DCP. Each en face image was exported into Adobe Photoshop and
binarized to obtain automatic threshold selections from greylevel histograms in order to
determine the percentage of white and black pixels. Retinal perfusion was calculated by
scoring the percentage of white pixels in relation to number of total pixels, according to
published protocols.¹⁵

Surgery

All patients underwent peribulbar anesthesia. After core vitrectomy, membrane blue was
introduced to stain the posterior vitreous (0.06% solution left on the surface of the fovea for
30 s; Membrane blue; Dorc, Netherlands). Posterior vitreous detachment was attempted with
active suction using a vitrectome. If an epiretinal membrane was present, it was removed. The
internal limiting membrane (ILM) was stained with membrane blue (45 s) and peeled up to
the vascular arcades in all eyes. Subretinal injection of BSS was performed using a 41-gauge
needle in the peeled area in all eyes. Air tamponade was performed subsequently. Patients
were advised to maintain head-up positioning for 1 h after surgery and prone positioning until
the next day.

Spearman’s rank correlation coefficient (rho Spearman) was used to investigate the strength
and direction of dependence between variables. The t-test was used to assess the significance
of Spearman’s rho. The following classification was used to interpret the strength of
Spearman’s rho:

1* \(|r| = 0 – no correlation
1* 0.0 < |r| \leq 0.1 - very weak correlation,
1* 0.1 < |r| \leq 0.3 - weak correlation,
1* 0.3 < |r| \leq 0.5 - moderate correlation,
1* 0.5 < |r| \leq 0.7 - strong correlation,
1* 0.7 < |r| \leq 0.9 - very strong correlation,
1* 0.9 < |r| \leq 1.0 - almost perfect correlation,
1* |r| = 1 - complete correlation.

The following tests were also used for statistical analysis: Shapiro–Wilk test (to evaluate the
normality of dependent variables), Levene test (to test the equal variance), ANOVA
Durbin/Skillings–Mack test, Wilcoxon test, t-Welch test Mann–Whitney test and ANOVA
with Kruskal–Wallis test; \( \alpha = 0.05 \) was considered as statistically significant. The analysis was
performed using R statistical package version 4.01.

RESULTS

We included 35 eyes of 35 patients (14 men, 21 women) with a mean age of 62 years (median,
64 years; range, 26–82 years) with either type 1 or type 2 diabetes. Fourteen eyes (6 men and
8 women) had received anti-VEGF injections in the past. Nine patients underwent pan-fundus laser photocoagulation at least five years before surgery. SD-OCT was performed in all eyes and initial CRT was 546 µm. It gradually decreased to reach statistical significance at week 1 (451 µm; median, 391 µm; p = 0.004). Final CRT was 306 µm (median, 242 µm), which was also significantly lower than the preoperative values (ANOVA Durbin/Skillings–Mack; p < 0.001).

The CCT was 266 µm before the surgery. It significantly increased at month 3, reaching 354 µm (p < 0.001) (Figure 1A), but normalized at the later time points (257 µm at 12 months after surgery). The mean diameter of the sFAZ was 401 µm (SD 417.5), which significantly decreased one week after surgery (293 µm; SD 257.6; p < 0.001) (Figure 3). This decrease continued until month 6 (149 µm; SD 89) (Figure 2) and increased again slightly at month 12 (359 µm). The mean diameter of the dFAZ was 1519 µm (SD 1479) before surgery and slowly decreased to 317 µm (SD 376) after 12 months. Statistical significance could not be determined, since dFAZ was impossible to measure in all eyes with DME before surgery due to the presence of numerous artifacts.

The sVD rate was 42.3% before surgery. This value decreased after surgery, reaching 41.6% at the end of the follow-up. The dVD rate 1 week after surgery was 28.9% and remained stable throughout the observation period (Figure 4). The initial visual acuity was 20/160 (0.97 LogMAR), (median, 0.1; ±0.1). Visual acuity slightly decreased one week after surgery and slowly improved during the following months. Final visual acuity (12 months after surgery) was 20/80 (0.62 LogMAR), (median, 0.2; ±0.16) and was significantly better than the preoperative visual acuity (ANOVA Durbin/Skillings-Mack; $\chi^2_{6,05} =25.8; p < 0.001$) (Table 1, Figure 1 B). Anti-VEGF injections performed before vitrectomy did not significantly influence the results.
The Spearman’s rho correlation test was performed to identify factors influencing the final visual acuity. The final outcome was not influenced by the need to administer anti-VEGF injections, or the number of anti-VEGF injections performed before surgery. The most important prognostic factors were preoperative visual acuity (rho = -0.0604; p < 0.001), preoperative CRT (rho = -0.359; p = 0.044) and diameter of the dFAZ at the time of edema resolution (rho = -0.728; p = 0.041) (Figure 5).

Vessel density, especially in the deep capillary layers, was impossible to measure in most eyes before surgery due to the presence of macular edema; thus, we analyzed sVD and dVD at the time of resolution of edema, as proposed earlier by Moon et al. We noted that at that timepoint, final visual acuity was significantly influenced by dVD (rho, 0.826; p = 0.022) (Figure 6).

Although recurrence of macular edema was not observed in any of the cases during the postoperative follow-up (12 months), long-term data (12–48 months) showed macular edema in 10 cases, mostly in patients (8/10) who were also treated with anti-VEGF injections prior to vitrectomy. These patients required a mean of 2.9 injections (range, 1–6) to stabilize the edema. We used Spearman’s rho correlation to evaluate the factors responsible for the recurrence of macular edema more than 12 months after vitrectomy. Among these, high initial CRT (rho = 0.346; p = 0.042), high CRT 12 months after surgery (rho = 0.568; p = 0.014), and low VD at the time of resolution of macular edema (rho = 0.579; p = 0.024) were responsible for the occurrence of macular oedema.

**DISCUSSION**

Vitrectomy with ILM peeling and subretinal BSS injection results in quick resolution of DME and subsequent improvement in visual acuity. It also reduces the diameter of the sFAZ, which might suggest a long-term protective effect of vitrectomy on the fovea in patients with diabetic retinopathy. Better results are expected in patients with better preoperative visual
acuity, lower CRT, and smaller dFAZ both before surgery and during the postoperative follow-up. The addition of a subretinal BSS injection may enhance the reduction in CRT, which is already reduced in the first postoperative month, much earlier than that observed in literature reports focusing on vitrectomy with ILM peeling alone.

Diabetic macular edema may occur in approximately 40% of diabetic patients during their lifetime. Currently, the gold standard treatment is regular anti-VEGF injections. Despite the excellent visual gains (7–12 letters) with this treatment, the treatment scheme may be difficult to maintain for some patients, either because of the distance to the clinic, time issues, or comorbidities. Another problem is the potential teratogenic effect of anti-VEGF drugs, which limits their use in younger patients planning to start or grow their families. Long-term anti-VEGF treatment is also more expensive than vitrectomy. Moreover 40%-50% of patients suffer from persistent DME.

The DRCR Study group suggested that an indication for vitrectomy in macular edema might be the coexistence of an epiretinal membrane, vitreomacular traction, or low visual acuity, while others have also proposed vitrectomy in cases of treatment-resistant DME. Our group previously reported the outcomes of vitrectomy with ILM peeling in patients with treatment-naïve DME and obtained good visual acuity results.

Whereas reduction of CRT was reported in most studies evaluating the role of vitrectomy, the changes in the choroidal tissue are still not well studied. Here, we observed increase of CCT shortly after vitrectomy, which later returned to its original values. We suspect that it might be associated with the fact that removing vitreous decreased viscosity of intraretinal fluids, along with increasing the diffusion of molecules around the eye, which in turn increase premacular oxygen concentrations. That might be responsible for a rapid increase of CCT after vitrectomy.
Tachi et al. reported that half of the patients treated with vitrectomy require approximately one year to show an improvement.\textsuperscript{22} Since a shorter duration of DME before treatment has been reported to be crucial for preservation of the ellipsoid zone,\textsuperscript{23} it can also be assumed that a long period of time to stabilize the retinal thickness after surgery might be harmful.\textsuperscript{24,25} Subretinal injections of BSS have been proposed to overcome this problem. Subretinal injections are performed nowadays in subretinal hemorrhages in neovascular AMD and during gene therapy administration. Most surgeons choose to perform paracentral injection in order not to induce damage to photoreceptors. However, already Takahashi and coworkers confirmed that damage to the photoreceptors might depend on the injection pressure, but even after injections performed at higher pressures, the ellipsoid zone normalized six weeks later.\textsuperscript{24} Since an earlier study showed that most of the tissue resistance in the retina originates in the ILM,\textsuperscript{25} a logical approach is to perform ILM removal at the injection site,\textsuperscript{26} which we also did in the current study. One of the limitations of vitrectomy is the period until normalization of the retinal thickness. Long-term edema or detachment can cause irreversible vision loss; thus, it seems logical to decrease CRT as soon as possible. To overcome this problem, intrasurgical subretinal BSS injections have been suggested. Subretinal injections are most often performed to displace submacular hemorrhages, such as those in neovascular age-related macular degeneration.\textsuperscript{27} Recently, these injections were also introduced to facilitate gene delivery in retinal dystrophies.\textsuperscript{28} More uncommon indications are foveal hard exudates in diabetes\textsuperscript{29} or diffuse DME. This technique has been confirmed to lead to faster resolution of DME when compared to standard vitrectomy. This technique might also be applied in repeated surgery of full thickness macular holes or for subretinal gene therapy.\textsuperscript{30} Several factors have been previously described to be important for persistent visual acuity gain, including photoreceptor integrity\textsuperscript{31} or DME-resolved status at 12 months after initiation.
of treatment.\textsuperscript{17} An OCT angiography-based study evaluated earlier factors responsible for final good visual outcome in patients treated with anti-VEGF and steroid injections. They concluded that dVD and dFAZ at baseline were significant predictors of visual acuity after 12 months of follow-up,\textsuperscript{17} which is not surprising since the DCP provides approximately 15\% of the photoreceptor oxygen supply.\textsuperscript{32} Interestingly, we obtained similar results after treatment with vitrectomy and BSS injection. This suggests that both techniques (anti-VEGF injections and vitrectomy) might similarly decrease the level of diabetic retinopathy and provide long-term satisfactory results in DME.

**CONCLUSIONS**

Recurrence of macular edema after vitrectomy was earlier reported to be approximately 15\%.\textsuperscript{7} In the current study, while we did not observe any such cases during the 12-month observation period, a recurrence rate of approximately 28\% was observed over the later time points. These patients were treated with a single anti-VEGF injection. Recurrences were more often observed in patients with a lower VD, when the macular edema had resolved.

The CRT decreased significantly as soon as one week after vitrectomy and slowly continued to decrease during the observation period. Visual acuity improvement (5 EDTRS letters) correlated with normalization of the foveal contour. Better initial visual acuity, lower CRT, and lower dFAZ are prognostic factors for a good final visual outcome after vitrectomy with subretinal injection of BSS. Decreased dVD at month six was another good prognostic factor for the final visual outcome.
FIGURES

Figure 1
A) Changes in central retinal thickness after vitrectomy for diabetic macular edema
B) Changes in visual acuity in time after vitrectomy for diabetic macular oedema.

Figure 2
A 65-year-old woman with diabetic macular edema before (A) and one week after vitrectomy (B). Swept-source optical coherence tomography shows a reduction in central retinal thickness. An increase in central choroidal thickness (red numbers) was noted.

Figure 3
Reduction in central retinal thickness in swept-source optical coherence tomography (B, D, F, H). A correlating decrease was observed in the area of the foveal avascular zone in the superficial retinal vessel layer in swept-source OCT angiography (A, C, E, G).

Figure 4
Vessel density in swept-source OCT angiography
A) Superficial retinal vessel layer
B) Binarization of A in Adobe Photoshop
C) Deep retinal vessel layer
D) Binarization of C in Adobe Photoshop

Figure 5
The foveal avascular zone in the deep retinal vessels layer might be difficult to estimate in the presence of diabetic macular edema. Its diameter at the moment of resolution is a prognostic factor for final visual acuity.

A) Swept-source optical coherence tomography shows diabetic macular edema
B) Swept-source optical coherence tomography shows resolution of diabetic macular edema after vitrectomy
C) A central artifact obscuring the deep retinal vessel layer in swept-source optical coherence tomography
D) Deep retinal vessel layer in swept-source optical coherence tomography angiography after edema resolution. Measurement of the diameter of the foveal avascular zone is possible.

**Figure 6**
A) Swept-source OCT performed after vitrectomy in a 64-year-old woman. The foveal contour is regular. Photoreceptor defects are visible
B) Low vessel density in the deep retinal vascular layer in swept-source OCT angiography. Final visual acuity is 20/400 (1.3 LogMAR).
C) Swept-source OCT performed after vitrectomy in a 65-year-old woman. The foveal contour is regular. Subfoveal photoreceptor defects seem to be preserved.
B) A normal vessel density in the deep retinal vascular layer in swept-source OCT angiography. Final visual acuity is 20/40 (0.3 LogMAR).

**Tables**

**Table 1**

Long-term results after vitrectomy in patients with DME.
REFERENCES


https://doi.org/10.1159/000327597.


Table 1

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V- visual acuity

CRT – central retinal thickness

MRT – maximum retinal thickness
**Precis**
Fovea avascular zone in superficial retina vessels layer (sFAZ) decreased after vitrectomy. Better VA was observed in patients with better preoperative VA, lower CRT, smaller dFAZ—both before surgery and during the postoperative follow-up.