

The Double-edged Sword of Vitrectomy for Macular Edema

Vitrectomy increases elimination of VEGF,
but drug clearance is also increased.

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As in-office treatment paradigms for retinal diseases have increasingly utilized intravitreal corticosteroids and anti-vascular endothelial growth factor (anti-VEGF) agents for a variety of retinal diseases, it is well known that vitrectomy can increase clearance of the pharmaceutical agent, and, in some cases, reduce treatment efficacy. In a simi-

lar mechanism of action, we hypothesized that vitrectomy can also enhance clearance of VEGF, leading to an improvement in macular edema. To test this hypothesis, hVEGF₁₆₅ injections were performed in rabbit eyes with and without pars plana vitrectomy (PPV).¹ Animals were euthanized at time points up to 7 days, and the vitreous was isolated. An enzyme-linked immunosor-

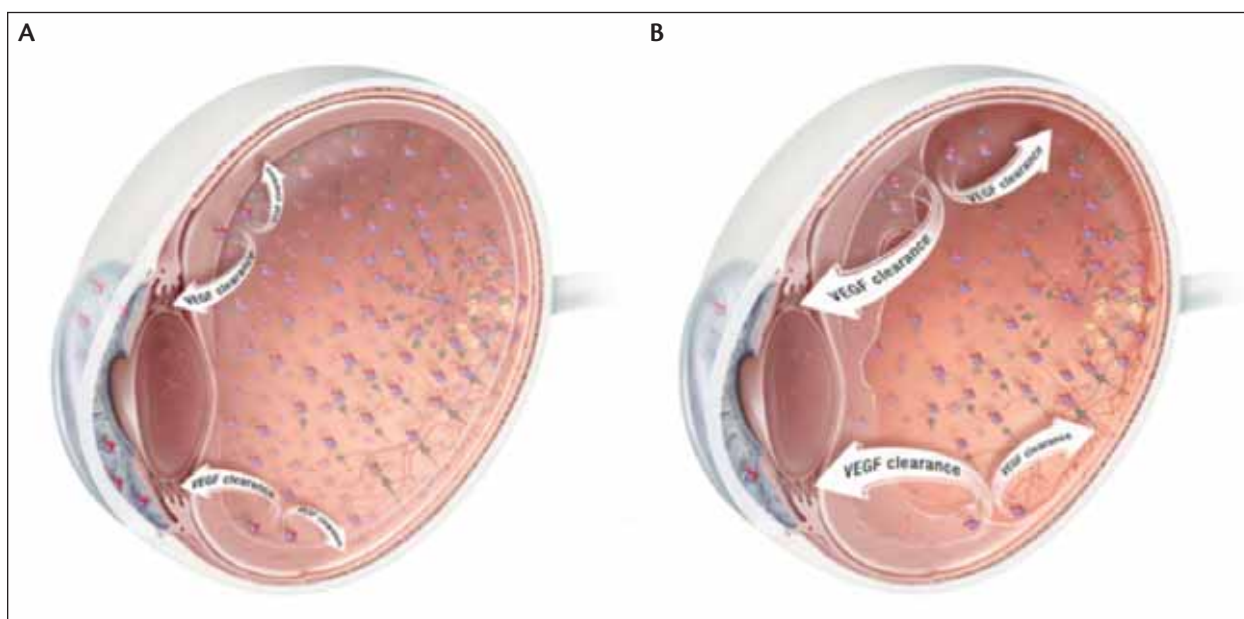


Figure 1. Illustration of an eye with diabetic macular edema and intact vitreous: VEGF (blue/red dimer symbol) is secreted from the ischemic retina into the vitreous, followed by elimination from the eye anteriorly through the aqueous humor and posteriorly through transretinal mechanisms (A). Illustration of the eye in A following a vitrectomy: the VEGF clearance from the eye is increased likely through both the anterior and posterior pathways, resulting in lower resident VEGF levels in the vitreous (B).

Large-molecular-weight anti-VEGF compounds have been reported to have greater effect on visual acuity in nonvitrectomized eyes compared with vitrectomized eyes.

bent assay was used to measure VEGF levels, and pharmacokinetic parameters were determined using a non-compartmental analysis approach (WinNonlin Pro Version 5.2; Pharsight, St. Louis, MO). Results demonstrated that the mean vitreous VEGF levels decreased more rapidly in eyes submitted to vitrectomy compared with nonvitrectomized eyes. Vitreous VEGF half lives ($T_{1/2}$) of vitrectomized eyes were approximately ten-fold shorter than normal eyes, and we concluded that VEGF clearance is increased following PPV (Figure 1).

CLINICAL IMPLICATIONS

The seminal paper in 1994 by Aiello et al² demonstrated that increased VEGF levels in the eye correlated with severity of retinal disease, with the highest levels seen in patients with ischemic central retinal vein occlusion (CRVO). The assumption is that with progressive retinal ischemia there is greater VEGF production in the eye and worsening of retinal complications such as neovascularization and macular edema. Conversely, with a reduction of VEGF levels in the eye, retinal complications may be reduced, as is evident when patients with proliferative diabetic retinopathy receive panretinal photocoagulation (PRP). The PRP results in involution of the neovascular process and, in some cases, improves macular edema.

Interspecies scaling methods can be used to predict human postvitrectomy vitreous VEGF concentrations from rabbit data generated in this study. Assuming the VEGF production rate for various disease states is the same for vitrectomized and nonvitrectomized eyes, and that measured human vitreous VEGF specimens were in an approximate steady state, the post-PPV VEGF concentration can be estimated by $C_{ss} = I/CI$, where C_{ss} is the steady state VEGF concentration, I is the VEGF production rate, and CI is VEGF clearance rate. The mathematical modeling predicts that with increased clearance of VEGF, the retinal disease may progress to a less severe phenotype. For example, although the vitreous VEGF concentration of a nonvitrectomized diabetic patient with active proliferative retinopathy is 2.6 ng/mL², after vitrectomy the VEGF concentration is predicted to decrease to 0.59 ng/mL, which is representative of the VEGF concentration in quiescent proliferative retinopathy.²

Reducing VEGF concentrations in the vitreous after vitrectomy may partially explain the improvement in macular thickness in some patients with macular edema. Unfortunately, vitrectomy can also increase the clearance of pharmaceutical agents injected into the vitreous; thus, vitrectomy can be viewed as a double-edged sword for patients with macular edema. It has been reported that intravitreally injected triamcinolone acetonide levels, as interpreted from aqueous humor drug sampling, are cleared from the vitreous faster in vitrectomized eyes.³ Likewise, large-molecular-weight anti-VEGF compounds have been reported to have greater effect on visual acuity in nonvitrectomized eyes compared with vitrectomized eyes, which is likely due to faster elimination of drug in vitrectomized eyes.⁴ A potential strategy to overcome the increased drug clearance in vitrectomized eyes is the use of a sustained-release biodegradable implant. The ocular pharmacokinetics of the implant may not be altered in vitrectomized eyes, and encouraging results have been observed in clinical studies.⁵

CONCLUSION

Vitrectomy for treatment of macular edema has both positive and negative effects. Although vitrectomy reduces VEGF by increasing VEGF elimination, the increased elimination also clears pharmaceutical agents from the vitreous more rapidly, yielding less effective pharmaceutical treatment results. Novel approaches to postvitrectomy pharmaceutical treatments using sustained-release formulations may be beneficial. ■

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