Editorial

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What is the effect of deferred laser treatment on reactivated retinopathy of prematurity after anti-VEGF injection?

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See "Revascularization of immature retinas with retinopathy of prematurity using combination therapy of deferred laser treatment after a single intravitreal bevacizumab injection" by Ju Seouk Lee, Ki Yup Nam, Ji Eun Lee, Joo Eun Lee, Sang Joon Lee

Retinal blood vessels of premature infants begin to form from the optic nerve head to the periphery according to the gestational age, and when the formation of retinal blood vessels is delayed or stopped, retinopathy of prematurity (ROP) occurs [1]. Angiogenesis is an important process in the development of ROP, and in particular, vascular endothelial growth factor (VEGF) is involved in regulating the development of retinal blood vessels [2]. When the concentration of VEGF in the retina is abnormally high, retinal neovascularization or plus disease appears [1,2].

Currently, laser ablation and anti-VEGF agent injection are available as an acute phase of ROP treatment to reduce the amount of VEGF. Laser ablation burns the avascular retina to reduce the number of VEGF-producing retinal cells, and has the effect of reducing the concentration of VEGF that will be formed later, rather than reducing the concentration of existing VEGF. On the other hand, intravitreal anti-VEGF injection is injected into the vitreous cavity and directly binds with VEGF, so it helps to normalize ROP by simply and quickly lowering VEGF concentration [3]. Currently, bevacizumab (Avastin), conbercept (Lumitin), and aflibercept (Eylea) are available off-label, and only ranibizumab (Lucentis) was first approved in Europe for the treatment of ROP [3]. The advantages and disadvantages of laser ablation versus anti-VEGF injection are summarized in Table 1.

The ophthalmologists decide whether to use laser ablation or anti-VEGF agent, but anti-VEGF treatment appears to be more beneficial than laser treatment for zone I ROP or aggressive ROP [4,5]. In a recent multicenter study on ROP conducted in Korea [6], anti-VEGF injection was preferentially selected for zone I ROP and posterior zone II (zone IIp) ROP, and laser ablation was selected for ROP located in zone II. This paper published in *Kosin Medical Journal* [7], evaluated a total of 40 consecutive infant eyes of 21 patients who received bevacizumab injection or laser ablation. Bevacizumab injection was performed in all cases of zone I ROP, and laser ablation was performed in all cases of zone II ROP. In addition, in the case of zone IIp ROP located between zone I and zone II, injection treatment was

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Table 1. The advantages and disadvantages of laser ablation versus anti-VEGF injection

	Laser ablation	Anti-VEGF injection
Treatment method	Laser ablation burns the peripheral retina to stop neovascularization.	Anti-VEGF agent immediately bind to the VEGF in the vitreous cavity and retina.
Administration	Laser treatment is not easy to learn and it can last for 60–90 minutes. Treatment should be performed in a neonatal intensive care unit or an operating room equipped with an intubation unit.	Intravitreal injections are performed aseptically under local anesthesia on awake infants at the bedside.
Treatment response	It may take one to 2 weeks for laser treatment to stop the progression of ROP.	It starts working right away. Usually, regression occurs as early as 1–3 days.
Follow-up periods	Since the avascular peripheral retina was ablated, follow-up up to 50–55 weeks of postmenstrual age may be recommended.	Long-term follow-up is required until retinal vascularization is complete.
Recurrence (=reactivation)	Reactivation after laser ablation is uncommon. Most cases of reactivation may be related to skip area.	Reactivation occurs more frequently after anti-VEFG injection. However, the degree of reactivation may vary depending on the severity of ROP, the type of anti-VEGF, and the injected dose.
Refractive error	Myopia progression is larger and more rapid in children with ROP who received laser treatment than injection treatment.	Two-year follow-up data from the BEAT-ROP study showed a significant decrease in the amount of myopia.
Visual fields	The wider the laser range, the more the peripheral visual field is disrupted.	It offers the potential to provide a wider visual field with anti-VEGF than with laser, by giving the peripheral retina an opportunity for blood vessels to grow.
Systemic effects	Anesthesia-related problems and mortality may occur.	VEGF is a necessary component for neural, vascular, and lung development. There is ongoing research to evaluate the long-term effects of VEGF suppression.
Complications related to procedure	Extensive laser ablation causes ocular inflammation and causes certain complications such as anterior segment ischemia or, rarely, laser-induced cataract formation.	Intravitreal injection-related procedures can cause conjunctival hemorrhage, increased intraocular pressure, hyphemia, vitreous hemorrhage, cataract, and endophthalmitis.

VEGF, vascular endothelial growth factor; ROP, retinopathy of prematurity.

selected in 71.43% (10/14) and rapid laser treatment was selected in 28.57% (4/14).

Reactivation of ROP commonly occurs after anti-VEGF injection compared to laser therapy and is accompanied by complete or incomplete regression of the original lesion [8,9]. After anti-VGEF treatment, the rate of retinal vessel formation is unprecedentedly slow. Reactivated ROP occurs when plus disease reappears or when neovascularization develops at the ridge lesions or advanced edge of vascular-avascular retina [10,11]. As a phenomenon different from the natural course of ROP, reactivation of ROP is an important issue in the era of current anti-VEGF therapy and should not be viewed as something like acute ROP [3,10]. However, there are no major clinical trial data on treatment guidelines for reactivation of ROP. Additionally, all forms of reactivation ROP do not require retreatment.

Martinez-Castellanos et al. [12] proposed a treatment algorithm for treatment failure and reactivation after injection of bevacizumab in type 1 ROP. They recommend that repeat anti-VEGF injection should be considered in the presence of flat neovascularization, and vitrectomy be performed in the case of fibrovascular proliferation or vitreous traction. Garcia Gonzalez et al. [13] reported that the treatment failure rate was low when prophylactic laser treatment was performed on the peripheral persistent avascular retina after injection of bevacizumab in ROP.

This paper in *Kosin Medical Journal* [7] mentions how much the retina is rescued by deferred laser when ROP reactivated after bevacizumab injection. In 42.86% (12/28 eyes) of the bevacizumab injection group, retinal blood vessels were successfully formed to the periphery, and in 57.14% (16/28 eyes) of them, deferred laser treatment was performed due to reactivation of ROP. In the deferred laser treatment group, 1/3 of cases of zone I ROP and all cases of zone IIp ROP. It took an average of 7.9 weeks to receive deferred laser treatment after bevacizumab treatment. In the deferred laser group, during the window period, retinal vessels in zone I were formed up to zone IIp, and retinal

vessels in zone IIp were formed to zone II, showing that laser treatment was possible in an area similar to that of the prompt laser.

This study is a retrospective study with a small number of infants and a short follow-up. Nonetheless, this study showed that if deferred laser was administered in reactivated ROP after anti-VEGF injection, the risk of systemic exposure from repeated injections and the risk of extensive retinal destruction by prompt laser could be reduced. Also, deferred laser therapy is another option for second-line treatment when reactivation occurs after injection, which could help provide new guidelines for reactivation ROP treatment. Additionally, in the future, large-scale studies are needed to determine the timing of treatment for reactivation and the long-term effects of various treatments.

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