Delayed Laser photocoagulation following intravitreal anti–vascular endothelial growth factor injection allows immature retinal vessels to regrow without recurrence of retinopathy of prematurity

Ki Yup Nam
Kosin University Gospel Hospital
Ji Eun Lee
Pusan National University School of Medicine
Joo Eun Lee
Inje University
Hyun Wong Kim
Inje University
Sang Joon Lee (hhiatus@gmail.com)
Kosin University https://orcid.org/0000-0001-6673-569X

Research article

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Abstract

Purpose: The effects of delayed laser photocoagulation (LP) for ROP patients who received intravitreal anti–vascular endothelial growth factor injections (IVAs) on peripheral vascularization and disease recurrence in ROP patients.

Methods: A total of 26 consecutive infant eyes of 14 patients who received IVA treatments were retrospectively investigated. The patients were divided into two groups depending on the initial treatment as follows: IVA group and prompt LP group. Recurrence of ROP, growth of the retinal vessels, and associated complications were evaluated.

Results: There were 16 eyes in the IVA group and 10 eyes in the LP group. In the IVA group, delayed LP was performed in six eyes due to recurrences of ROP. In 16 eyes of the IVA group, the retinal vessels grew upto Zone III in eyes received IVA only. Among the IVA groups, Delayed LP was needed in six eyes due to ROP recurrence following IVA. Delayed LP was performed average 7~8 weeks after IVA, which could give the immature neurovascular tissues time to continue vascular development upto Zone II without further ROP recurrence. However, the prompt LP group did not show vessel development beyond the laser scar.

Conclusions: Delayed LP following IVA might provide a chance for retinal vessel development in the immature retina to continue without unexpected ROP recurrences.

Background

Retinopathy of prematurity (ROP) is one of the main causes of childhood blindness. The number of cases of severe ROP is growing due to increases in the survival rates of premature infants [1]. Currently, laser photocoagulation (LP) is the standard treatment for ROP. However, in the Early Treatment for ROP (ET-ROP) trial, 9.1% of patients had unfavorable structural outcomes [2]. A large area of the peripheral retina is destroyed in the ablative process and normal vascularization generally cannot be achieved after LP treatment or cryotherapy. Data from the multicenter Cryotherapy for ROP (CRYO-ROP) trial indicated that the apparent increase in myopia severity was because eyes in which treatment prevented retinal detachment were likely to be highly myopic, most likely due to the retinopathy itself [3]. The ET-ROP trial indicated that approximately 70% of eyes with high-risk, pre-threshold ROP during the neonatal period were likely to be myopic during infancy and the early preschool years [4]. In particular, Zone 1 ROP and the presence of plus disease, both indicators of severe acute-phase ROP, affect the refractive error development of the eye [4]. Retinal ablation naturally leads to visual field defects, which is a major problem in infants with Zone 1 ROP who received laser or cryotherapy. Moreover, LP resulted in unfavorable functional and structural outcomes in 64.0% and 72.5% of Zone 1 ROP eyes, respectively, in the ET-ROP study [5]. Other treatment options that can aid in the development and maturation of premature and underdeveloped retinas and vessels are needed to limit or prevent the adverse effects of conventional ablative treatment.

Intravitreal injections of anti–vascular endothelial growth factor (VEGF) (IVAs) were recently developed and are used widely for ROP. The IVA method has several advantages compared to laser treatment. The procedure is simple and less time-consuming, and the recurrence rate after IVA treatment is significantly lower than that after LP [6, 7]. IVAs can also reduce myopic progression, avoid peripheral retina destruction, and allow for the continuation of vessel growth into the peripheral retina [6–9].

Despite the low recurrence rate, however, there remains a concern regarding the timing of recurrences and the appropriate follow-up period after IVA. Because the interval between IVA and recurrence is relatively long and varies from several weeks to months, careful follow-up is required after IVA until vascularization is complete to prevent unexpected recurrences [7, 10, 11]. Nonetheless, there are no appropriate follow-up protocols for after IVA. Besides long-term follow-up to ensure avoidance of ROP recurrence, another concern is the safety of multiple IVA injections in premature infants. A single IVA lowered blood VEGF for a minimum of seven to eight weeks in a human study [12, 13]. The reduction of blood VEGF, which is essential for the development of multiple organs including the retinas and brain, might have effects on infant growth.

Considering issues such as the necessity of long-term follow-up to confirm complete neurovascular growth, hard to predict the recurrence of ROP, and the potential risk of systemic side effects after multiple IVAs, more than a single IVA might be carrying too much clinical burden and potential systemic risks. To avoid the multiple injections, combination therapy of laser photocoagulation and AVI can be performed. [14] But, laser photocoagulation for Zone 1 ROP induced refractive error and constriction of visual field.[4, 15] If so, delayed laser photocoagulation after single IVA might be an option to avoid the potential risks of multiple IVA injection or laser photocoagulation. However, there is no information regarding to the effect of the delay how much the immature retina grow during the delayed period and how long the delayed period is. Thus, the present study evaluated the effects of delayed laser photocoagulation on the amount of retinal regrowth and delayed period.

Methods

This was a retrospective study and the protocol was approved by the Institutional Review Board of Kosin University Gospel Hospital. We adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from the parents of all patients.

Medical records of consecutive ROP patients who received IVA at three institutions in Busan, South Korea between 2009 and 2010 were reviewed. A total of 26 eyes (14 patients) who were followed-up with for at least six months after treatment were included. The eyes that received IVA were divided into two groups depending on initial treatment: IVA group or LP group. The IVA group included the eyes that received IVA only or IVA followed by delayed LP at the point of ROP recurrence. Conversely, the LP group included the eyes that received LP at ROP recurrence.

The following information was collected: sex, gestational age, birth weight, postmenstrual age (PMA) at IVA or LP, the number of IVA treatments, follow-up period, surgical intervention, and ROP stage and zone.

Routine fundus examinations for ROP screening were conducted by three retina specialists at each institution according to the ET-ROP guidelines using indirect ophthalmoscopy with scleral depression under topical anesthesia. Zones and stages of ROP were classified according to the Revised International Classification for ROP. [16]. The anteroposterior location of ROP was described by a retinal specialist at each center according to the Committee for the Classification of ROP. We divided Zone 2 into posterior (Z2p) and anterior (Z2a) halves. The posterior half of Zone 2 was defined as the area outside of Zone 1 that did not reach the halfway point of the ora serrata, while the anterior half of Zone 2 was defined as the area that did not reach the ora serrata but which passed over the halfway point of Zone 2.

Treatments were performed by three retina specialists and selected at each doctor's discretion, with all following the ETROP guidelines.[5, 16] Infants who had any stage of ROP with plus disease in Zone 1, stage 3 without plus disease in Zone 1, stages 2 or 3 with plus disease in Zone 2, or aggressive posterior ROP were treated. Follow-up examinations were performed once or twice per week after treatment until ROP regression. Delayed LP were performed in cases of worsening ROP, such as reappearance of plus disease or stage 3 ROP. All LP procedures were performed using a diode laser with an 810-nm wavelength instrument under general anesthesia. IVAs were performed in the operating room under general anesthesia. After preparation of the lid and conjunctiva with 5% povidone iodine, 0.625 mg (0.025 mL) of bevacizumab (Avastin; Genentech Inc., San Francisco, CA, USA) was injected intravitreally at a point 1.5 mm from either the nasal or temporal limbus using a 30-gauge needle under an ophthalmic surgical microscope. Topical antibiotics were prescribed after injections.

T-tests for independent means, the Mann–Whitney rank-sum test, chi-squared test, and Fisher's exact test were used for statistical analyses. P-values less than 0.05 were considered to be statistically significant. Means and standard deviations are presented as mean (SD). GraphPad Prism (Version 6.03; GraphPad Software. Inc., La Jolla, CA, USA) was used for analysis.

Results

Demographic characteristics

The IVA and LP group included 16 eyes and 10 eyes, respectively (Fig.1). The gestational ages of patients in the IVA group and LP group were 26.58 (± 2.5) and 25.37 (± 1.22) weeks, respectively (p = 0.144), and mean birth weights were 875.9 (± 330.1) g and 842 (± 199.8) g, respectively (p = 0.78). As such, the IVA group did not differ significantly from the LP group in terms of gestational age and birth weight. However, the birth weight of subgroups IVA with delayed LP was significantly lighter compared with IVA only and LP group. (Table 1).

ROP stage and zone

The ten Zone 1 eyes who received a single IVA only presented that the immature retinas re-grew and reached to Zone 3 without any additional therapy. (Table 2) But the ten eyes who received laser photocoagulation did not show the regrowth beyond the laser scar. The Zone 2p and 2a ROP received laser therapy did not show development of immature retina, but the Zone 1 ROP received IVA only showed the development upto Zone 3. So then, the eyes who needed delayed laser after a single IVA showed that two Z1 eyes showed growth of the retinal vessels to Z2p, while the four Z2p eyes showed growth of the retinal vessels to the Z2a region at regression. The average delay of laser photocoagulation was 7.9 (± 1.6) weeks after AVI.

Adverse effects

All eyes in the study group showed regression of plus disease within two to six days after the intravitreal injection. Patients with ROP with pupillary rigidity and tunica vasculosa lentis also presented complete regression of retinal neovascularization within two to three weeks.

Short-term adverse effects of IVA within two weeks after injection included intraocular pressure elevation (n = 1), subconjunctival hemorrhage (n = 4), and retinal hemorrhage (n = 1) among 32 eyes. There were no occurrences of infectious endophthalmitis or retinal detachment within two weeks after the injection. In 16 eyes that were followed up with for at least six months, no systemic complications were observed during that period according to the opinion of doctors in the pediatric department. There were no newly developed or aggravated systemic diseases. All patients showed fixation and follow. Only one patient in the IVA and LP groups, respectively showed exotropia due to macular dragging.

Discussion

This study showed that delayed laser photocoagulation after IVA had some benefits on development of immature neurovascular tissues over prompt laser photocoagulation. Especially Zone 1 and Zone 2p ROP were changed into Zone 2p and Zone 2a, respectively during the delayed period. Average period of the delay was about 7 ~ 8 weeks after IVA. We supposed that delayed laser photocoagulation after a single IVA can be another option for recurred ROP after IVA to minimize the potential systemic side effects caused by multiple IVAs and myopic shift after laser photocoagulation.

The current standard treatment for ROP is LP of the avascular peripheral retina. The ET-ROP trial reported that early LP for high-risk, pre-threshold disease resulted in better visual and structural results than did conventional LP for threshold disease, and recommended laser retinal ablation for type I ROP[2]. However, LP complications should be considered. Destruction of the peripheral retina can cause myopic changes and visual field defects [6, 8, 12]. In previous studies, the mean refractive error at five or seven years after LP was reported to be − 2.3 to − 6.7 diopters (D) [15, 17–20]. Hwang et al. reported that the myopic change was more severe in Zone 1 ROP than in Zone 2 ROP, and the mean spherical equivalent values were − 10.1 ± 10.5 D and − 4.7 ± 4.6 D, respectively [8].

The myopic shift in ROP patients decreased in eyes who received IVA instead of laser photocoagulation. Hwang et al. reported that the mean spherical equivalent was 0.6 D in Zone 2 ROP with IVA treatment, which was significantly lower than that of − 4.7 D in the LP treatment group. In Zone 1 ROP, the mean spherical equivalents were − 3.7 D and − 10.1 D in the IVA and LP groups, respectively, but the difference was not statistically significant.[8] Otherwise, Geloneck et al. showed that In addition, visual fields are better preserved with IVA compared to LP because IVA can lead to further growth of peripheral retinal vessels. IVA also better reduces the recurrence of ROP after treatment compared to LP. The Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT ROP) study reported that the rates of recurrence were 6% and 27% in the IVA and LP groups of Zone 1 ROP, respectively, and the difference was statistically significant [7].

Despite the low recurrence rate, there is a concern regarding the timing of recurrences and the follow-up period after IVA. The reported intervals between bevacizumab treatment and recurrence in the BEAT-ROP study were 19.2 (± 8.6) weeks and 14.4 (± 0.8) weeks in Zone 1 and Zone 2 ROP, respectively. There also exist several case reports to date describing ROP recurrence after IVA. Hoang et al. and Kong et al. reported that ROP recurred at two months and 11 months after initial IVA, respectively [10, 11]. The intervals from initial IVA treatment to recurrence are relatively long and variable, and are affected by multiple factors such as the systemic condition of the infant, population origin, and the type of anti-VEGF agent [10, 11]. Any unexpected recurrence of ROP after initial IVA during the follow-up period should be of concern to clinicians, even though there is a relatively low rate of such recurrence. Thus, infants receiving IVA treatment for ROP require careful follow-up until vascularization is complete [7]. However, complete examination of the fundus to the peripheral retina is difficult to achieve in babies older than 50 to 60 weeks, and there is no definite protocol for follow-up after IVA treatment.

To avoid these problems, the combination treatment of either LP with IVA or IVA with LP may have advantages versus monotherapy [14, 21–23]. However, in previous studies, IVAs were used as adjuvant treatments and performed with LP simultaneously. According to our results, initial LP may interfere with further retinal vascularization. Thus, a combination of initial IVA followed by deferred LP may increase the chances for the continuation of retinal vessel development and prevent unexpected recurrences of ROP. It is certain that the achievement of complete ROP regression by only a single IVA is the best course of treatment. However, due to the variable intervals of recurrences, careful fundus examination of the peripheral retina is needed continually until full vascularization of the retina occurs. For some cases in which long-term follow-up is not possible, deferred, elective LP after initial IVA may be an option to minimize destruction of the peripheral retina, decrease myopic progression, and protect the visual fields versus initial LP, without the need for long-term follow-up with a concern for recurrences. The recommended interval is eight to 12 weeks according to our results and those of previous studies.

Only mild ocular adverse effects such as transient intraocular pressure elevation, subconjunctival hemorrhage, and retinal hemorrhage were observed. No systemic side effects associated with IVA were found during the observation period in the present study. Furthermore, these results of systemic effects

were similar to findings in recent several reports about the systemic side effects of anti-VEGF injection treatment for ROP [24, 25].

This study has several limitations. First, it was retrospective in nature and had no randomized control group. The follow-up period was about six months, which is relatively short and therefore does not allow for any conclusions about the long-term effects of IVA and LP on ROP. The number of children included was also small. In addition, our study could not compare the detailed systemic effects between IVA and LP.

Conclusions

In this study, initial IVA only or IVA with deferred LP for ROP was better than LP in terms of retinal vessel growth continuation. Thus, for cases in which long-term follow-up is not possible, deferred LP after eight to 12 weeks of initial IVA may be a suitable treatment option for ROP to avoid ROP unexpected recurrence. However, further prospective investigations of the long-term effects of this treatment combination including a greater number of subjects with ROP are required.

Abbreviations

LP: laser photocoagulation, IVAs: intravitreal anti–vascular endothelial growth factor injections, ROP: Retinopathy of prematurity, ET-ROP: Early Treatment for ROP, CRYO-ROP: Cryotherapy for ROP, VEGF: anti–vascular endothelial growth factor, PMA: postmenstrual age, BEAT ROP: Bevacizumab Eliminates the Angiogenic Threat of ROP

Declarations

Ethics and consent to participate: The study was protocol was reviewed and approved by the Institutional Review Board of Kosin University Gospel Hospital. We adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from the parents of all patients.

Consent for publication: Not applicable.

Availability of data and materials: All the data supporting the findings was contained within the manuscript.

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K.Y.N.; writing—review and editing, Ji.E.L. and S.J.L.; visualization, K.Y.N. and J.H.L.; supervision, S.J.L.; project administration, S.J.L.

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Tables

Table 1. Basic characteristics of the three groups

	IVA group		LP group
	IVA only	IVA-delayed LP	
Number of eyes, n (%)	10 (38.46%)	6 (23.07%)	10 (38.46%)
Male (eyes/patients)	5/3	2/1	8/4
Female (eyes/patients)	5/3	4/2	2/1
Mean GA (weeks)	27.47 ± 2.77	25.10 ± 0.9	25.37 ± 1.22
Mean birth weight (g)	1028.5 ± 330.1	622 ± 164.7*	842 ± 199.8

IVA: intravitreal anti–VEGF antibody injection; LP: laser photocoagulation

* Significance (P = 0.019), Kruskal–Wallis test.

Table 2. Initial and final statuses of ROP

	Initial state			Final state		
	IVA group		LP group	IVA group		LP group
	IVA only	IVA-LP		IVA only	IVA-LP	
Zone 1	10 (100.0%)	2 (33.3%)				
Zone 2p		4 (66.7%)	2 (20.0%)		2 (33.3%)	2 (20.0%)
Zone 2a			8 (80.0%)		4 (66.7%)	8 (80.0%)
Zone 3				10 (100%)		

IVA: intravitreal anti–VEGF antibody injection; LP: laser photocoagulation; Zone 2p: posterior half of Zone 2; Zone 2a: anterior half of Zone 2.

Figures

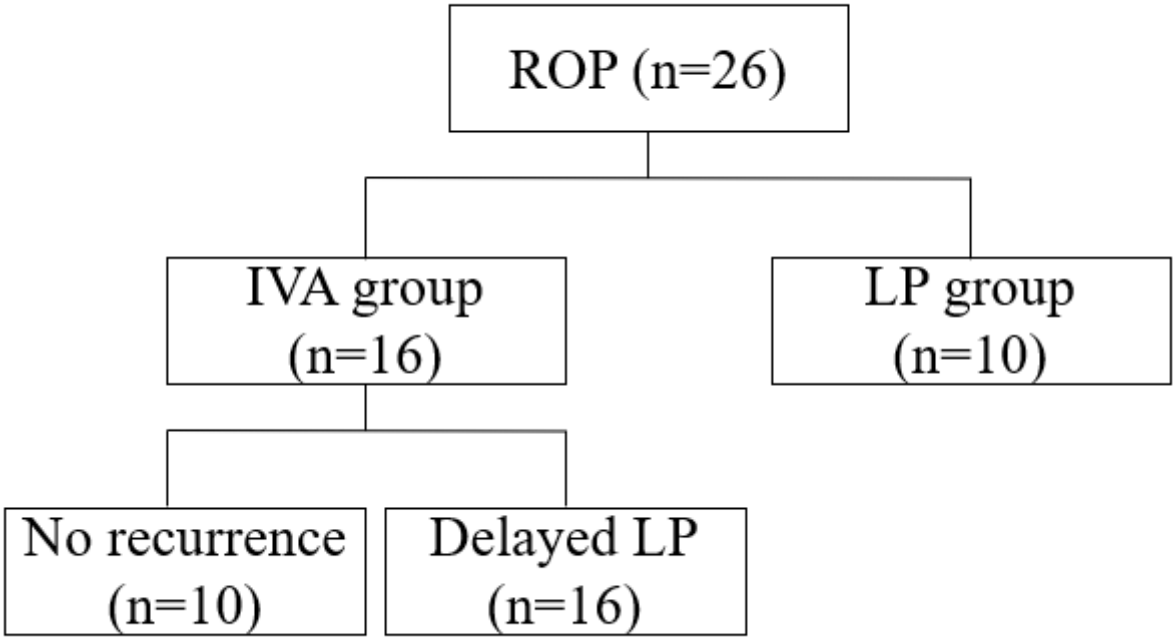

Figure 2

The IVA and LP group included 16 eyes and 10 eyes, respectively