



Risk factors for myopia at 1-year corrected age following laser photocoagulation for retinopathy of prematurity

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Abstract

Background/Objectives The prevalence of myopia is higher in preterm infants who underwent laser photocoagulation (LPC) for retinopathy of prematurity (ROP). The aim of this study was to investigate factors associated with myopia in preterm infants who undergo LPC for ROP.

Subjects/Methods We retrospectively analysed the medical records of preterm infants born at Kyushu University Hospital (October 2008–March 2018) at ≤ 32 weeks of gestational age or with birth weight ≤ 1500 g. We evaluated the associations between nine clinical factors and the spherical equivalent at 1-year corrected age by performing multivariable linear regression in LPC-treated ROP patients.

Results Among the 485 infants enrolled, 76 developed ROP requiring treatment. Of these, 71 underwent LPC, which was provided to 63 infants as the primary treatment (LPC alone or the combination therapy of LPC and intravitreal injection of bevacizumab [IVB]) and to eight infants as additional LPC after IVB monotherapy. The results of a refractive examination at 1-year corrected age were available for 110 eyes of 56 infants (78.9%). The mean \pm standard deviation of the SE value was -0.5 ± 3.0 dioptres (D). Multivariable linear regression analysis revealed a significant association between laser spot count and SE value ($\beta = -0.081 \pm 0.040$ D per 100 spots [mean \pm standard error], $p = 0.045$).

Conclusions Our results suggest that an increased laser spot count observed during ROP treatment associates with myopia.

Introduction

Despite advances in treatment, retinopathy of prematurity (ROP) remains a leading cause of childhood blindness [1]. The current standard treatment for ROP is laser photocoagulation (LPC), whose efficacy was established by the Early Treatment for ROP (ETROP) trial [2]. However, the ETROP trial and other studies demonstrated that the prevalence of myopia increased in LPC-treated ROP patients, due to ocular structural sequelae [3–6].

On the other hand, the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity trial showed that compared with LPC, an intravitreal injection of bevacizumab (IVB) decreased the recurrence rate of zone I

ROP [7], and over the past decade the intravitreal injection of anti-vascular endothelial growth factor agents (anti-VEGF therapy) has become more common as the primary treatment for severe ROP [8]. Although anti-VEGF therapy can also improve the structural outcome and reduce the incidence of myopia compared with LPC [9, 10], approximately 10–40% of anti-VEGF-treated patients with ROP require additional treatment due to recurrence [8, 11]. The potential development of myopia in patients who have undergone additional LPC after IVB treatment must therefore be monitored.

Infants with ROP tend to develop myopia due to the arrested development of the anterior segment [12, 13]. LPC worsens these ocular structural changes, and the prevalence of myopia is significantly higher in LPC-treated ROP patients than in patients with regressed ROP [14, 15]. However, the risk factors of myopia after LPC are still controversial [16]. We conducted the present study to investigate the relationship between nine candidate factors (gestational age [GA], birth weight [BW], corrected weeks of age and body weight at the first treatment, zone, stage,

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laser spot count, laser wavelength, and type of primary treatment [LPC, LPC + IVB, or IVB]) and the spherical equivalent (SE) value in LPC-treated ROP patients at 1-year corrected age.

Subjects and methods

Subjects

This study was performed in accordance with the tenets of the Declaration of Helsinki. Having obtained approval from the Institutional Review Board at Kyushu University Hospital, we conducted a retrospective chart review of the infants who underwent ophthalmic examinations at the Kyushu University Hospital from October 2008 through March 2018. We presented information of this study on our institutional website and informed all parents of their right to opt out. An ROP screening examination was provided to all infants born at ≤ 32 weeks of GA or with a BW ≤ 1500 g. We selected the infants who had undergone LPC and whose SE results at 1-year corrected age were available for our analyses of the associations of clinical factors with SE.

Primary treatment

The ROP staging of each subject was decided based on the International Classification of Retinopathy of Prematurity Revisited [17]. LPC, LPC + IVB (0.625 mg/0.025 ml), or IVB had been performed as the primary treatment for the infants with 'type 1 ROP' as described in the ETROP trial (stage 2 or 3 in zone II with plus disease, stage 3 in zone I with or without plus disease, or stage 1 or 2 disease in zone I with plus disease) [2] or worse ROP. LPC was applied to the entire avascular area with half laser burn width. A diode laser (808 nm wavelength; DC-3000, Nidek, Aichi, Japan) was used for 58 eyes of 29 infants until December 2012, and a Nd-YAG laser (532 nm wavelength; MC-500, Nidek) was used for 52 eyes of 27 infants thereafter. The settings of laser ablation with 808 nm and 532 nm wavelength were set at a power of 200–400 mW for 300 msec and a power of 80–100 mW for 300 msec, respectively. Bevacizumab was injected with a 30-gauge needle 1.5 mm posterior to the limbus. LPC and IVB were provided to ROP patients requiring treatment under intravenous sedation.

Additional laser photocoagulation

Follow-up examinations after treatment were performed on a weekly or biweekly basis until the patient's ROP regressed or vascularization reached zone III. Recurrence was defined as a new appearance of plus disease, neovascularization, ridge, or proliferative membrane. All recurrences

were treated with LPC. In addition to these criteria, additional LPC was performed for IVB-treated ROP patients to prevent late recurrence [18–20] when an avascular area remained before the patient's discharge or when the arrest of vascularization was accompanied by abnormal hyperpermeability observed through fluorescein angiography.

Refraction

An auto-refractometer (HandyRef, Nidek) was used to measure the refraction at 1-year corrected age. If the use of this device was not possible, the refraction was measured with manual retinoscopy. All refraction readings were obtained after the instillation of 1% tropicamide, 2.5% phenylephrine hydrochloride, and 1% cyclopentolate hydrochloride.

Statistical analysis

Using multivariable linear regression, we evaluated the association of the nine above-described factors with the SE value. In addition, in view of the effect of ROP severity on the SE value, a stratified analysis by zone was performed using Student's *t* test.

All analyses were carried out using SAS software (ver. 9.3, SAS, Cary, NC). GA, BW, corrected weeks and body weight at first treatment, and laser spot count were treated as continuous variables, and the other parameters as categorical variables. Using the factors that were significant in univariable analysis, we conducted multivariable-adjusted linear regression analysis. A two-sided *p* value < 0.05 was considered significant.

Results

ROP screening examination was provided to 485 infants. Of these, 232 (48%) developed ROP, and 76 (16%) developed ROP requiring treatment. LPC ($n = 53$), LPC + IVB ($n = 10$), or IVB ($n = 13$) were provided to these infants as the primary treatment (Fig. 1). Among the 53 LPC-treated ROP patients, recurrence occurred in four (8%), while among the 10 treated with LPC + IVB, recurrence appeared in one (10%). Among the 13 ROP patients treated with IVB monotherapy, eight infants received additional LPC (recurrence, $n = 5$ [38%]; remained avascular area, $n = 2$; abnormal fluorescein leakage, $n = 1$). A total of 71 infants thus received LPC. Of these 71 infants, refractive examination results at 1-year corrected age in 110 eyes of 56 infants (the bilateral ROP occurred in 54 infants and the asymmetric ROP occurred in 2 infants) were available. The reasons for the exclusion of 15 patients were as follows: (1) eight patients could not be examined because of relocation, (2) five patients did not visit our department at the

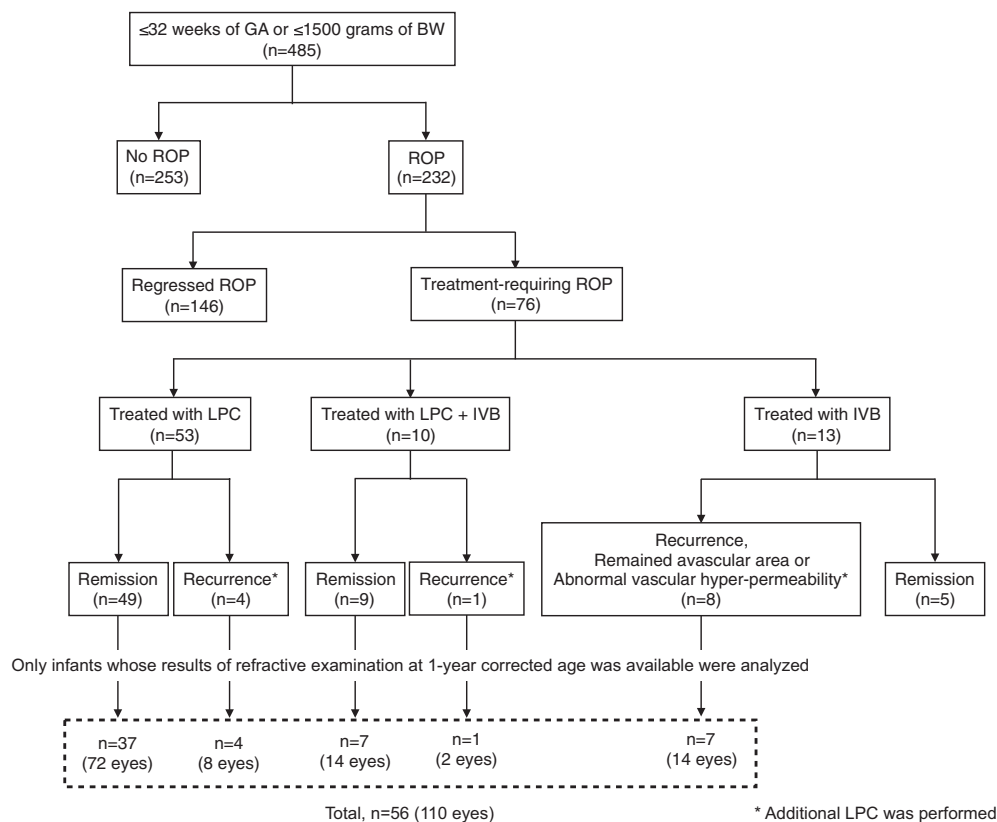


Fig. 1 Flow chart of patient selection and classification. Among 485 infants, 56 infants (110 eyes) were analysed in this study. * Additional LPC was performed.

Table 1 The characteristics of the infants with ROP.

No. of eyes examined	110
GA, wks ^a	24.7 ± 1.5
BW, g ^a	626 ± 180
Corrected wks at 1st treatment, wks ^a	35.5 ± 2.7
Body weight at 1st treatment, g ^a	1272 ± 412
Zone	Zone I = 36, Zone II = 74
Stage	Stage 2 = 28, Stage 3 = 82
Laser spot count ^a	1481 ± 733
Laser wavelength	532 nm = 52, 808 nm = 58
Type of primary treatment	LPC = 80, LPC + IVB = 16, IVB = 14

^aData are mean ± standard deviation.

scheduled date, and (3) two patients died before 1-year corrected age.

Table 1 summarizes the characteristics of the 56 infants, including their GA, BW, corrected weeks and body weight at first treatment, zone, stage, laser spot count, laser wavelength, and type of primary treatment. The mean ± standard deviation of the SE value at 1-year corrected age was -0.5 ± 3.0 dioptres (D). Table 2 provides the results of the linear regression analyses. In the univariable analysis, laser spot

count ($\beta = -0.102 \pm 0.039$ D per 100 shots, $p = 0.009$, Fig. 2) and use of 808 nm laser ($\beta = -1.460 \pm 0.564$ D, $p = 0.011$) were significantly associated with the SE value.

We then performed a multivariable analysis using both laser spot count and 808 nm laser use as variables. Only laser spot count was significantly related to the SE value at the patients' 1-year corrected age ($\beta = -0.081 \pm 0.040$ D per 100 shots, $p = 0.045$, Table 2).

The severity of ROP is defined by a combination of zone and stage

Considering the effect of ROP severity on the SE value, we classified all eyes into zone I or zone II ROP and investigated whether the ROP stage influence the SE value. In both the zone I ROP and the zone II ROP, there was no significant difference in the SE value between stage 2 and stage 3 ($p = 0.608$ and $p = 0.771$, respectively, Table 3).

Discussion

Our findings provide the first demonstration that laser spot count during ROP treatment is significantly associated with myopia, based on a quantification of the influence of laser

Table 2 Linear regression analysis of candidate factors for the SE value.

Candidate factor	Crude		Multivariable-adjusted	
	β (mean \pm standard error)	<i>p</i> value	β (mean \pm standard error)	<i>p</i> value
GA	0.130 \pm 0.191	0.499		
BW, per 100 g	-0.017 \pm 0.162	0.917		
Corrected wks at 1st treatment	0.083 \pm 0.107	0.441		
Body weight at 1st treatment, per 100 g	0.006 \pm 0.071	0.933		
Zone I	0.174 \pm 0.618	0.779		
Stage 3	0.075 \pm 0.666	0.910		
Laser spot count, per 100 shots	-0.102 \pm 0.039	0.009	-0.081 \pm 0.040	0.045
808 nm laser	-1.460 \pm 0.564	0.011	-1.127 \pm 0.580	0.055
Type of primary treatment:				
LPC	Reference			
LPC + IVB	-0.056 \pm 0.835	0.946		
IVB	-0.718 \pm 0.883	0.418		

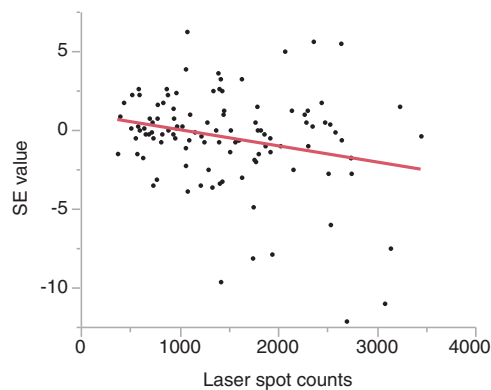


Fig. 2 Scatterplots of the spherical equivalent (SE) values and laser spot counts. The red line represents the regression line ([SE value] = 1.029 - 0.001 * [laser spot count], $R^2 = 0.061$).

spot count on the SE value. Our observation of a significant correlation between laser spot count and SE value suggests that laser scarring caused ocular structural sequelae (e.g., a thinner anterior chamber depth and a steeper corneal curve) which could promote myopia [16]. This finding is consistent with the results of a study showing that laser spot counts were significantly larger in infants with myopia (SE value \leq -0.25 D) than in those without myopia (SE value $>$ -0.25 D) [21].

It is known that the more severe the ROP, the greater the myopia, even if untreated [22]. In Table 2, neither zone nor stage were shown to affect the SE value alone, but the severity of ROP is defined by a combination of zone and stage. The stage of the infants analysed in this study was either (1) zone I, stage 2 with plus, (2) zone I, stage 3 with plus, (3) zone II, stage 2 with plus, (4) zone II, stage 3 with plus. According to the ROP activity scale [23], all of these are classified as “severe,” so there is no difference in severity. To confirm the impact of ROP severity on the SE value, a stratified analysis by zone was performed. However, there was no

Table 3 Stratified analysis by zone to examine the effect of ROP severity on the SE value.

	Stage 2	Stage 3	<i>p</i> value ^a
A. Zone I ROP			
<i>n</i>	8	28	—
SE value, diopter ^b	-0.937 \pm 3.238	-0.210 \pm 3.577	0.608
B. Zone II ROP			
<i>n</i>	20	54	—
SE value, diopter ^b	-0.388 \pm 2.672	-0.604 \pm 2.886	0.771

^aStudent’s *t* test was performed.

^bData are mean \pm standard deviation.

significant difference in the SE value between stage 2 and stage 3. These results suggest that laser spot count is an independent risk factor for myopia.

In addition, a marginally significant correlation between the use of the 808 nm laser and myopia was found in the present study. However, we cannot conclude that a 532 nm laser is better than an 808 nm laser. The effect size of both laser spot count and 808 nm-laser use decreased in the multivariable-adjusted analysis, implying that these factors are not completely independent. Indeed, there was a significant difference in laser spot count between patients treated with 532 nm versus 808 nm lasers in the present study (532 nm = 1264 \pm 520 shots, 808 nm = 1677 \pm 838 shots [mean \pm standard deviation], $p = 0.002$, *t* test). LPC was performed at half-width in all patients, but there was a significant difference in the number of ablations. It was reported that 532 nm laser spots on the retina are more easily observed than 808 nm laser spots [15]. We therefore speculate that the infants who underwent LPC with the 808 nm laser may have received a greater number of photocoagulations than necessary.

An 808 nm laser is considered more effective than 532 nm laser in ROP treatment because of its ability to burn the deeper layer of the retina [15, 16]. An 808 nm laser also has the advantage of reducing the risk of developing cataract [24]. In our population, cataract occurred only in the 532 nm laser group (1 in 52 cases [2%]), although not so severe as to require lensectomy. However, an 808 nm laser has been reported to be more at risk of promoting myopic shift than a shorter wavelength laser [25]. In addition, several reports revealed that a 532 nm or 659 nm laser has therapeutic effects equal to those of an 808 nm laser [26, 27]. Since myopia and cataract are major complications related to vision prognosis, we suggest that further investigations are needed to study the effects of laser wavelength on therapeutic efficacy and incidence of complications.

The limitations of this study are as follows. (1) Its retrospective nature made it difficult to determine the causal relationship between laser spot count and myopia. (2) The relative proportion of severe ROP cases requiring treatment has increased due to the improvement in the survival rate of preterm infants [28, 29]. Differences in the general status of premature infants might cause bias deriving from factors related to neonatal management. (3) The laser wavelength was changed during the study enrolment period, and we did not treat ROP patients with different wavelengths in the same period. (4) LPC was performed by a total of five ophthalmologists. Indeed, only one ophthalmologist was involved in the ROP treatment for the entire period, and each of the other four used either the 532 nm laser only or the 808 nm laser only. Considering that the laser spot count required for treatment can be expected to differ depending on the skill level of the ophthalmologist, this might have caused differences in laser spot counts.

In conclusion, our analyses revealed a significant association between laser spot count and SE value in LPC-treated patients with ROP. Preterm infants who have received many laser shots may be at risk of developing myopia at 1-year of corrected age.

Summary

What was known before

- LPC is the standard treatment for ROP
- The prevalence of myopia is higher in ROP patients who received LPC

What this study adds

- An increased number of laser spots is related to myopia following LPC for ROP

- Further investigation is needed on the effects of laser wavelength on therapeutic efficacy and incidence of complications

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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