Investigating the Factors Affecting Myopia in Retinopathy of Prematurity after Laser Treatment

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Research Article

Keywords: spherical equivalent (SE), corneal refraction (CR), crystalline lens power (CLP), Retinopathy of prematurity (ROP), VEGF

Posted Date: June 14th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-605679/v1>

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Abstract

To elucidate the mechanism of myopia development in laser-treated retinopathy of prematurity (ROP) eyes, we investigated the effect of the number of laser shots applied on the myopic variables. A total of 33 eyes of 17 infants with laser-treated ROP were included. Cycloplegic retinoscopic refraction testing was carried out and the spherical equivalent (SE) was calculated. Relationships between SE and various variables (including the number of laser shots applied) were examined. In addition, an age- and axial length (AL)-matched control group without ROP was prepared to compare ocular structural parameters. Although there was no statistical difference in AL between two groups ($p = 0.88$), SE was significantly more myopic in the ROP group ($p < 0.001$). SE was associated with AL, corneal refraction (CR), and crystalline lens power (CLP) in the ROP group. Of these three factors (AL, CR, and CLP), only CLP was significantly correlated with the number of laser shots applied ($p = 0.003$); no correlations were observed between the number of laser shots and AL or CR ($p = 0.15$ and 0.10 , respectively). Very similar tendency was observed in the analysis of the difference between right and left eyes in each child.

Introduction

Retinopathy of prematurity (ROP) is a retinal ischemic disease caused by the development of abnormal retinal vessels in prematurely born infants.¹ Previous studies revealed that laser treatment had no impact on axial length (AL),²⁻⁶ although spherical equivalent (SE) of laser-treated eyes with ROP significantly shifted towards myopia.³⁻⁷ An accepted hypothesis is that laser treatment leads to a destruction of the peripheral retina and parts of the choroid, which may interfere with a possible disruption in the development of the anterior segment and may potentially lead to higher rate of myopia.^{1,8} Importantly, Connolly et al. investigated the myopic status in ROP eyes treated with laser and cryotherapy in a randomized controlled clinical trial. They suggested that the excess crystalline lens power (CLP) caused by the tissue destruction associated with laser treatment was another dominant component of the myopia in those eyes.⁹ In particular, in eyes with laser treatment, CLP bore a strong correlation to refractive outcomes, with a correlation coefficient of 0.885.⁹

We recently reported that there was a correlation between laser shots applied and the degree of myopia in eyes with laser-treated ROP at the age of 3 years.¹⁰ This finding was consistent with a previous study showing eyes treated with laser treatment had a higher prevalence of myopia than eyes treated with anti-vascular endothelial growth factor (VEGF) monotherapy.¹¹ However, our previous study was conducted without including other detailed parameters related to myopia such as AL, CLP, corneal refraction (CR), and anterior chamber depth (ACD).

In the current study, we investigated the effect that the number of applied laser shots had on these detailed myopic variables in eyes with ROP after laser treatment. In addition, an age- and AL-matched control group without ROP was prepared and various ocular structural parameters were compared between the eyes with laser-treated ROP and the control eyes.

Methods

This study, conducted with the approval of the Institutional Review Board of the University of Tokyo, adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the parents of each of the participants, and we retrospectively reviewed the medical records at the outpatient clinic of Tokyo University Hospital.

Subjects

In the ROP group, we included eyes with ROP that had histories of laser treatment and that underwent cycloplegic retinoscopic refraction testing between January 1, 2004 and December 31, 2018. Eyes with apparent eye diseases other than ROP and children who had undergone any intraocular surgery or received any anti-VEGF therapy were excluded from the ROP group.

For comparison, the following were assigned as the age- and AL-matched control group: i) infants with no known eye disease who visited the University of Tokyo Hospital within the same period for regular check-up; ii) infants who underwent cycloplegic retinoscopic refraction testing; and iii) infants between 3 and 8 years of age. As a result, 33 eyes of 17 infants and 14 eyes of 7 infants were enrolled as the ROP group and the control group, respectively.

Treatment And Clinical Examination

All of the eyes with ROP had undergone laser treatment. The laser-treated eyes were in either the threshold or prethreshold stage of ROP according to the ETROP guideline.¹² The laser treatments were performed by one of two ophthalmologists (T.I. and M.N.) until favorable structural outcomes were obtained in all eyes. Cycloplegic retinoscopic refraction testing was carried out, and the spherical equivalent (SE) was calculated as the spherical power + $\frac{1}{2}$ of the cylindrical power. At the same time, corneal refraction (CR), AL, and anterior chamber depth (ACD) were measured using optical biometry (OA-2000; Tomey, Nagoya, Japan). CLP was calculated using the modified Sanders-Reetzlaff-Kraff formula according to previous studies.^{9,13} In the ROP group, birth weight was also collected.

Statistical analysis

Mann-Whitney U test was used to compare demographics of each group, with the exception of sex ratio and laterality, which was evaluated using the Chi-squared test.

In the ROP group, the relationship between SE and the variables of age, sex, birth weight, CR, AL, ACD, and CLP were investigated using the liner mixed model. The linear mixed model is equivalent to ordinary linear regression in that the model describes the relationship between the predictor variables and a single outcome variable. However, standard linear regression analysis makes the assumption that all

observations are independent of each other. In the current study, measurements were nested within subjects and thus were dependent of each other. Ignoring this grouping of the measurements will result in the underestimation of standard errors of regression coefficients. The linear mixed model adjusts for the hierarchical structure of the data, modeling in a way in which measurements are grouped within subjects to reduce the possible bias of including both eyes of one patient.^{14,15} The model selection was then performed to identify the optimal linear mixed model for SE using the second-order bias-corrected Akaike information criterion (AICc) index, from all 2⁷ patterns consisted of 7 variables (age, sex, birth weight, CR, AL, ACD, and CLP). The AIC is an established statistical measurement used in model selection, and the AICc is a corrected version of the Akaike information criterion index, which provides an accurate estimation even when the sample size is small.¹⁶ The selected variables through the model selection were regarded as statistically significant.¹⁷ In addition, correlations between CR, AL, ACD, and CLP, and the number of laser shots applied were investigated using the Pearson's correlation test.

Thereafter, using both eyes with ROP from same infants (16 pairs), the difference in the SE (Δ SE, calculated as the value in the right eye minus that in the left eye) was calculated. Then the association between Δ SE and the variables of age, sex, birth weight, and the differences in CR (Δ CR), AL (Δ AL), ACD (Δ ACD), and CLP (Δ CLP) between the two eyes were investigated using linear regression analysis, and the model selection using the AICc index, respectively; the optimal model was identified from 2⁷ patterns consisted of 7 variables (age, sex, birth weight, Δ CR, Δ AL, Δ ACD, and Δ CLP). Moreover, correlations between Δ CR, Δ AL, Δ ACD, and Δ CLP, and the differences in number of laser shots applied between the two eyes (Δ Shot) were calculated using Pearson's correlation test.

All statistical analyses were carried out using *R* statistical software (version 3.6.3; <http://www.r-project.org/>). P values in multiple comparisons were corrected using the Hochberg correction.

Results

The demographic data of enrolled eyes are shown in Table 1. The ROP group consisted of 6 eyes (18.2%) in Stage 2, and 27 eyes (81.8%) in Stage 3, which presented in Zone I in 4 eyes (12.1%) or Zone II in 29 eyes (87.9%). The mean birth weight in the ROP group was 771.9 ± 253.2 g (mean $\pm$ standard deviation). Cycloplegic retinoscopic refraction testing was carried out at 5.0 ± 1.5 years of age in the ROP group, and at 5.20 ± 1.9 years in the control group, respectively ($p = 0.45$). Although there was no statistical difference in AL between the ROP group and the control group ($p = 0.88$; Mann-Whitney U test), the SE value was significantly more negative (more myopic) in the ROP group compared to the control group ($p < 0.001$; Mann-Whitney U test). Significantly greater CR, shallower ACD, and greater CLP were observed in the ROP group compared to the control group ($p < 0.001$, $p < 0.001$, and $p = 0.004$, respectively; Mann-Whitney U test).

Table 1
Demographics of the subjects

Parameter	ROP	Control	P value
Laterality (right/left)	17/16	7/7	1
Age, years	5.03 ± 1.5	5.20 ± 1.9	0.45
Sex (male/female)	16/17	4/10	0.35
LogMAR	0.20 ± 0.25	0.04 ± 0.08	0.02
SE, D	-3.02 ± 4.96	1.41 ± 2.37	< 0.001
Sphere, D	-2.48 ± 4.78	1.61 ± 2.35	0.007
Cylinder, D	-1.07 ± 1.32	-0.39 ± 1.31	0.003
CR, D	47.1 ± 1.8	44.1 ± 1.6	< 0.001
K1, D	46.0 ± 1.9	43.2 ± 1.3	< 0.001
K2, D	48.1 ± 1.9	44.9 ± 1.9	< 0.001
ACD, mm	3.11 ± 0.36	3.45 ± 0.21	< 0.001
AL, mm	22.1 ± 1.5	22.0 ± 1.0	0.88
CLP, D	23.8 ± 5.2	20.0 ± 1.8	0.004
<i>*The data represent the means ± standard deviation. ROP, retinopathy of prematurity; SE, spherical equivalent; CR, corneal refraction; ACD, anterior chamber depth; AL, axial length; CLP, crystalline lens power.</i>			

As shown in Table 2, the optimal linear model identified for SE in ROP eyes was as follows; SE = 77.2–1.78 (Standard Error [Stderr] = 0.021, $p < 0.001$) x AL – 0.52 (Stderr = 0.021, $p < 0.001$) x CR – 0.68 (Stderr = 0.007, $p < 0.001$) x CLP (AICc = 3.7).

Table 2
Relationships between SE and each of age, sex, birth weight, CR, AL, ACD, and CLP in laser-treated eyes with ROP

Parameter	Univariate analysis			Optimal model		
	Coefficient	Stderr	P value	Coefficient	Stderr	P value
Age	0.044	0.056	0.44	N.S.		
Sex	0.24v	2.33	0.92	N.S.		
Birth weight	0.0087	0.0042	0.054	N.S.		
CR	-0.76	0.550	0.19	-0.52	0.021	< 0.001
AL	-2.18	0.35	< 0.001	-1.78	0.021	< 0.001
ACD	8.52	2.72	0.0069	N.S.		
CLP	-0.85	0.093	< 0.001	-0.68	0.007	< 0.001
SE, spherical equivalent; CR, corneal refraction; AL, axial length; ACD, anterior chamber depth; CLP, crystalline lens power; N.S., not selected.						

Pearson's correlation test results showed significant correlation between the number of laser shots applied and CLP ($p = 0.003$, Fig. 1). In contrast, no correlations were observed between the number of laser shots applied and each of AL, ACD, and CR ($p = 0.15$, 0.65 , and 0.10 , respectively; Pearson's correlation test).

As shown in Table 3, the optimal linear model for ΔSE was; $\Delta SE = 0.006 - 1.74$ (Stderr = 0.029 , $p < 0.001$) $\times \Delta AL - 0.58$ (Stderr = 0.049 , $p < 0.001$) $\times \Delta CR - 0.69$ (Stderr = 0.014 , $p < 0.001$) $\times \Delta CLP$ (AICc = -6.9).

Table 3

Relationships between Δ SE and each of age, sex, birth weight, Δ CR, Δ AL, Δ ACD, and Δ CLP in laser-treated eyes with ROP

Parameter	Univariate analysis			Optimal model		
	Coefficient	Stderr	P value	Coefficient	Stderr	P value
Age	-0.063	0.056	0.28	N.S.		
Sex	-0.36	1.76	0.84	N.S.		
Birth weight	0.0028	0.0034	0.44	N.S.		
Δ CR	-2.02	1.04	0.072	-0.58	0.049	< 0.001
Δ AL	-2.17	0.39	< 0.001	-1.74	0.029	< 0.001
Δ ACD	21.2	8.51	0.026	N.S.		
Δ CLP	-0.91	0.24	0.0020	-0.69	0.014	< 0.001
Δ SE, differences in spherical equivalent; Δ CR, differences in corneal refraction; Δ AL, differences in axial length; Δ ACD, differences in anterior chamber depth; Δ CLP, differences in crystalline lens power; N.S., not selected.						

The Pearson's correlation test identified a significant correlation between the difference in the number of laser shots applied and Δ CLP (coefficient = 0.59, p = 0.017, Fig. 2 and Table 4). There were no correlations between the difference in the number of laser shots applied and each of Δ CR, Δ AL, and Δ ACD (p = 0.86, 0.21, and 0.20, respectively; Pearson's correlation test; Table 4).

Table 4

Correlations between the difference in the number of laser shots applied and each of Δ AL, Δ ACD, and Δ CR

Parameter	Coefficient	P value
Δ CR	0.05	0.86
Δ AL	0.33	0.21
Δ ACD	-0.34	0.20
Δ CLP	0.59	0.017
Δ CR, differences in corneal refraction; Δ AL, differences in axial length; Δ ACD, differences in anterior chamber depth; Δ CLP, differences in crystalline lens power.		

Discussion

In the current study, various parameters related to myopia were compared between laser-treated ROP (33 eyes of 17 infants) and age- and AL-matched control groups (14 eyes of 7 infants). As a result, there were

significant differences in SE, CR, ACD, and CLP between the ROP group and the control group, despite the non-significantly different AL.

In laser-treated ROP eyes, SE was significantly related to CR, AL, and CLP. Furthermore, Δ SE was associated with Δ CR, Δ AL, and Δ CLP. Finally, the number of laser shots applied was associated with CLP, but not with AL and CR, and the difference in the number of laser shots was associated with only Δ CLP.

Previous studies have compared myopic changes in eyes with ROP. Algawi et al. suggested that the number of eyes encountered myopia was significantly smaller in the laser group (40%) than the cryotherapy group (92%).¹⁸ Knight-Nanan et al. reported that 94.1% of a cryotherapy-treated group were myopic while 45.5% were myopic in a laser-treated group after 3 years of follow-up.¹⁹ Connolly et al. reported that those treated with laser had a mean SE of -4.48 D, whereas this value was -7.65 D in the cryotherapy-treated eyes.⁹

Consistent with previous reports, our current results suggested laser-treated ROP eyes were significantly more myopic than the age- and AL-matched eyes. Moreover, in the current study, the degree of myopia in ROP eyes was significantly associated with CR, AL and CLP (Tables 2 and 3). Interestingly, AL was selected as an explanatory variable for the degree of myopia in laser-treated ROP, whereas there was no significant difference in AL between the ROP group and the control. Our result suggested AL is a non-negligible component of myopia-related parameters in laser-treated ROP eyes similar to normal eyes, however further study is needed to investigate the temporal change of AL in ROP children.

Connolly et al. also indicated CLP was more increased in cryotherapy-treated eyes than in laser-treated eyes, which was attributed to the greater tissue destruction of peripheral retina caused by cryotherapy, which disrupted the maturation of the anterior segment; *i.e.* zonules, the ciliary body, and the lens.⁹ However, no reports investigated which refractive parameters were associated with the number of laser shots and influenced the degree of myopia.

In the current study, we identified that CLP (but not CR and AL) was affected by the number of shots applied ($p = 0.003$, Fig. 1). There was also a significant association between the difference in the number of laser shots applied and Δ CLP (Fig. 2 and Table 4). Taken together, it was suggested that the degree of myopia in laser-treated ROP eye is increased predominantly through increased CLP.

Lee et al. reported that ACD was significantly shallower in laser-treated ROP eyes than in eyes treated using anti-VEGF.⁸ In the current study, ACD was significantly shallower in laser-treated ROP eyes compared to control eyes (Table 1). In contrast, there was no significant relationship between ACD and the degree of myopia as a result of multivariate analysis and model selection (Table 2). These contradicting results may be due to the different calculation of CLP in the current study; following previous studies,^{9,13} the CLP was calculated using the modified Sanders-Reetzlauff-Kraff formula in which only the values of AL, keratometry measurement, and the refractive error were used. In other words, CLP

was calculated including the effect of ACD, and indeed CLP was significantly correlated with ACD. In future, CLP estimation (excluding the effect of ACD) would be needed for laser-treated ROP eyes.

Recently, laser treatment and anti-VEGF therapy have been widely applied for ROP in many countries.^{11,12,20-22} Indeed, anti-VEGF therapy has been shown to achieve better refractive and anatomic outcomes in general than laser treatment.⁸ As shown in the current study, and consistent with a previous report,¹¹ anti-VEGF therapy may be better than laser treatment in reducing subsequent progression of myopia, because it is unlikely that anti-VEGF therapy causes tissue destruction compared with laser treatment. However, careful consideration is still needed when choosing between the two treatments as anti-VEGF therapy is reportedly associated with delayed vascularization compared to laser treatment.⁸ Mintz-Hittner reported that the mean time to recurrence was 16.0 weeks after anti-VEGF therapy, as compared with 6.2 weeks after laser treatment.²³ In other words, treatment cannot be regarded as successfully completed until no active disease or clinically significant tractional elements are confirmed on completion of vascularization.²³

There are several limitations in this study. Firstly, as the laser treatment was conducted by two clinicians, performance of the laser procedure (such as laser power and duration) was not completely consistent when applied among the patients. This discrepancy may be attributed to a non-negligible effect on the degree of tissue destruction caused by the laser treatment, resulting in the difference in development of myopia.

In the current study, the difference of laser shots applied showed a significant association with Δ CLP, suggesting the relevance of our results. However, a prospective study with rigid protocols will help us understand this issue in detail. Secondly, the measurement of refractive errors was performed in patients of different ages. In laser-treated ROP eyes, the myopic change might partly progress with elongated axial length. Thus, further studies should be performed to investigate myopia-related parameters at the same age in ROP and control eyes.

In conclusion, the SE value was significantly more myopic in the laser-treated ROP group compared to the control group. In the laser-treated ROP eyes, the SE value was related to CR, AL, and CLP. The number of laser shots was associated with CLP, but not with AL and CR, suggesting CLP was a primary component of the refractive error of laser-treated ROP eyes.

Declarations

Conflict of Interest

The authors have no competing interests.

Author contributions:

S.A., T.I. and R.A. wrote the main manuscript text. S.A. prepared the figures. Datasets were prepared by S.A., T.I., K.K., M.K., A.F., M.I., and R.O., All authors reviewed the manuscript.

Acknowledgments

This research was supported by grants from the Japan Science and Technology Agency (JST)-CREST and Grant 17K11418 from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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Figures

Figure 1

Correlation between the number of laser shots applied and CLP. There was a significant correlation between the number of laser shots applied and CLP ($p = 0.003$; Pearson's correlation test) CLP: crystalline lens power

Figure 2

Correlation between the number of laser shots applied and Δ CLP. A significant correlation was identified between the difference in the number of laser shots applied and Δ CLP ($p = 0.017$; Pearson's correlation test) Δ CLP: difference in crystalline lens power