EXTENDED REPORT

Effect of peripheral retinal ablation with cryotherapy versus diode laser photocoagulation on axial length in the growing rabbit eye

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Aims: To evaluate and compare the effects of peripheral retinal cryotherapy and diode laser photocoagulation on axial length, anterior chamber depth, and lens thickness in developing rabbit eyes.

Methods: 26 eyes of 6 week old Abbit rabbits were randomly assigned to undergo laser photocoagulation or cryotherapy of the peripheral retina. Eight eyes of four untreated rabbits served as controls. Biometric and intraocular pressure measurements were performed at 0, 5, and 10 weeks after treatment.

Results: Five rabbits died, leaving 10 rabbits (20 eyes) in the study group and two (four eyes) in the control group. Average axial lengths for the control, laser treated, and cryo treated eyes were 15.72 mm, 16.08 mm, and 16.11 mm, respectively, at baseline and 17.48 mm, 18.09 mm, and 19.4 mm, respectively, at 10 weeks after treatment ($p=0.028$, paired Wilcoxon test). Anterior chamber depth increased from 2.2 mm to 2.5 mm in both treatment groups, and from 2.14 mm to 2.28 mm in the control group. Lens thickness averaged 5.11 mm in the control group and 5.38 mm in the treatment groups before treatment, and 6.34 mm, 6.31 mm, and 6.38 mm, respectively, 10 weeks after treatment.

Conclusions: Peripheral retinal cryotherapy causes a significantly greater elongation of the eye compared to diode laser photocoagulation in a rabbit model.

Myopia is commonly associated with retinopathy of prematurity (ROP).^{1–4} Several reports have shown that eyes treated with laser photocoagulation for threshold ROP were less myopic than eyes treated with cryotherapy.^{5–9} Connolly *et al*,¹⁰ in a prospective study using A-scan ultrasonography, cycloplegic refraction, and keratometry suggested that the lens power was the predominant factor contributing to the excess myopia in eyes treated with cryotherapy versus eyes treated with laser for threshold ROP. They also reported a shorter axial length and a thicker lens in cryo treated than in laser treated eyes. By contrast, Kent *et al*⁴ noted longer axial and posterior segment lengths in cryo treated eyes with ROP than in laser treated and untreated eyes. All these studies reported on human subjects with ROP, a disease which by itself alters the ocular growth.

The aim of this study was to compare the anterior chamber depth, lens thickness, and axial length of eyes treated with diode laser photocoagulation or trans-scleral cryotherapy in a normal rabbit model. Histopathological studies were performed to identify changes in the sclera and ciliary body.

METHODS

The study was approved by the institutional review board, and the animals were treated in accordance with the ARVO statement for the use of animals in ophthalmic and vision research. Seventeen 6 week old pigmented Abbit rabbits weighing 500–650 g were randomly divided into study ($n=13$) and control ($n=4$) groups. Infant rabbits were chosen to evaluate the treatment effect on the eye during the period of maximum growth. After the pupils were dilated with 0.5% cyclopentolate and 2.5% phenylephrine (Akorn, Inc, Buffalo Grove, IL, USA), the rabbits were anaesthetised with intramuscular ketamine (5 mg/kg) and xylazine (5 mg/kg) and ear tagged for follow up. Axial length, anterior chamber depth, and lens thickness were measured in each eye with an A-scan biometer with a frequency of 8 MHz (Allergan-Humphrey Systems, Dublin, CA, USA) using the

technique described by Butcher and O'Brian.¹¹ The average value of the three best images was recorded for each eye.

In the animals in the treatment group, the eyes ($n=26$) were randomly assigned to undergo cryotherapy or laser treatment. One eye was randomly assigned to laser treatment and the fellow eye was assigned to cryotherapy, in order to mimic the randomised controlled studies performed on human subjects.^{6–10} Trans-scleral cryotherapy was performed using a cryosurgical system (Mira, Waltham, MA, USA) with a tip diameter of 1.5 mm. Maximal freezing capability of -80°C was obtained at the probe tip. Applications were placed over a circumferential 360° 3 mm wide band in a confluent, non-overlapping configuration over the peripheral retina, avoiding the ciliary body and long ciliary arteries and nerves: 15–20 cryo burns were delivered to each eye. The treatment end point was defined as a white retinal reaction without vitreous freezing on indirect ophthalmoscopy. Shortly after treatment the retinal area appeared grey.

Peripheral laser photocoagulation was performed with an indirect diode laser (810 nm) photocoagulator (Iris OcuLight Photocoagulator, Iris Medical, Mountain View, CA, USA) equipped with a 28 dioptr condensing lens. A circumferential band of three lines consisting of approximately 500 μm spots a half spot diameter apart was delivered to the peripheral retina. The ciliary body as well as the long ciliary arteries and nerves were avoided. Between 1800 and 2600 applications were placed in each treated eye. Laser power and duration were adjusted to produce white lesions. Power ranged from 200–400 mW, and duration from 200–300 ms.

Biometric measurements of the anterior chamber depth, lens thickness, and axial length were obtained under general anaesthesia before treatment and repeated at 5 weeks and 10 weeks. The examiner was blinded to the treatment modality. At conclusion of the 10 week examination, the animals were sacrificed by intravenous injection of 22%

Abbreviation: ROP, retinopathy of prematurity

Table 1 Changes in mean (SD) axial length over time in the three groups

	Baseline (week 0)	5 weeks	10 weeks	p Value*	
	Mean (SD)	Mean (SD)	Mean (SD)	Week 0 v week 5	Week 0 v week 10
Laser (10 eyes)	16.08 (0.85)	17.14 (0.70)	18.09 (1.07)	0.022	0.007
Cryotherapy (10 eyes)	16.11 (0.85)	17.80 (0.73)	19.24 (1.07)	0.005	0.005
Controls (untreated) (4 eyes)	15.72 (0.48)	16.65 (0.32)	17.48 (0.48)	0.068	0.068

*Paired Wilcoxon test.

phenobarbital (2 ml), and both eyes were enucleated. The globes were fixated in 4% formalin without removal of the vitreous and without incising the globe. Fixation in formalin continued for 7 days at room temperature. After fixation, the tissue was processed by dehydration, embedded in paraffin, sectioned, and stained with haematoxylin and eosin.

Statistical analysis was performed using SPSS software (SPSS for Windows, release 11.5; SPSS Inc, 2002, Chicago, IL, USA). Comparisons were analysed by paired Wilcoxon test and Mann-Whitney test with independent samples.

RESULTS

Five of the 17 rabbits died (probably because of their very young age), leaving 10 rabbits in the treatment group (20 eyes) and two rabbits in the control group (four eyes).

There was no statistically significant difference in mean weight between the study and control groups, either initially or at 5 weeks and 10 weeks after treatment.

Mean laser power was 265.4 (SD 69) mW; mean duration of treatment was 207.7 (SD 27) msec; and mean number of laser spots was 1992 (SD 231).

Axial length

The axial length increased in all eyes. However, the difference between the initial examination and the 5 week and 10 week examination was statistically significant only in the cryo and laser treated eyes, but not in the untreated eyes (table 1). Comparisons between the laser and cryo treated eyes, the laser treated eyes and control eyes, and the cryo treated and control eyes yielded no significant differences at baseline ($p = 0.8$, $p = 0.6$, and $p = 0.6$, respectively, paired Wilcoxon and Mann-Whitney tests). At 5 weeks and 10 weeks, the cryo treated eyes were significantly longer than the control eyes ($p = 0.016$, $p = 0.024$, Mann-Whitney test), and at 10 weeks, the cryo treated eyes were significantly longer than the laser treated eyes ($p = 0.028$, paired Wilcoxon test). At 5 weeks, the laser treated eyes were also significantly longer than the control eyes ($p = 0.047$, Mann-Whitney test), but the difference did not achieve significance at 10 weeks ($p = 0.12$, Mann-Whitney test).

Anterior chamber depth

The anterior chamber depth (table 2) increased significantly between the initial and the 10 week examinations in the cryo

and laser treated eyes, with no statistically significant difference between the study groups ($p = 0.67$ and $p = 0.48$, respectively, paired Wilcoxon test). The control eyes showed a lesser change, which was, however, not significantly different from the laser treated eyes at any of the time points ($p = 0.559$, $p = 0.943$, $p = 0.088$, respectively, Mann-Whitney test), or from the cryo treated eyes at baseline or 5 weeks ($p = 0.689$, $p = 0.667$, Mann-Whitney test). The only statistically significant finding for this variable was between the cryo treated eyes and the controls at 10 weeks ($p = 0.05$).

Lens thickness

All the groups exhibited similar increases in lens thickness. Statistically significant lens thickening was noted in both the laser and cryo treated eyes between the baseline and the 5 week and 10 week examinations (table 3), with no statistically significant difference between the study groups at any time point ($p = 0.65$, $p = 0.67$, $p = 0.07$, respectively, paired Wilcoxon test). The changes in lens thickness in the controls were not statistically significant because of the low number of eyes. This was also true for comparisons with control eyes (laser treated v controls: $p = 0.253$, $p = 0.777$, $p = 1.0$, respectively; cryo treated v controls: $p = 0.334$, $p = 1.0$, $p = 0.435$, respectively; Mann-Whitney test for two independent variables).

Table 4 shows the intraocular pressure data in the three groups at the three time points. There was no statistically significant difference in the intraocular pressure before and after laser treatment and cryotherapy ($p = 0.69$, $p = 0.43$, respectively; paired Wilcoxon test).

Histopathology

Cryo treated eyes

The area of treatment revealed peripheral chorioretinal scars with retinal atrophy up to the pars plana. Some areas demonstrated intraretinal peripheral macrocystoid oedema and a chronic inflammatory reaction. Heavy pigment dispersion was noted in the ciliary body along the longitudinal muscle, and there were numerous pigment laden macrophages in the supraciliary zone. The pigment dispersion was more marked in the cryo treated than the laser treated eyes. Additionally, proliferation of retinal and ciliary pigmented and ciliary non-pigmented epithelial cells was noted. Adhesion and condensation of vitreous fibres to the areas

Table 2 Changes in mean (SD) anterior chamber depth over time in the three groups

	Baseline (week 0)	5 weeks	10 weeks	p Value*	
	Mean (SD)	Mean (SD)	Mean (SD)	Week 0 v week 5	Week 0 v week 10
Laser (10 eyes)	2.20 (0.19)	2.19 (0.15)	2.48 (0.22)	0.77	0.033
Cryotherapy (10 eyes)	2.19 (0.16)	2.22 (0.13)	2.50 (0.17)	0.609	0.017
Controls (untreated) (4 eyes)	2.14 (0.08)	2.17 (0.08)	2.28 (0.14)	0.197	0.102

*Paired Wilcoxon test.

Table 3 Changes in mean (SD) lens thickness over time in the three groups					
	Baseline (week 0)	5 weeks	10 weeks	p Value*	
	Mean (SD)	Mean (SD)	Mean (SD)	Week 0 v week 5	Week 0 v week 10
Laser (10 eyes)	5.38 (0.48)	5.96 (0.36)	6.31 (0.27)	0.008	0.005
Cryotherapy (10 eyes)	5.7 (0.54)	5.94 (0.38)	6.38 (0.28)	0.012	0.011
Controls (untreated) (4 eyes)	5.11 (0.14)	5.91 (0.23)	6.34 (0.16)	0.068	0.068

*Paired Wilcoxon test.

Table 4 Changes in mean (SD) intraocular pressure (IOP) over time in the three groups							
	IOP pretreatment	IOP post- treatment	IOP 5 weeks	IOP 10 weeks	p Value†	p Value*	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		Week 0 v week 5	Week 0 v week 10
Laser (10 eyes)	15.46 (3.97)	16.31(6.17)	16.30 (4.00)	15.60 (3.47)	0.694	0.71	0.677
Cryotherapy (10 eyes)	15.46 (3.36)	17.00 (5.29)	17.40 (5.13)	14.30 (3.43)	0.431	0.474	0.384
Controls (untreated) (4 eyes)	16.00 (2.62)	–	17.00 (6.48)	16.25 (2.63)	–	0.461	0.465

*Paired Wilcoxon test.
†IOP difference before and after treatment.

of the chorioretinal scars (located in the vitreous base) were seen. There was no atrophy of the ciliary body or ciliary processes. The superficial sclera demonstrated slight tissue disorganisation (fig 1).

Laser treated eyes

The area of treatment demonstrated a chorioretinal scar with hyperplasia of the retinal pigment epithelium cells. Pigment granules and pigment laden macrophages were noted in the area of the scar and in the atrophic retina and choroid anterior to the scar, as well as in the supraciliary zone near the chorioretinal scar. The ciliary body was characterised by pigment dispersion along the longitudinal muscle. In some eyes, pigment dispersion was noted to reach the anterior chamber angle. The ciliary processes were normal in all the eyes (fig 2).

DISCUSSION

The Cryotherapy for Retinopathy of Prematurity trial¹² reported a higher rate of myopia of 8 dioptres or more in cryo treated compared to untreated eyes at all ages after 3 months. Both groups showed an increase in the prevalence of high myopia between 3 months and 12 months of age. The

authors explained these findings by cryotherapy’s putative preservation of the retinal structure in eyes which, left untreated, would have progressed to retinal detachment.

Kent *et al*,⁴ in a comparison of treatment modalities, found that laser treatment for ROP was associated with less myopia than cryotherapy, with a positive correlation of the vitreous cavity and axial lengths with the refractive outcome. The cryo treated eyes had a shallower anterior chamber depth and thicker lens compared to eyes without ROP; a decreased axial length compared to untreated eyes; and increased axial and posterior segment lengths compared to laser treated eyes. The authors concluded that the myopia in treated eyes with ROP is attributable not only to the axial length but also to the tendency towards anterior segment arrest associated with stage 3 ROP. However, the eyes given the different treatments were not from the same patients, and the study was not prospective or randomised.

In another retrospective study, Paysse *et al*¹³ found that in patients with threshold ROP, diode laser photocoagulation was associated with a better long term structural outcome and visual acuity than cryotherapy, with no difference in refractive error. According to Knight-Nanan and O’Keefe,⁷

Figure 1 Cryo treated eye. A, peripheral chorioretinal scar with retinal atrophy near the pars plana. B, vitreous condensation is seen adjacent to the atrophic retina. C, moderate pigment dispersion is evident in the choroid and ciliary body with numerous macrophages laden with pigment in the supraciliary zone. D, proliferation of the non-pigmented epithelial cells in the ciliary body. E, disorganisation of the superficial sclera (haematoxylin and eosin x 20).

Figure 2 Laser treated eye. A, peripheral chorioretinal scar with retinal atrophy and gliosis. B, retina is firmly attached to the area of the scar and artefactually detached posterior to the scar. C, heavy pigment dispersion is seen in the choroid in the area of the scar. D, numerous pigment laden macrophages are seen in the choroid posterior to the scar. E, normal scleral structure showing no histological evidence of damage to its collagen fibres (haematoxylin and eosin x 20).

diode laser photocoagulation was also associated with lower rates of myopia than cryotherapy at 3 years' follow up (94% v 45% of patients), and with lower rates of high myopia (55% v 0%). These findings were confirmed by Al-Ghamdi *et al*⁹ in a retrospective study (−1.80 dioptres for laser versus −9.21 dioptres for cryotherapy).

Choi *et al*¹⁴ found that cryotherapy and the presence of cicatricial retinopathy were predictive factors of myopia in premature infants. The degree of myopia was related to the depth of the anterior chamber, the thickness of the lens, and the change in axial length, but not to the keratometric value.

In a prospective 10 year follow up study, Ng *et al*¹⁵ found better structural and functional outcome in laser treated eyes than cryo treated eyes. The cryo treated group had more retinal dragging, and the degree of retinal dragging was inversely proportional to visual acuity. Using the same study design, Connolly *et al*¹⁰ noted significantly less myopia in the laser group. The cryo treated eyes had a mean shorter axial length, shallower anterior chamber, and thicker lenses. The authors concluded that the lens power bore the strongest relation to refractive outcome in both groups. However, their follow up study included only 25 of the original 66 treated patients (≈38%), with variability of participation in each of the tests.

As preterm infants mature, the axial length increases, the anterior chamber depth deepens, and the corneal curvature flattens, while the lens thickness remains stable.¹⁶ All the studies described above demonstrate that myopia is associated with ROP, and that eyes treated for threshold ROP by cryotherapy are more myopic than those treated by laser. The myopia in stage 3 treated eyes is not explained solely by axial length, and the lens power and anterior segment contribute as well. It is not always clear, however, whether the myopia is caused by the ROP or by the treatment.

By contrast with these studies, all of which used human subjects with ROP, our study examined the influence of laser versus cryotherapy on ocular growth in healthy rabbit eyes.

Whitmore *et al*,¹⁷ in a study of the effects of trans-scleral cryotherapy and blue-green laser photocoagulation of the anterior retina in rabbit eyes, found that the treated eyes had a decreased axial length, average equatorial diameter, average corneal diameter, and average total ocular volume. They concluded that these treatments slow the growth of the anterior and posterior segments, with no relation to the age of the rabbits or the amount or type of treatment. They attributed the growth retarding effect of cryotherapy and laser either to the influence of the retinal tissue on ocular growth or to the destruction of hyalocytes in the cortical vitreous at the vitreous base, leading to less vitreous production and arrest of the normal expansion of the globe. However, these authors performed strong confluent cryoapplications, extending the ice ball into the cortical vitreous, and confluent laser burns, whereas we performed mild and non-confluent cryotherapy and laser applications, simulating the technique of retinal ablation for ROP. This may have led to less retinal and vitreal damage.

Although perhaps not directly applicable to ROP in humans, our results indicate that peripheral retinal ablation by cryotherapy induces greater increase in both the total axial length and the anterior chamber depth in the developing eye than diode laser photocoagulation. The differences in eye elongation were not caused by differences in intraocular pressure.¹⁸ Although steepness and flatness of the cornea may influence the anterior chamber depth and contribute to the myopia, these are not available, since keratometry was not performed in this study. There were no differences in lens thickness in either group from controls.

The histopathological study of the cryo treated eyes showed chorioretinal atrophy at the scars, vitreous condensation,

proliferation of the non-pigmented ciliary epithelium, inflammatory reaction, and pigment migration. The laser treated eyes, by contrast, demonstrated more confined retinal damage, no changes in the ciliary epithelium, and less pigment dispersion, compared with the cryo treated eyes. No circumferential changes were noted histologically in the ciliary body either in the cryo or in the laser treated eyes.

We postulate that the slight disorganisation of the outer sclera seen in the cryo treated group (fig 1) might have affected the ocular growth, thereby contributing to the excess elongation. Previous studies suggested that disulphide bonds between fibrils in the sclera can be reduced in eyes with pathological myopia. If that were the case, sheets of sclera could slide over each other, allowing some elongation of the sclera. However, the disulphide bonds were not studied histologically.¹⁹ The mechanism underlying the eye elongation remains unclear. In previous studies, laser photocoagulation, like cryotherapy, was associated with chorioretinal adhesions in rabbit eyes.²⁰ However, the adhesions were more precise and selective, dispersing fewer viable retinal pigment epithelium cells and creating less breakdown of the blood-retinal barrier.²¹ Hann *et al*²² reported that neither method led to significant scleral weakening relative to paired untreated controls. Knight-Nanan and O'Keefe⁷ suggested that the larger areas of chorioretinal scarring produced by cryotherapy could lead to a greater reduction in chemical mediators and tip the balance in favour of factors that cause corneal flattening or increased axial growth. This might explain the greater prevalence of high myopia in cryo treated versus diode laser treated eyes. Alternatively, the larger areas of chorioretinal adhesion and destruction of the normal chorioretinal architecture could change the structure of the sclera, making it more susceptible to stretching.

In summary, in this animal model both the total axial length and the anterior chamber depth were greater in the cryo treated eyes than in the diode laser treated or the control eyes, with no difference in lens thickness. These findings differ from those in previous animal models and human series, which showed a shorter axial length in the cryo treated eyes and attributed the cryotherapy induced myopia to the thicker lens and its power. Although diode laser photocoagulation is the preferred treatment for ROP, cryotherapy is still performed in developing countries. We therefore suggest that further studies be performed to explore the influence of cryotherapy and laser treatment on ocular growth.

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