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ARTICLE

Is the severity of refractive error dependent on the quantity and extent of retinal laser ablation for retinopathy of prematurity?

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Abstract

Background/Aim To test the hypothesis severity of acquired refractive error in Retinopathy of Prematurity (ROP) is dependent on the quantity of laser treatment delivered.

Methods Two groups (treated and untreated infants) were age and weight matched. Data on the number of laser burns and Retcam II retinal images were analysed using computer aided design software to determine the proportion of area treated. Data were collected until the age of 6 years.

Results The study comprises 43 infants (86 eyes). Twenty-one infants (42 eyes) in the treated group, mean gestational age (GA) was 26.40 (±2.5) weeks versus 27.30 (±1.7) weeks in the matched untreated group ($P = 0.650$). Birth weight (BW) in the treated group was 812 g (±86) and 804 g (±135) ($P = 0.185$) in the untreated group. Mean refractive error at 72 months was −2.23 (±4.06) in the treated group and +2.04 (±0.90) in the untreated group ($P < 0.005$). At 72 months 50% of treated eyes were myopic versus 19% of controls ($P = 0.013$). Mean laser burns applied were 1855 (±659), mean proportion of retina treated 45% (±10). Myopic eyes had a mean treatment area of 49% (±13) versus 43% (±10) hypermetropia and 42% (±5) emmetropia ($P = 0.030$). A larger treatment area was associated with a higher degree of myopia and anisometropia at 72 months ($P < 0.050$). These associations were not found for hypermetropia.

Conclusions The extent of myopia after retinal laser ablation for ROP is higher if a greater number of laser burns or a larger proportion of the retina is treated.

Introduction

Treatment of Retinopathy of Prematurity (ROP) underwent a transition when laser treatment replaced cryotherapy. Cryotherapy was associated with complications including significant myopia [1]. In the Early Treatment for ROP study (ETROP) earlier treatment of high risk pre-threshold ROP improved grating visual acuity (VA) and retinal structural outcomes at 9 months corrected age, but the infants still develop significant myopia [2]. No studies have correlated the level of myopia acquired by infants with the quantity of retinal laser treatment delivered. This study aimed to test the hypothesis that the amount of acquired refractive error is dependent on the quantity of diode laser treatment delivered and the proportion of retina treated for ROP.

Subjects and methods

A retrospective analysis was carried out on infants screened for ROP between May 2005 and September 2010 in the University Hospital of Wales. Ethics approval was obtained thorough the Integrated research application system in the United Kingdom. The stage and severity of ROP was scored according to the International Classification of ROP [3]. In addition, disease in zone 2 was subclassified into anterior and posterior disease. Infants treated for ROP with diode retinal laser ablation were included in the analysis. Gestational and birth weight (BW) matched infants with untreated stage 3 ROP were identified for a comparative group in the same study period. Exclusion criteria were the presence of stage 4 or 5 disease at first screen, use of an intravitreal anti vascular endothelial growth factor (antiVEGF) and demise before the age of 6 years. Data were collected from first

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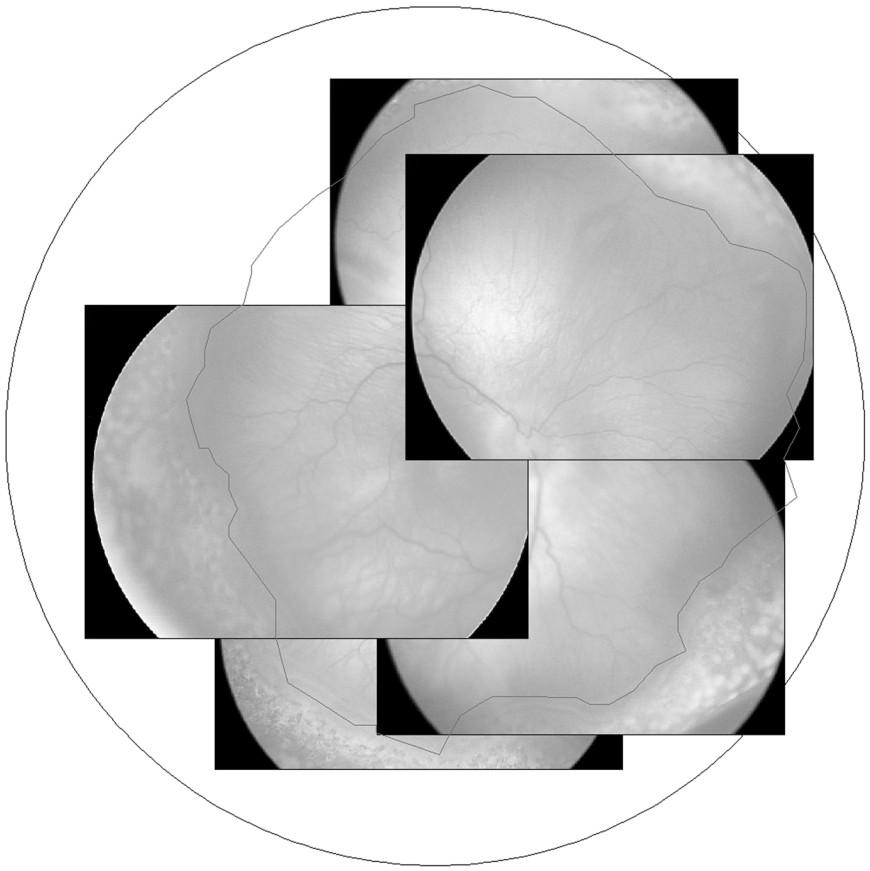

Fig. 1 An Infants right eye analysed using AutoCAD software, the circle represents the presumed outer limits of the retina after indented examination and image analysis (o), a 2 D polyline (inner line) is enclosing untreated retina, hence treatment area calculable (t). The program is set to measure the area enclosed by the perimeters. A ratio of treated versus non treated retina was calculated

screening for ROP and all subsequent screening episodes. Also collected was data at first laser treatment and at the following ages: 6 weeks and at 3, 6, 12, 24, 36, 48, 60 and 72 months. Any confounders for developing high refractive error or poor visual outcomes were identified.

The Oculight(R) SLx 810 nm diode laser (IRIS Medical, Göttingen, Germany) was used in all cases for laser application. The laser treatment parameters were determined from the theatre log and medical notes, which used a standardised ROP screening chart. Retcam II (Clarity medical systems, Inc USA) images were analysed using Autodesk AutoCAD 2010 (Computer Aided Design (CAD) software, Autodesk, Inc. Mill Valley, California, USA) to quantify the proportion of area treated. The powerful software has design, engineering (electronic, mechanical and aerospace), architectural and project management capabilities. A montage of the retinal images was created to build an image of the retina as far anterior as the images would allow. An outer perimeter was drawn to represent the outer quadrant of the retina (o), the border of this was determined by examining numerous retinal images used during screening and treatment, identifying the far periphery, until no laser scars were seen and identifying the ora serrata. ROP treatments at our centre are followed by an indented retinal examination to ensure all the avascular retina is treated, this reassures us the border (o) has been accurately placed. A 2 D polyline was used to surround the retina treated (t). An accurate, although arbitrary (for our purpose) area was calculated by the software for (o) and (t), this was used to calculate the percentage (%) of retina treated as (t/o*100). The image analysis was restricted to the number of images available; every effort was made to use images from the same day of treatment and or examination at 2 weeks (Fig. 1).

To validate the AutoCAD method, the area of the treated retina was also determined independently by two investigators T Y-Z and MP with a Kappa score of 0.8. In addition, a separate model utilising retinal photographs was used. The linear diameter (ora to ora) was measured, the treated retina in vertical, horizontal and diagonal meridians was measured. The treatment area was estimated and averaged for these meridians. Kappa scores were 0.7 between investigators utilising this method. Correlation between this method and the AutoCAD method was strong at 0.7.

Statistical analysis

SPSS version 20.0 (IBM Corp, Armonk, NY, USA) was used for data analysis. Descriptive analysis was carried out. The

Kolmogorov–Smirnov test and plots for normality were used to determine data spread. The Mann–Whitney and Chi Square statistic were used for comparative data. Regression analysis has been used for continuous data. To adjust for inter eye correlation Generalized Estimating equations were utilised. A confidence interval of 95% and a $P < 0.05$ was considered significant. Retrospective power calculated at 0.80, alpha error 0.05, at medium effect size a sample of 64 adequate.

Results

A total of 43 infants have been included in this study.

Infants screened but not requiring treatment

The non-treated control group was composed of 44 eyes of 22 infants with stage 3 ROP. The mean GA was 27.3 weeks (±1.7) weeks and mean BW was 812 g (±86). There were equal number of males and females. Eighty-two percent (82%, $n = 18$) were Caucasian patients and the remainder (18%, $n = 4$) were of African origin. The stage 3 ROP was in zone 2 in 66% ($n = 29$) of eyes and zone 3 in 34% ($n = 15$). Twenty-five percent of eyes (25%) had five or more clock hours of disease. ROP features fully regressed in all eyes.

VA data are shown in Table 1. No patient had an unfavourable visual acuity (i.e. a VA worse than 1.00 logMAR). Nineteen percent (19%, $n = 6$) of patients were noted to have myopia at 72 months. However, 81% were hypermetropic; 75% between 0.25 and 3.00D, 6% between 3.00 and 6.00 D. No eye in the non-treated group had a spherical equivalent (SE) greater than or equal to + or −6 D. Mean astigmatism at 72 months was 1.25D (±0.60), no eyes had high astigmatism (greater than 3.00D) (Table 1). Two infants had a family history of high myopia (one of these patients had SE −1 right eye and −3 left eye at 72 months), the same infant was the only one with significant anisometropia (greater than 1.50D) at any follow up.

None of the untreated eyes developed strabismus, macular dragging, cataract, ocular hypertension, retinal detachment, ambylopia or needed for further surgery. All cases had documented binocularity recorded on orthoptic tests.

Infants treated with Diode laser

The treated group composed of 42 eyes of 21 infants. The mean GA was 26.40 (±2.5) weeks and mean BW was 804 g (±135). Mean post conceptual age (PCA) at first laser treatment was 37 weeks. Thirty-three percent (33%, $n = 7$) were male. Ninety-one percent (91 %) ($n = 19$) were Caucasian and 9% ($n = 2$) were Asian.

Severity of ROP at treatment was zone 1 (Z1) in 12% of eyes and zone 2 (Z2) in 88% of eyes and stage 3 disease in 100%. Five or more clock hours of disease in 57% with plus disease in 100%. When reclassified posterior zone 2 (PZ2) + Z1 = 36%, and remaining Anterior (AZ2) cases = 74%. All ROP features regressed after laser treatment. None of the eyes required re-treatment.

Visual acuity (VA) data are presented in Table 1. No patient had an unfavourable VA (i.e. VA worse than 1.00 LogMAR). Fifty percent (50%) of eyes were myopic at 72 months, 31% between 0.25 and 3D, 0% between 3 and 6 D and 19% had myopia greater than 6D. One eye was emmetropic (4%), 46% eyes were hypermetropic with 40% between 0.25 and 3D, 2% were between 3 and 6D. A higher myopic refractive error (greater than −4 D or −6 D) at 60 and 72 months was associated with a less favourable visual outcome (VA less than or equal to 0.3 logMAR) ($P = 0.02$). Patients with disease in Zone 1 had a higher mean level of

Table 1 All factors between infants not requiring treatment and those treated reached statistical significance ($P < 0.05$)

	Time-point (months)	Infants not requiring treatment	Infants treated with Diode laser
Mean VA	60 m	0.102 logMAR (± 0.08)	0.238 logMAR (±0.15)
Mean VA	72 m	0.070 logMAR (± 0.05)	0.252 logMAR (±0.17)
VA better than or equal to 0.3 logMAR	24 m	94% ($n = 34$ eyes)	75% ($n = 28$ eyes)
VA better than or equal to 0.3 logMAR	48 m	94% ($n = 36$ eyes)	84% ($n = 32$ eyes)
VA better than or equal to 0.3 logMAR	72 m	100% ($n = 26$ eyes)	72% ($n = 32$ eyes).
Greater than 1.00 D cylinder	24 m	38% (34 eyes)	39% (28 eyes)
Greater than 1.00 D cylinder	48 m	28% (36 eyes)	46% (32 eyes)
Greater than 1.00 D cylinder	72 m	33% (26 eyes)	42% (32 eyes)
Mean SE	60 m	+0.163 (± 1.348)	−2.040 (±4.460)
Mean SE	72 m	+2.040 (± 0.900)	−2.230 (±4.059)

VA visual acuity

myopia −4.90 in contrast to zone 2 disease −3.36, this did not reach statistical significance ($P = 0.310$). For PZ2 + Z1 refractive error was −4.40, versus remainder of AZ2 this was +0.90 ($P = 0.01$).

The mean number of laser burns applied for all eyes were 1855 (±659). The mean proportion of retinal area treatment as quantified using CAD was 45% (±10) in all groups. The proportion of retina area treated and the laser burns were strongly correlated (0.68, $P = 0.02$). A greater number of laser burns and a larger treatment area were both associated with a greater degree of myopia at 60 and 72 months ($P < 0.05$). Laser burns in those developing myopia was 2199 (±634) and 1603 (±510) hypermetropia ($P < 0.05$). Those developing myopia had a mean treatment area of 49% (±13) versus 43% (±10) hypermetropia and 42 (±5) emmetropia ($P = 0.03$). There was no statistically significant association between the number of laser burns or the area of treatment and eyes developing an astigmatic error greater than 1 D ($P = 0.20$).

A larger treatment area was associated with a greater level of myopia (SE) greater than −4 and −6 D (SE greater than −4 D, $P < 0.005$) and (SE greater than −6 D, $P = 0.02$). Only low levels of hypermetropia were noted in the treated group, with no eye having more than +4 D. No statistical significance was found between the amount of laser burns/area of retina treated and hypermetropia of any level ($P = 0.24$).

Mean astigmatism at 72 months was 1.22 D (±1.35), 10% ($n = 2$) had greater than 3.00 D of astigmatism (see Table 1). This was with-the-rule in 70% ($n = 21$) eyes, the remainder was against the rule. Significant (≥1.00 D) anisometropia was present in 68% at 72 months. The mean VA in the eyes with significant anisometropia was 0.303 logMAR (±0.196), which was worse than those without it 0.196 logMAR (±0.782) ($P = 0.03$). For the eyes developing a higher level of significant anisometropia (≥3.00 D), a greater number of laser burns mean 2358 (±988) was used in the eye developing the larger myopic refractive error versus mean of 2204 (±436) to the fellow eye with the smaller refractive error ($P = 0.02$). Overall infants who did not develop significant anisometropia (≥1.00 D) received fewer laser burns to their eyes with a mean of 1822 (±438) as compared with 2326 (±944) shots in the infants who did ($P < 0.005$).

A higher number of eyes had significant anisometropia in the eyes where a higher mean proportion of retinal area was treated 55% (±14) versus the eyes which did not, mean 50% (±4.9), ($P = 0.04$). In the same group with significant anisometropia a larger mean proportion of retinal laser area, of 43% (±12) resulted in higher levels of myopia −7.53, versus a mean of 30% (± 5) treated proportion, which resulted in a mean −4.75 ($P = 0.003$).

Complications noted were strabismus in 10% (two infants) and binocularity was absent in 14% (three infants). Amblyopia was recorded in 5% (two eyes). One eye (2%) developed macular dragging, VA was 0.65 logMAR in this eye. Overall the presence of any complication was not statistically associated with a VA <0.3 logMAR ($P = 0.68$). One eye (2%) required further surgery for strabismus.

Discussion

Our study has found myopia to be more prevalent in infants treated for ROP. Seventy-two percent of eyes had a VA better than or equal to 0.3 logMAR at 72 months. These findings although encouraging still alert us that a small number do not achieve good vision. A higher refractive error (greater than −4.00 or −6.00 D) at 72 months was associated with a worse visual outcome.

Eyes developing a higher refractive error and significant anisometropia received the highest number of laser burns than the eyes without significant anisometropia, which received half as many laser burns. These findings were confirmed when CAD was used to assess the proportion of area treated, with a higher treatment area associated with a greater degree of anisometropia. The higher amount of ametropia was in the eye receiving the largest area of treatment. Most importantly the mean VA in the eyes with significant anisometropia was worse than those without.

In our study the rate of myopia in the treated eyes was 50%, the mean SE at 72 months was −2.230 (±4.059). Myopia following both cryotherapy and laser ablation for ROP has been confirmed in various studies [1, 2, 4, 5]. Studies have shown poorer VA outcomes (VA worse than 6/60) with myopia [6]. The rates of myopia in ROP laser treated eyes have been reported to be 50–77% [6–9]. In one study from Saudi Arabia the rates of myopia greater than 6 D was 16.7–28.9% with strabismus present in 30% [7]. McLoone found 35% had greater than 4.00 D of myopia after laser for ROP [8]. Mean myopia has been reported as −3.70 D at 5.2 years, −3.87 at 7.8 years, −2.87 at 5 years after ROP treatment in various studies [6, 7, 10]. Our findings are in keeping with the literature; however, we demonstrate that this is associated with the area of retina treated and absolute laser burns applied.

Severe complications following laser were rare in our study. Strabismus surgery was required in one infant. Binocularity was absent in 14% of patients. One eye developed macular dragging and had the worst recorded VA from of 0.65 logMAR. In one study from the literature the levels of unfavourable visual outcomes (defined as VA 6/60 or worse) following laser treatment were reported in as many as 6.9% of eyes other studies showed 21.1% of eyes achieved a V/A of 6/12 [7].

Laws et al. found posterior disease to be related to more severe levels of myopia, in this study the numbers were also too small to draw specific conclusions about the eyes with posterior disease [5]. We found infants with disease in Z1

had a higher level of myopia −4.90 in contrast to Z2 disease −3.39, this finding did not reach statistical significance, which is likely due to the few patients with disease in Zone 1 in our study. However, when disease was reclassified there were higher levels of myopia in PZ2 + Z1 versus AZ2, this reached statistical significance.

We found mean astigmatism at 72 months was 1.22 D for treated eyes, 42% with 1.00 D or more and 10% greater than 3.00 D of astigmatism. None of the cases had a purely cylindrical anisometropia. Studies reporting levels of astigmatism greater than 1.00 D after laser ROP treatment has ranged from 50% at 12 months, to 43% at 3 years [5, 11, 12]. Mean astigmatism was 1.60 D at 12 months and 2.96 ± 1.58 D in another study, with 35% having greater than 3 D of astigmatism [5, 6]. The ETROP study found that by age 6 years, 50% of eyes treated at high-risk prethreshold ROP developed astigmatism ≥1.00 D and 25% had astigmatism ≥2.00 D [12, 13]. Other studies have shown laser-treated eyes developing a mean astigmatism of 3.47 D, and SE of −4.49 D. In the same study 46 eyes (98%) had astigmatism ≥0.5 D and 50% had high astigmatism (≥3.00 D) [14].

It is clear that anisometropia is an important factor in these infants. Anisometropia has been shown to be a significant risk factor for a VA of 6/15 or worse in laser treated eyes ($P = 0.002$) [6]. A study found the rate of cylindrical anisometropia to be 4% and spherical anisometropia 8% after ROP laser [15]. Other studies reported that anisometropic amblyopia is increased in eyes with spherical anisometropia greater than or equal to 2.00 D and cylindrical anisometropia greater than or equal to 1.50 D [16].

Our study is the first to report refractive and visual outcomes by quantifying laser burns applied and the proportion of retina area treated using CAD. Using the CAD model adds accuracy for determining the proportion of retina treated with laser. It does not account for any Islands of normal retina within the enclosed area, this could be ignored as the retinal photos from infants after treatment show the area of treatment always becomes confluent.

Limitations of this study include its retrospective design. We have used a GA and BW matched control group that was not treated for comparison. The group confirmed a much higher rate of hypermetropia than the treated group. Myopia of prematurity exhibits a relatively highly curved cornea, shallow anterior chamber and thicker lens [12]. We do not routinely measure infants AL and therefore cannot make conclusions about the area treated or untreated in relation to the size of the eyes or above factors in the infants. We also did not routinely collect keratometry, anterior chamber depth readings. Studies have found higher and steeper keratometric values in pre-term ROP infants [17]. These factors might be important in the unexpected refractive findings e.g. the hypermetropic eyes that received laser. We propose future studies that consider these when analysing post treatment refractive errors in infants.

Our study has shown that myopia is of higher magnitude if a greater number of laser burns are applied and or a greater proportion of retinal area is treated. The severity of myopia may be related to the area of avascularity and hence the number of laser burns it therefore may be a reflection of retinal immaturity. However, we did not measure this in aged matched infants with ROP who did not have treatment. It is acknowledged that as this is a retrospective study the area of avascularity was not measured in these infants.

We advocate further research into methods for titrating laser treatment in ROP. With the advent of AntiVEGF treatment, further research should be looking to answer if combined therapy reduces the quantity of laser required [18, 19]. Using CAD offers a novel approach for estimating the area of retina treated with laser and correlates to the treatment area.

Highlights

What was known before

- ROP laser results in myopia and astigmatism. High refractive error and anisometropia are risk factors for poorer visual outcomes.

What this study adds

- Quantifying the ROP laser shows a greater amount of laser results in greater myopia. This was not the case for hypermetropia. A larger amount of laser delivered is associated with a higher degree of anisometropia, ametropia. Eyes without significant anisometropia received half as many laser burns.

Compliance with ethical standards

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

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