Retinopathy of prematurity treatment in the South West of England: long-term outcomes 1997-2008

BY ANNA PANG, JON PARK, ANTHONY QUINN AND ROLAND LING

Retinopathy of prematurity (ROP) is a condition that affects the developing retinal vascular system of pre-term babies. If left untreated, ROP can lead to severe visual impairment. The severe visual impairment caused by untreated ROP can be prevented by screening 'at risk' infants in order to identify those who have developed ROP at an early stage to faciliate prompt retinal ablative treatment to drastically reduce the risk of further ROP progression.

ROP is classified by severity (stages 0-5), location (Zone I-III), the extent of retinal involvement (clock hours), and by the presence of 'plus' disease. Stages 1 and 2 without plus disease will resolve spontaneously and are thus considered mild stages of severity, not requiring intervention [1]. Stages 4 and 5 are characterised by retinal detachment and at this point even with surgical intervention prognosis is poor. It is therefore important to identify infants with stage 3 ROP who warrant prompt retinal ablation to prevent progression to sight-threatening stage 4 or 5 disease.

The Cryotherapy for Retinopathy of Prematurity study (CRYROP) coined the term, 'threshold' ROP [2]. Threshold ROP is the stage at which infants have approximately a 50% risk of retinal detachment, and if treated at this stage, retinal detachment risk is reduced by approximately 50%. Threshold ROP was considered to be Stage 3 ROP disease within Zone I and II in the presence of plus disease of five contiguous or eight non-contiguous clock hours. Until 2004, threshold ROP was the recommended level for retinal ablation therapy. The Early Treatment of Retinopathy of Prematurity (ETROP) study sought to identify the outcomes of earlier versus standard intervention and thus established a randomised control trial comparing the outcomes of treatment at 'pre-threshold ROP' versus 'threshold ROP' [3]. Pre-threshold ROP was defined as any ROP in zone I with plus disease, stage 3 in zone I without plus disease, and stage 2 or 3 disease in zone II with plus disease. The study found that early treatment of high risk prethreshold ROP significantly reduced unfavourable outcomes in both primary (visual) and secondary (structural) measures [3,4].

Not uncommonly, neonates from regional centres who fulfil criteria for treatment, in the absence of centres with the ability to undertake treatment close by, will require transfer to a distant tertiary referral centre. This need for distant transfer will often delay treatment beyond the 48 hour period that is recommended by the International Committee for the Classification of Retinopathy of Prematurity, as supported by the UK Royal college of Ophthalmologists 2008 Guidelines [1]. The ROP service at the West of England Eye Unit, Exeter was founded in 1997, and is based at what was a district general hospital until 2000, when it became a teaching hospital of the Penisula Medical School (Royal Devon and Exeter Hospital). It provides ROP retinal ablation treatment for the far South West of England, encompassing hospitals in Devon, Cornwall and West Somerset. A very important benefit of a regional service is the ability to treat promptly (within a 24 to 48 hour period) from the time at which diagnosis of pre-threshold ROP has been made, and hopefully avoids the complications that may arise from a delay in treatment.

The aim of this study was to identify whether our regional experience, over a ten year period (1997 to 2008) compares favourably to standards established by the Royal College of Ophthalmology ROP guidelines. It also aimed to compare our long-term outcomes (at least four years) with the ETROP study [3,4]. Thirdly, the study examined whether or not demographic factors for infants requiring treatment (such as early postnatal weight gain) could be used to identify those screened requiring treatment in accordance with the WINROP algorithm [5,6]. The project also assessed the safety of the service, since the infants in this cohort are the youngest patients in our hospital to receive general anaesthesia.

Table 1: Royal College of Ophthalmology guidelines for the Treatment of Retinopathy of Prematurity (2008) [1].

Treatment indicated	Zone I, any ROP with plus Zone I, stage 3 without plus disease Zone II; stage 3 with plus disease
Treatment should be considered	Zone II, stage 2 with plus disease
Time from diagnosis to treatment	48 Hours
Treatment modality	Transpupillary diode laser therapy first line (argon laser second line)
Treating surgeon	Babies with ROP should be treated by ophthalmologists who have appropriate competency

Materials and methods

The medical notes of infants treated for ROP between 1997 and 2008 were identified through a PLATO search using the following key terms: age less than six months, retinal ablation therapy, laser, retinopathy of prematurity, eye day

case unit. The results from this PLATO search were then cross-referenced with ROP logbooks obtained from the neo-natal unit, although such logbooks from January 2002 to March 2009 were unavailable.

The medical notes were retrospectively reviewed and demographic and peri-natal features were recorded (gestational age, birth weight, gender, multiple birth, medical comorbidities and serial weight gain).

Features related to ROP diagnosis and treatment were identified from ophthalmology notes or referral letters (when externally referred) including: ROP stage, zone and extent at diagnosis, age at diagnosis, time from diagnosis to treatment, type and duration of treatment, complications (ocular and anaesthetic / systemic) and the grade of the treating surgeon and anaesthetist.

Treatment outcomes for these treated infants at four or more years were recorded (long-term outcomes included visual acuity, refractive error, structural outcomes and presence of strabismus). For infants who had been referred from external sources, the lead paediatric ophthalmologists from these services were contacted to identify treatment outcomes from patient notes.

The study findings with respect to treatment criteria were compared to the current Royal College of Ophthalmology guidelines for the Treatment of Retinopathy of Prematurity, 2008 (see Table 1), which applied to all babies treated after 2006. Prior to 2006 comparison was made relative to the existing College Guidelines at that time which were formulated in 1995 [7]. For babies treated prior to 2006, the 1995 guidelines stipulate treatment at 'threshold disease', i.e. stage 3, five or more contiguous or eight or more non-contiguous clock hours, with plus disease. The recommended treatment modality was cryotherapy or laser (argon or diode), and such treatment should occur within three days.

The treatment outcomes (structural and functional) and standards for safety for this study were compared with the ETROP outcomes [3,4].

Serial weight gain, when available, was entered into the WINROP algorithm (designed by premAcure) [5,6], which would stipulate whether an 'alarm' would have been designated to the infant indicating risk for developing pre-threshold ROP.

Results

ROP diagnosis and treatment

Table 2: Demographic data and medical co-morbidity.

Number of infants	22
Number of eyes treated	43 (21 infants bilateral, 1 infant unilateral)
Gender	14 male, 8 female
Number of infants as part of a multiple pregnancy	8 (7 twin, 1 triplet)
Mean gestational age	25.25 weeks (range 23 weeks to 28 weeks and 2 days)
Mean birth weight	758 grams (range 490 to 1260 grams)
Medical co-morbidity	Sepsis (n=11), chronic lung disease (n=9), respiratory distress syndrome (n=8), patent ductus arteriosis (n=8), intra ventricular haemorrhage (n=4), necrotising enterocolitis (n=2), inguinal hernia (n=2), anaemia (n=2), cerebral palsy (n=1) and cerebral visual impairment (n=1)

Table 3: Long-term functional and structural outcomes at four years (with comparison to ETROP [4] where applicable).

Number with long-term follow-up	19 patients (37 eyes) at 4 years
Favourable visual acuity (better than 6/60)	100% (compared to 75.3% in ETROP)
Normal visual acuity (better than 6/12)	70.3% (compared to 34.6% in ETROP)
Average refractive error	Spherical equivalent of minus 0.75 dioptres (range minus 10.5DS to plus 2.75DS)
Average astigmatism	0.65 dioptres (range 0.5 to 1.75)
Unfavourable structural outcome	2 eyes (5.4%) with macula folds and localised peripheral detachment (compared to 9.1% in ETROP). No eyes had macula-involving retinal detachment, retro-lental mass or cataract. 6 eyes (16.2%) had mild degrees of macula drag
Strabismus	11 patients (57.8%) had strabismus, although only 1 patient (5.2%) required strabismus surgery (at the age of 2 years). Forms of strabismus included esotropia (n=4), exophoria (n=3), exotropia (n=2) and oblique muscle dysfunction (n=3)

In total, 22 infants (43 eyes) were treated for ROP between 1997 and 2008. Basic demographic data and medical co-morbidities are shown in Table 2.

At the time of diagnosis of treatment-requiring ROP, all 43 eyes had stage 3 disease. In 41 eyes, the stage 3 was identified in zone II and in two eyes within zone I-II. Forty-two eyes had 'plus' disease and in one eye there was 'no plus' disease. Fifteen babies (29 eyes) underwent treatment between 1997 and 2005 (diagnosed under treatment criteria at threshold disease and managed relative to College Guidelines, 1995 [7]). Seven babies (14 eyes) underwent treatment after 2006 (corresponding to a change in treatment criteria to pre-threshold disease and managed relative to College Guidelines, 2008). All eyes (100%) met the College Guidelines (either threshold or pre-threshold depending upon year of treatment) for treatment criteria.

The mean age at which ROP was diagnosed was 37 weeks gestational age (range 31 weeks to 41 weeks and six days) or 11 weeks and six days post birth. The time from diagnosis to treatment was within 24 hours (n=13), within 48 hours (n=7) and within 72 hours (n=1). There was no referral letter present in the notes of one patient and thus the date of diagnosis was unclear. All eyes underwent argon or diode laser retinal ablation to the avascular zone up to the ridge. No patient required retreatment when treatment was initially carried out by our service.

All infants were treated by consultant ophthalmologists (AGQ and RHL) who received ROP treatment training in their fellowship and subsequently regularly perform both ROP screening and

treatment. All infants received a general anaesthetic, provided by a consultant paediatric anaesthetist.

Fourteen of the 22 infants were already receiving care at the Royal Devon and Exeter Hospital (same site as West of England Eye Unit, Exeter). The remaining infants were referred and transferred for treatment from Taunton, Truro and Torbay.

Long-term treatment outcomes at four years

Three of the 22 patients were lost to follow-up at four years. For the remaining 19 patients, long-term outcomes, relative to ETROP, are shown in Table 3.

Prediction of ROP requiring treatment based on WINROP algorithm

Post-natal weight gain data was available for 17 patients. In 13 of 17 patients (76.5%), an 'alarm' would have been assigned according to the WINROP algorithm [5,6]. Four patients (23.5%) had 'no alarm' assigned.

Ocular and systemic complications during treatment

The mean duration of anaesthesia was 108 minutes (45 minutes to 225 minutes). No ocular complications were documented in any of the 43 eyes, and this compares favourably to 16.4% rate of ocular complications in the ETROP study [3,4]. Systemic / anaesthetic information was available for 19 of the 22 infants. There were no documented complications in 15 of these 19 cases. Four infants had systemic complications (26.6%), which is slightly higher than the 16.7% reported by the ETROP study [3,4]. These systemic complications consisted of two cases of bradycardia and one episode of apnoea. One infant had a difficult extubation, requiring six hours of ventilation following the procedure. These systemic complications were considered transient and not directly linked to any long-term adverse outcomes.

Discussion

This is the first study to report long-term treatment outcomes for retinal ablation therapy for ROP, provided by the Exeter regional ROP service. This service serves Devon, Cornwall and West Somerset and the treatment occurs in a regional teaching hospital in Exeter. This service review demonstrates that the service exceeds College recommended standards for treatment delivery as well as treatment outcomes (relative to landmark ETROP study) in nearly all areas.

Reassuringly, relative to the College Guidelines [1,7], all 23 treated infants met the treatment criteria for threshold disease (prior to 2006) and pre-threshold disease (from 2006). All infants were treated within the recommended College timescale (within 48 hours for 2008 College Guidelines and 72 hours for 1995 College Guidelines). Adhering to such timely treatment highlights an important advantage of our regional treatment service, which negates the need to send infants to distant tertiary centres, which can delay prompt treatment. Long distance transfer of such babies is also a logistical and clinical challenge for the neonatal units involved, so our regional paediatric colleagues and patient families welcome our service.

All infants were treated by an ophthalmologist with appropriate competency, and therefore this aspect of the College Guidelines was met.

Prior to 2006, all treated babies were treated by argon laser, which met the relevant College Guideline from 1995. After 2006, babies were treated with either diode or argon laser and the College Guidelines from 2008 now support the use of diode laser, rather than argon laser. Previously the safety and efficacy between argon and diode laser has been considered similar [8]. The shift towards diode laser was governed by a purported reduced risk of cataract formation (0.003% versus 1%) [9,10]. However, a recent study reported a 1.9% risk of cataract at six months following diode laser treatment [11]. None of the authors are aware of cataract formation following the use of either argon or diode laser in babies they have treated. However, given the more recent College Guidelines, a change to diode laser as the only treatment modality for both treating ophthalmologists has occurred.

This study's findings with respect to long-term outcomes relative to the ETROP study [3,4] are reassuringly favourable. In this study, 5.4% of eyes had an unfavourable structural outcome, relative to 9.1% of eyes in the ETROP study [4]. In this study, all eyes (100%) had a favourable visual acuity, relative to 75.3% of eyes in the ETROP study [4]. A greater proportion of eyes achieving normal visual acuity (>6/12 Snellen) was greater in our study (70.3%) than in the ETROP study (34.6%) [4].

The rate of anaesthetic complications (26.6%) was slightly higher than that documented in the ETROP study (16.7%) [4]. All complications were transient and no long-term adverse outcomes occurred. The authors are aware that general anaesthesia is not the only way in which a baby can be prepared for ROP laser. However, given the lack of serious complications over a 10-year period and fact that no babies at all required re-treatment, the authors advocate general anaesthesia as a safe way to facilitate comprehensive ROP treatment to ensure excellent visual outcomes.

The recent WINROP study has proposed that infants who will develop pre-threshold ROP requiring treatment can be detected from trends in early post-natal weight gain alone [5,6]. The study's retrospective use of the WINROP algorithm was able to use serial post-natal weight gain data to predict that 76.5% of the treated babies needed treatment. Therefore, 23.5% of treated babies would have had no 'alarm' and would not have been treated incorrectly had this been adopted in isolation. With current College Guidelines relating to ROP screening, only approximately 10% of babies screened need treatment. This implies that approximately 90% of babies are unnecessarily examined, which is a drain on resources and is transiently uncomfortable and potentially clinically upsetting for these delicate infants. Hopefully, in the future, adoption of algorithms such as the WINROP algorithm will allow fewer babies to be screened, whilst still safely detecting all babies that need treatment.

There is increasing pressure to centralise ROP services and to transfer patients requiring ROP treatment greater distances to tertiary centres [12]. Indeed, certain groups in the past have advocated treatment services covering larger geographical populations [13]. However, this would seem unnecessary if a regional teaching hospital can demonstrate excellent care. It is important to consider the benefits of a regional teaching hospital providing excellent care for ROP. Firstly, timely delivery of treatment enabled by a centre geographically closer to the site of referral is critical for long-term visual and functional outcomes. Secondly, the convenience for families having to travel shorter distances cannot be undervalued. Thirdly, transferring an infant long distances generates both logistical and clinical challenges for neonatal units and this challenge is reduced by a more local service.

One of the limitations of this study is the retrospective nature of the methodology combined with the loss of some neonatal ROP logbooks. The study number of treated infants is therefore likely to be smaller than the actual number due to potentially missed cases.

Our centre is now prospectively reporting all treated ROP cases to the national study group based at Moorfields, in association with the British Ophthalmic Surveillance Unit (BOSU). This landmark prospective study will hopefully further demonstrate the level of care for ROP in the UK, and allow a benchmark audit standard that regional centres such as ours can compare to.

In summary, this study provides reassuring data that infants in the South West of England are receiving timely treatment for ROP and this is associated with excellent long-term outcomes. Such a regional service based at a relatively local teaching hospital negates the need to send infants long distances to a tertiary centre. This localised treatment ensures vital timely treatment, excellent visual long-term outcomes and relatively minimal disruption to the neonatal teams involved, families and, of course, the infants themselves.

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AUDIT-BASED RECOMMENDATIONS:

- Screening and treatment for ROP can be conducted safely in regional areas provided that ophthalmologists experienced in the screening and treatment of ROP carry out the service. This can reduce the need to transfer babies to distant units, which is disruptive for the baby, family and staff.
- Favourable treatment outcomes, both structural and visual (comparable to ETROP standards) can be met if treating ophthalmologists adhere to the current guidelines for the screening and treatment of ROP (Royal College of Ophthalmologists and Royal College of Paediatrics and Child Health).
- Retinal ablative treatment in the pre-term infant can be performed safely under general anaesthesia, if carried out by experienced anaesthetic staff.
- Early serial weight gains alone are not able to predict all babies requiring ROP treatment.

Miss Anna Pang,
Paediatric Fellow,
Royal Devon and Exeter NHS Foundation Trust,
Exeter, UK.

Declaration of Competing Interests
None declared.

Mr Jon Park,
Retinal Fellow,
West of England Eye Unit,
Royal Devon and Exeter NHS Foundation Trust,
Barrack Road, Exeter,
EX2 5DW, UK.

Declaration of Competing Interests
None declared.

Mr Anthony Quinn,
Consultant Ophthalmologist (specialising in Paediatric Ophthalmology),
Royal Devon and Exeter NHS Foundation Trust,
Exeter, UK.

Declaration of Competing Interests
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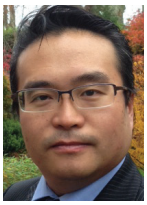

Mr Roland Ling,
Consultant Ophthalmologist (specialising in Surgical and Medical Retina),
Royal Devon and Exeter NHS Foundation Trust,
Exeter, UK.

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