Time to Regain Birth Weight - A Marker to Predict the Severity of Retinopathy of Prematurity?

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Abstract

Background: Poor weight gain in the first few weeks of life has been studied as a predictor of retinopathy of prematurity (ROP). Our aim was to assess whether time taken to regain birthweight be used as an additional marker to identify infants needing treatment for ROP.

Methods: In this retrospective study, preterm infants (<27 weeks gestational age at birth) born during the period from 1/1/2010-31/12/2015 at a level 3 neonatal intensive care unit in Australia were included. 27 cases (ROP needing treatment) were identified. Controls (ROP not needing treatment or no ROP) were matched with cases on gestational age at birth and birthweight (1:4 ratio). Data were collected from the database and medical records.

Results: The median (IQR) gestational age for cases and controls were 24 (24-26) and 25 (24-26) weeks respectively and median (IQR) birthweight for cases and controls were 675 (635-810) and 773 (666-884) grams respectively. Cases were more likely to be intra uterine growth restricted (18.5% vs 3.7%, $p=0.015$) and had increased weeks on oxygen (median 11.9 vs 9.1, $p=0.028$). Median (IQR) time to regain birth weight in cases and controls were 9 (6-13) and 7 (5-10) days respectively. Time to regain birthweight approached statistical significance when adjusted for duration of oxygen (aOR 1.08, 95% CI 1.00-1.17, $p=0.054$). The area under the curve from the time to regain BW ROC analysis with adjustment for IUGR and duration of oxygen was 0.73 (95% CI 0.62-0.83).

Conclusion: Time to regain BW has potential to aid prediction of ROP needing treatment.

Introduction

Retinopathy of prematurity (ROP) is a retinal neovascular disease seen in the low birthweight preterm infants [1]. Severe forms of ROP can lead to retinal detachment and blindness if not identified and treated at the right time [2]. ROP is one of the major causes of childhood blindness, in both developed and developing countries [3]. Improved survival of preterm infants and perinatal services has led to an increased incidence of severe ROP [3].

The aetiopathogenesis is complex and multifactorial. Arrest of the normal retinal vascular development is followed by an abnormal compensatory vascularization which leads to ROP. In phase 1 of ROP development, hyperoxia and loss of growth factors provided in utero to the fetus result in suppression of growth, and arrest of retinal vascularization. Subsequently, in phase 2, hypoxia causes stimulation of growth factor induced vasoproliferation in the increasing metabolically active, poorly vascularized retina [4].

These two phases result from alteration in levels of insulin like growth factor (IGF)-1 and vascular endothelial growth factor (VEGF) [5]. IGF-1 is needed for normal retinal vascularization [6–9] and it also influences VEGF- induced retinal vascular growth [7, 10]. Low IGF-1 following preterm birth due to loss from maternal sources and poor endogenous production [6, 11–13] impedes retinal vessel development.

IGF-1 is regulated by calorie and protein intake [14]. Endogenous production of IGF-1 increases with age and size allowing VEGF activity, and proliferative retinopathy develops [15].

Prenatal factors such as premature placental dysfunction increase the risk of ROP in preterm infants following postnatal exposure to risk factors [16]. Low gestational age (GA) [17] and birthweight (BW) [18] are major risk factors for ROP. Excessive supplemental oxygen, sepsis, necrotizing enterocolitis, intraventricular hemorrhage, anemia, apnea, and blood transfusion have been described as risk factors for ROP and have been hypothesized to act by lowering serum IGF-1 levels [15].

The association between low IGF-1 and poor postnatal weight gain in the development of ROP has been shown by the research work of Smith, Hellstorm et al which have led to the use of postnatal growth as a surrogate measure for serum IGF-1 [19, 20]. Algorithms based on postnatal weight gain (WINROP, CHOP ROP, ROP score) have shown variable sensitivity in detecting infants at risk of developing ROP in different populations. These algorithms have the potential to reduce the number of eye examinations for ROP [15].

The risk of developing ROP has been shown to be associated with poor weight gain in the first few weeks of life. Extreme preterm infants are vulnerable to have low energy intake during their early neonatal intensive course, which has been associated with poor weight gain in the first four weeks of life [21]. Suboptimal postnatal weight gain in the first 2 weeks of life has been found to be an independent risk factor for ROP needing treatment.

Screening infants for ROP involves repeated ophthalmologic examinations by trained ophthalmologists, which are not free from adverse event [1]. Pain, stress to infants, hypoxemic and apneic episodes and feed intolerance have been associated with ophthalmic examinations for ROP [22]. Of all the infants undergoing screening, only 10% needed treatment for ROP [23]. Our study aimed to determine whether time taken to regain BW can be used as an early additional marker for identifying infants at risk of developing ROP needing treatment.

Materials And Methods

Design and setting

A retrospective case control study in a tertiary level NICU in Australia.

Ethics approval

This study was approved by the hospital Governance Committee (GEK07622) and the institutional research screening committee.

Participants : All preterm infants (< 27 weeks gestational age at birth) admitted between January 2010 and December 2015, were enrolled for analysis. Cases were defined as preterm infants who underwent treatment for ROP. Controls defined as preterm infants who had ROP not needing treatment or no ROP. Controls were matched with cases on GA at birth and BW on a 1:4 ratio with equal distribution between

no ROP and ROP not needing treatment. Infants who had congenital anomalies or critical cardiac conditions were excluded from the study.

Data collection

The following data was collected from each infant's medical record and neonatal database using a standardized, pre-piloted data collection form.

Antenatal risk factors: Chorioamnionitis, preeclampsia, diabetes mellitus, oligohydramnios, and premature rupture of membrane, antenatal glucocorticoids

Delivery details: Place of birth, GA, BW, gender, growth status, mode of delivery and Apgar scores.

Post-delivery care: Time to regain BW, duration of mechanical ventilation and noninvasive ventilation, duration of oxygen therapy, treatment for patent ductus arteriosus, necrotizing enterocolitis, postnatal steroids, need for blood transfusion, culture positive sepsis, duration of hospital stay, presence of intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) on head scans and death before discharge were collected.

Outcomes

The primary outcome was to determine whether the 'time taken to regain BW' can be a useful marker in identifying the infants needing treatment for ROP. The secondary outcomes were to assess the effect of chorioamnionitis, blood transfusion, antenatal steroids, duration of oxygen and culture positive sepsis as risk for ROP needing treatment.

Guidelines for management of ROP in the NICU:

Screening criteria

Neonates born < 31 weeks postmenstrual age, regardless of BW and neonates with BW < 1250 grams, regardless of postmenstrual age at birth were screened for ROP. Neonates born greater than 31 weeks gestation at birth, BW > 1250g, with additional problems, were screened at the discretion of the treating Neonatologist.

The screening examination for ROP followed the guidelines proposed by American Academy

Of Ophthalmology and Pediatrics and the Association for Pediatric Ophthalmology and Strabismus. The first screening examination was performed at 30 to 31 week postmenstrual age in infants born at < 27 weeks GA and at 4-5 weeks postnatal age in infants born at 27- to 32-week GA. After the first evaluation, if the subject did not have ROP, the neonate was evaluated at 2–4 week intervals until full vascularization. If the patient had active or rapid progressive lesion, the subject was evaluated more frequently, depending on the clinical findings.

Treatment for ROP in the unit was primarily laser surgery and the treatment decisions were based on the Early Treatment ROP guidelines. Laser was performed with advanced ROP particularly stage III with Plus disease, significant pre-Plus or Aggressive Posterior ROP (AP-ROP) after review by the Ophthalmologist and treating Neonatologist. Anti VEGF treatment was used for infants who had Zone 1 disease and in infants who were unstable to undergo laser surgery.

Statistical method

Continuous data were summarized with medians, interquartile ranges (IQR) and ranges (R), and categorical data as frequency distributions. Conditional logistic regression analysis was used to univariately compare characteristics between cases and controls, and multivariable modelling to examine the effect of time to regain BW on ROP needing treatment. An assessment of potential confounders including chorioamnionitis, duration of oxygen, blood transfusion, antenatal steroids and culture positive sepsis was made using a forward selection method to avoid over-parameterization. Univariate and adjusted effects were summarized as odds ratios (OR) and adjusted OR (aOR) respectively, with 95% confidence intervals (CI). The predictive potential of time to regain birthweight on ROP needing treatment was further assessed using area under the curve (AUC) constructed from probabilities generated from the conditional logistic regression models. Time to event data, including duration of continuous positive airway pressure, mechanical ventilation, nasal high flow and oxygen were summarized using Kaplan-Meier survival estimates and compared using the log rank test, with deaths before discharge censored for analysis. IBM SPSS (version 22.0, Armonk, NY) and Cytel Studio (version 8.0, 2007) statistical software were used for data analysis. p-values < 0.05 were considered statistically significant.

Results

Twenty seven cases [Laser (n = 25), Anti VEGF (n = 2)] were matched on a 1:4 ratio with 108 controls on GA and BW. The median (IQR) GA for cases and controls were 24 (24–26) and 25 (24–26) weeks respectively, and the median (IQR) BW for cases and controls were 675 (635–810) and 773 (666–884) grams respectively. Cases were more likely to be intra uterine growth restricted (IUGR) (18.5% vs 3.7%, p = 0.015) and had increased weeks on oxygen (median 11.9 vs median 9.1, p = 0.028). Other demographic and clinical characteristics were similar between cases and controls. All cases (n = 27) and 103/108 (95.4%) controls were given blood transfusions.

Median (IQR) time to regain BW in cases and controls were 9(6–13) and 7(5–10) days respectively. On univariate analysis, there was no significant association between time to regain BW and the development of ROP needing treatment (OR 1.06, 95% CI 0.99–1.14, p = 0.108). After adjusting for duration of oxygen (aOR 1.10, 95% CI 1.02–1.18, p = 0.015), this association approached statistical significance (aOR 1.08, 95% CI 1.00–1.17, p = 0.054). This increase was still observed after additional adjustment for IUGR, the characteristic imbalanced at baseline (time to regain BW: aOR 1.08, 95% CI 1.00–1.17, p = 0.059). Other risk factors assessed in the model including chorioamnionitis, antenatal steroids and culture positive sepsis were not statistically significant (all p-values > 0.05). The AUC for the unadjusted model with time to regain birthweight was 0.60, 95% CI 0.47–0.72 and for the adjusted model with additional covariates,

oxygen duration and IUGR, was 0.73, 95% CI 0.62–0.83 demonstrating some predictive potential for ROP needing treatment.

Discussion

Our analysis of this retrospective data showed that the time to regain BW was longer in infants who needed treatment for ROP and approached statistical significance after controlling for duration of oxygen between the groups. Duration of oxygen was the only significant risk factor for ROP needing treatment when secondary outcomes were assessed. The infants in our study were extreme preterm (≤ 27 weeks PMA at birth) and had very low birth weight (≤ 1260 grams) with cases being more growth restricted.

IGF-1, a peptide and its importance in prenatal, postnatal growth and role in development of retinal vasculature has been studied extensively. Postnatal growth being a good surrogate measure of serum IGF-1 has led to development of surveillance models which use GA, BW and postnatal weight gain to identify infants at risk of developing ROP. These models are limited by their sensitivity, lack of generalizability especially in non-Caucasian populations [24].

Association between postnatal weight gain and severe ROP has been studied by multiple investigators and it is important to discuss these studies. Earlier studies looked at the postnatal growth in the first four to six weeks of life and its association with severe ROP. A prospective study of 345 preterm infants by Filho et al [25] (GA < 32 weeks, BW < 1500 grams) found that poor weight gain at 6 weeks of life was a significant risk for ROP (small and appropriate for gestational age groups) and in a different study, Filho et al [20] concluded that low weight gain by 6 weeks of age was a risk for severe ROP ($n = 317$). Further support for poor weight gain by 6 weeks of age and risk for severe ROP are supported by studies of Wallace et al [26] and Allegaert et al [27]. Studies from developing nations also have shown that decreased weight gain proportions at 4th and 6th weeks of life are risk factors for severe ROP [28, 29].

Three studies have looked at the relationship between postnatal weight gain in the first 2 weeks of life and ROP. In a prospective study by Aydemir et al [30], the infants with severe ROP had significantly lower weight gain at 2 and 4 weeks postnatal age ($P = 0.041$ and $P = 0.017$ respectively) and time to regain BW was longer in infants with severe ROP ($P = 0.003$). Culture proven sepsis, blood transfusion volume, days on mechanical ventilation and oxygen supplementation were significant risk factors in the severe ROP group [30]. Kim et al [3] compared early postnatal weight gain in association with ROP needing treatment (48 preterm infants with ROP requiring treatment vs. 163 preterm infants with no ROP or ROP requiring no treatment). On univariate analysis, time to regain BW, blood transfusions and oxygen supplement days were significantly higher in the ROP needing treatment group. They also noted that relative weight gain in the second, fourth and sixth week of life was significantly lower in the group needing treatment for ROP. On logistic regression, duration of oxygen supplementation ($FiO_2 > 0.4$) and relative weight gain in second week of life were the only significant risk factors. Vinekar A et al [24] looked at the time to regain BW in more mature preterm neonates (mean GA = 31 ± 2 weeks) in the NICU's ($n = 68$) of a developing country. The authors found that number of days to regain BW was significantly different between no ROP

vs. type 1 and no ROP vs. type 2 and type 1 vs. type 2 ($P < 0.001$). A risk stratification of their data (based on number of days taken to regain BW) showed that those who regained BW less than 10 days, 11–20 days and > 20 days had low, moderate and high risk for type 1 or 2 ROP respectively [24]. In our study, time to regain BW was longer in infants who needed treatment for ROP which is similar to observations noted in studies which have looked at early postnatal weight gain and ROP [3, 24, 30]. Further, duration of oxygen supplementation was the only secondary outcome which was statistically significant between cases and controls.

It is important to discuss growth status at birth. We found that the number of infants with IUGR was more in cases as compared to controls (18.5% vs. 3.7%, p-value: 0.015). Studies have found inconsistent results for small for gestational age (SGA) being a risk factor for severe ROP. Filho et al [25] found SGA not to be a risk factor for severe ROP, while Allegaert et al [27] reported SGA to be a risk factor for developing threshold ROP. However, a recent systematic review and meta-analysis found SGA to be associated with increased odds for severe ROP and suggested SGA to be considered in risk assessment of ROP evaluation [31].

The limitations of this study are its retrospective nature, smaller sample, lack of data on weight gain when neonates were in critical condition and weight gain after the neonate reached BW. The findings of our study can help to develop a model to identify babies who are at a lesser risk of ROP and require less frequent eye examinations. This will reduce the number of eye checks an infant has to undergo for ROP screening, and has potential to reduce health care costs on a larger scale.

Conclusion

Time to regain BW has potential to predict ROP needing treatment and further investigation is warranted. Phase 1 of the ROP pathogenesis corresponds to the time to regain BW. It is possible that the infants who needed treatment for ROP were at higher risk due to the low energy intake which possibly resulted in IGF-1 mediated vascularization arrest. More research is needed to develop a deeper understanding of the relationship between poor weight gain in the early neonatal period and developing severe ROP. Optimizing early weight gain by aggressive nutritional strategies may cause a reduction in infants with ROP needing treatment.

Table 1
Demographic and clinical characteristics

	Case (n = 27)	Control (n = 108)	p-value
Male	19 (70.4%)	61 (56.5%)	0.274
Inborn	26 (96.3%)	103 (95.4%)	1.000
IUGR	5 (18.5%)	4 (3.7%)	0.015
Chorioamnionitis	8 (29.6%)	20 (18.5%)	0.176
Antenatal steroids (complete)	18 (66.7%)	73 (68.9%)	0.927
Caesarean section	18 (66.7%)	49 (45.8%)	0.061
Apgar < 7 at 1 minute	25 (92.6%)	90 (83.3%)	0.366
Apgar < 7 at 5 minutes	9 (33.3%)	30 (27.8%)	0.725
Time to regain birthweight	9 (6–13)	7 (5–10)	0.114
PDA treated	20 (74.1%)	79 (73.1%)	1.000
NEC	1 (3.7%)	6 (5.6%)	1.000
IVH	3 (12.0%)	4 (3.8%)	0.280
PVL	1 (12.5%)	1 (2.7%)	0.720
Culture positive sepsis	9 (33.3%)	28 (25.9%)	0.439
Mechanical ventilation	26 (96.3%)	103 (95.4%)	1.000
Mechanical ventilation (days)	30.8 (8.5–44.6)	11.3 (2.2–34.4)	0.191
CPAP	27 (100%)	103 (95.4%)	0.648
CPAP (days)	44.6 (37.2–55.8)	44.8 (35.5–55.7)	0.997
Nasal high flow	16 (59.3%)	67 (62.0%)	0.958
Nasal high flow (days)	10.0 (0-19.3)	11.1 (0-18.8)	0.632
Duration of oxygen (weeks)	11.9 (7.0-17.9)	9.1 (4.0-13.4)	0.028
Postnatal steroids	2 (7.4%)	7 (6.5%)	1.000
Blood transfusion	27 (100%)	103 (95.4%)	0.622
Oxygen at 36 weeks	19 (70.4%)	64 (59.3%)	0.417

Data represents median (IQR) or number (%). IUGR-intrauterine growth restriction, CPAP-continuous positive airways pressure, PDA-patent ductus arteriosus, NEC-necrotizing enterocolitis, IVH-intraventricular hemorrhage, PVL-periventricular leukomalacia, NICU-neonatal intensive care unit.

	Case (n = 27)	Control (n = 108)	p-value
Home oxygen	3 (11.1%)	8 (7.4%)	0.763
Died during NICU stay	-	2 (1.9%)	1.000
<i>Data represents median (IQR) or number (%). IUGR-intrauterine growth restriction, CPAP-continuous positive airways pressure, PDA-patent ductus arteriosus, NEC-necrotizing enterocolitis, IVH-intraventricular hemorrhage, PVL-periventricular leukomalacia, NICU-neonatal intensive care unit.</i>			

Table 2
ROP specific characteristics

Maximum stage	Case (n = 27)	Control (n = 108)	p-value
None	-	54 (50.0%)	< 0.001
I-II	5 (18.5%)	44 (40.7%)	
≥III	22 (81.5%)	10 (9.3%)	
Plus present	17 (63.0%)	1 (0.9%)	< 0.001
<i>ROP = Retinopathy of prematurity</i>			

Table 3

Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for characteristics assessed in the multivariable model

	Unadjusted OR (95% CI)	Adjusted OR# (95% CI)	p-value
Time to regain birthweight	1.06 (0.99–1.14)	1.08 (1.00-1.17)	0.054
Oxygen (weeks)	1.08 (1.01–1.17)	1.10 (1.02–1.18)	0.015
Chorioamnionitis	2.12 (0.72–6.25)	2.18 (0.68-7.00)	0.191
Antenatal steroids (complete)	0.96 (0.39–2.34)	0.83 (0.31–2.20)	0.709
Positive blood culture for sepsis	1.44 (0.57–3.60)	1.54 (0.59-4.00)	0.380
IUGR	14.44 (1.63-129.02)	9.29 (1.05–91.83)	0.055
<i># Adjusted odds ratios for chorioamnionitis, antenatal steroids and positive blood culture represent the covariate effect when fitted in the final model that included time to regain birthweight and duration of oxygen therapy.</i>			

Declarations

Ethics approval and consent to participate

This study was approved by King Edward Memorial hospital Governance Committee (GEK07622) and research screening committee. Written consent was not obtained from parents.

Consent for publication

Not applicable

Availability of data and material

The data that support the findings of this study are available from the authors upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AA: Literature search, data collection, study design, writing the first and final version of manuscript.

EN, DD: Statistical analysis, Amendment to draft and final version of manuscript.

SA, SR, AG, GL: Concept, study design, and supervision of first and final version of the manuscript.

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Figures

Figure 1

Box plot comparing time to regain birthweight on ROP needing treatment

Figure 2

ROC curve illustrating predictive potential of time to regain birthweight on ROP needing treatment