

Management of Severe Retinopathy of Prematurity in Jaffna

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Abstract

Introduction and objectives: Treatment of Retinopathy of Prematurity (ROP) is revolutionised by the use of Anti-Vascular Endothelial Growth Factor agents over the last decade. This study describes the results of the treatment in the newest paediatric ophthalmology unit in Sri Lanka-Teaching hospital, Jaffna. **Methods:** Retrospective analysis of the ROP screening and treatment data at the paediatric ophthalmology unit at teaching hospital was carried out. All the screening and treatment sessions were carried out under topical anaesthesia. Out of the 118 babies who underwent screening examinations, 12 babies had severe ROP requiring treatment with intravitreal injection of Bevacizumab. In conclusion intravitreal injection of Bevacizumab is very successful in managing severe Zone 1 and Zone 2 ROP although prolonged follow up is mandatory to detect recurrences of ROP.

(Key Words: Retinopathy of prematurity, Bevacizumab, childhood blindness)

Introduction

Retinopathy of Prematurity (ROP) is an important cause of blindness in both developing and developed countries. This condition occurs in the developing retina of the premature infant. With improved care and modern screening and management protocols the blindness is very rare in high income countries. (1) Prematurity can be defined according to the gestational age and the birth weight. Infants who

suffer from meningitis, septicaemia and respiratory distress needing prolonged oxygen therapy are more at risk of developing severe disease.

ROP is a progressive condition where it begins as a demarcation between the vascular and avascular retina. This is known as Stage 1 ROP. (2) Stage 2 is a three dimensional ridge when exudation occurs to the demarcation. Stage 3 is manifested by extra retinal vasoproliferation (Figure 1). This is the ideal stage to treat. (3,7). Stage 4 and 5 are various degrees of retinal detachment which has poor prognosis even if treated.

Retina is divided into three zones to describe the locality of the condition (Figure 1). Zone 1 is a circle centred around the optic disc with a radius of twice the disc-macula distance. Zone 2 is also a circular area centred on the disc with a radius of the distance of disc to nasal ora-serrata. Zone 3 is a crescent shaped area of the peripheral retina in the temporal side. ROP in Zone 1 and adjacent Zone 2 (posterior Zone 2) has the potential of generating severe ROP which can result in retinal detachment and irreversible blindness.

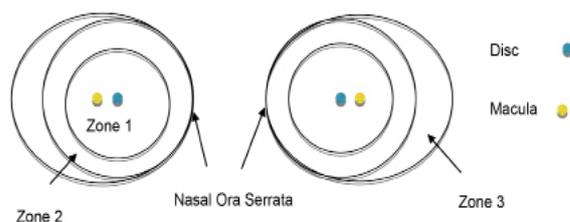
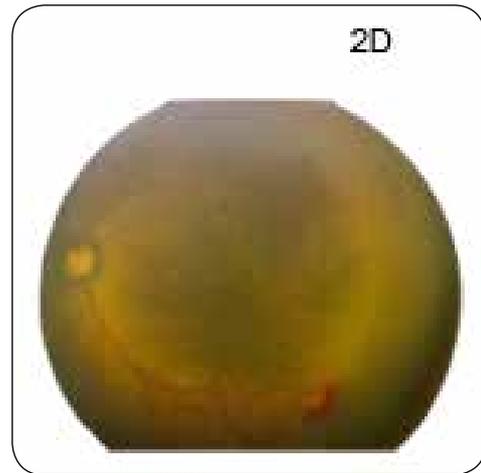
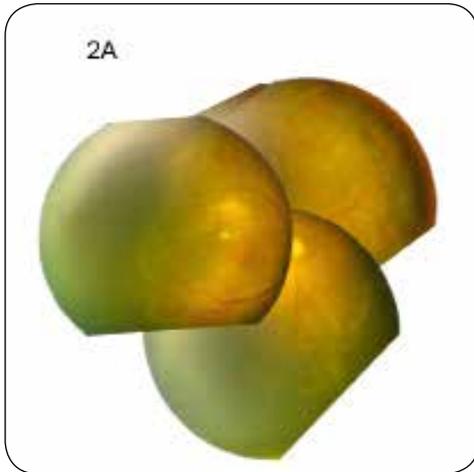


Figure 1. Zones of the retina².

Plus disease is dilatation of retinal venules and tortuosity of retinal arterioles (Figure 2).



This occurs due to arteriovenous shunting in the ridge. Presence of Plus disease is a main indicator for treatment.

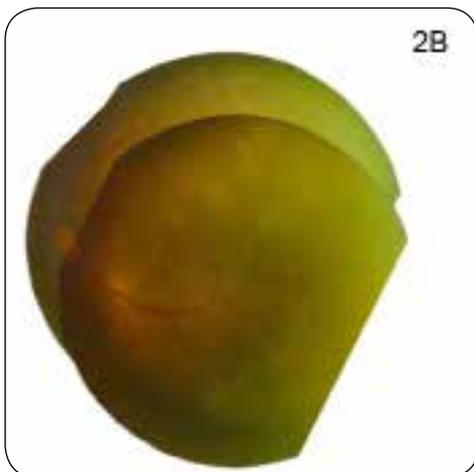
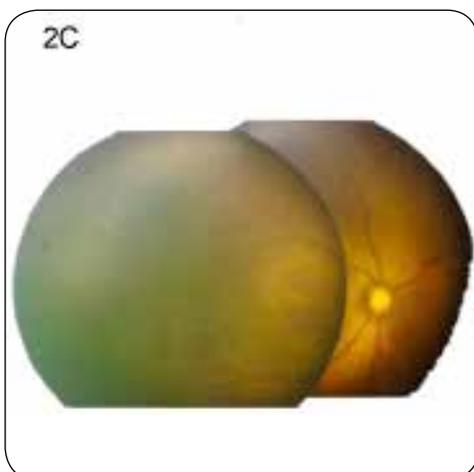


Figure 2 Zone 1 Stage 3 ROP with Plus Disease in a baby with gestational age of 28 weeks and birth weight 995g. Figure 2A: Right eye at diagnosis. Figure 2B : Left eye at diagnosis. Figure 2C: Right eye 1 week after Bevacizumab injection. Figure 2D: Left eye 1 week after Bevacizumab injection. (RETCAM Images from authors' unpublished case series from Lady Ridgeway Hospital, Colombo)



Screening for ROP in premature infants is a worldwide standard procedure. Local guidelines set by the College of Ophthalmologists of Sri Lanka advice to screen infants born at 32 weeks of gestation or below and infants with a birth weight 1500g or less. Infants who had stormy neonatal period due to illness should also be screened for ROP even if their weight is more than 1500g or gestational age is more than 32 weeks. The first screening examination should be done at 3 - 4 weeks post natal.

ROP occurs in two phases. Firstly, there is vaso-obliteration leading to hypoxia of the non-perfused avascular retina, followed by the second stage hallmarked by retinal neovascularization. This can lead to tractional retinal detachment resulting in irreversible blindness. (4)

First ever multi centre randomised clinical trial CRYO - ROP was carried out in the United States in the 1980's. This trial demonstrated superior anatomical and visual outcome from Cryopexy of

the avascular part of the retina than from observation of the babies who developed threshold ROP. (5) In late 1990's Early Treatment for ROP (ETROP) study carried out and demonstrated treatment for pre-threshold ROP with Laser ablation of the peripheral retina is superior to Cryopexy. But the laser treatment has its own complications such as induction of very high myopia, loss of visual field and glaucoma.

With better understanding of the pathophysiology of ROP, role of Vascular Endothelial Growth Factor (VEGF) was brought into frontier of the management of ROP. Bevacizumab is an anti VEGF recombinant humanised monoclonal antibody with off label use in other retinal conditions such as diabetic retinopathy and age related macular degeneration for many years. (6) Use of Bevacizumab injection into the vitreous cavity in ROP was analysed systematically in the BEAT-ROP (Becavizumab Eliminates Angiogenic Threat in ROP) in 2010. (7) This multi centre randomised control trial demonstrated Bevacizumab injection has superior anatomical and visual outcome compared to conventional Laser therapy. Injection of 0.625mg of Bevacizumab in to the vitreous cavity of an infant with significant ROP is the gold-standard therapy at present.

Paediatric ophthalmology services to the northern province of the country was available from 2017. Before 2017, the practice was to transfer the babies with severe ROP to Kandy or Colombo for further management. With the appointment of a consultant paediatric ophthalmologist to the Teaching Hospital, Jaffna the management of all the ROP cases were carried out locally. Aim of this study is to describe the success of the ROP screening and treatment in Teaching Hospital, Jaffna.

Methods

Premature babies were referred by the neonatal intensive care unit (NICU) according to the above described criteria. Babies who were in NICU were seen in the incubator in house and after the discharge from NICU they were seen as out patients in the eye clinic. Pupils were dilated with Tropicamide 0.8% + Phenylephrine 5% solution

applied 2-3 times. After installing Proparacaine 0.5% topical anaesthetic drops, a paediatric lid speculum was placed. Indirect ophthalmoscopy was carried out with a 20D condensing lens by the consultant paediatric ophthalmologist. Findings were entered in patient clinic book and handed over to the mother of the baby with proper explanation and an information leaflet. Backup record was kept in the hospital. Table 1 outlines the indications for intravitreal Bevacizumab injection. Only Zone 3 stage 3 ROP was treated with 532nm Green Laser. All the treatment carried out under topical anaesthesia. All the babies were followed up until the retinal vasculature reach the temporal ora serrata, which is the final event of the retinal vessel development. Babies who received intravitreal injections were reviewed on day 1, day 7 and every 2 - 3 weeks until the retinal vessels reach the temporal ora serrata.

Retrospective analysis of ROP patient records from September 2017 to August 2018 was carried out.

Indications for intravitreal Bevacizumab injection
Zone 1 any ROP with Plus disease
Zone 1 Stage 3 ROP with or without Plus disease
Zone 2 Stage 3 with or without Plus disease
Zone 2 Stage 2 with Plus disease

Table 1 indications for intravitreal Bevacizumab injection

Results

A total number of 118 babies were screened for ROP at the Eye Department, Teaching Hospital, Jaffna by the Consultant Paediatric Ophthalmologist over the period of 12 months. Only 12 (10.2%) had severe ROP needing intravitreal injection of Bevacizumab. Another 4 (3.4%) had Zone 3 Stage 3 ROP treated with Laser treatment alone. 19 babies (16.1%) had milder degrees of Zone 2 and 3 ROP without plus disease. These babies did not receive any treatment and spontaneous regression of ROP was observed. The other 83 babies (70.3%) did not developed any stage of ROP and they were

discharged from the follow up once the retinal vasculature reached temporal ora serrata.

Out of the 12 babies with severe ROP 10 were from the NICU, Jaffna Teaching Hospital. Other two babies were transfers from Base Hospital, Kilinochchi and District General Hospital Vavuniya.

Mean gestational age for the babies who developed severe ROP was 27.6 weeks. Range for this group was 26-30 weeks and the Standard deviation was 1.56. Mean birth weight of this cohort was 958g. Range was 720 to 1500g and the standard deviation was 227.

Diagnosis of severe ROP in this group of babies was made at an average of 33.6 gestational age with a range of 32 to 35 weeks with a standard deviation of 1.15. Diagnosis of severe ROP was made at a mean gestational age of 6 weeks.

ROP Status	Number	%	Management
Severe Zone 1 and Posterior Zone 2 ROP (Table1)	12	10.2%	Intravitreal Bevacizumab injection
Zone 3 Stage 3	4	3.4%	532nm Green Laser
Spontaneous Regression	19	16.1%	Observation
No ROP	83	70.3%	Observation
Total	118	100%	

Table 2. Distribution of ROP according to the management.

These babies were followed up to a mean post-menstrual age of 55 weeks when the retinal vasculature reached temporal ora serrata. Some babies were discharged as early as 51 weeks but some needed follow up until 63 weeks (range for follow up was 51-63 weeks with a standard deviation of 4.18). Only one baby (8.3%) developed a recurrence of ROP during follow up and he was

treated with 532nm Green Laser. Recurrences requiring a second injection of Bevacizumab was not observed in this cohort. No complications such as tractional retinal detachment, endophthalmitis or cataract was noted. All the babies had retinal vascular development completed at the time of discharge. No patient had disc dragging or macular dragging. All the babies who developed severe ROP had fixation and following at the time of discharge from the follow up. No baby had nystagmus at the time of discharge. One family defaulted follow up at 45 weeks of PMA but was able to communicate and get back to the follow up schedule.

Babies who never developed ROP and babies with spontaneously regressed ROP were analysed together. They were born at an average gestational age of 32 weeks. Range was 26 to 36 weeks with a standard deviation of 2.39. Their mean birth weight was 1427g with a range of 655 - 2690g and a standard deviation of 395. Babies who developed Zone 3 stage 3 ROP were excluded from analysis as management of this condition is not well described in international guidelines.

Two sample t-Test analysis was performed to find out whether the difference between the mean values of gestational age and birth weight of the two groups (the group who developed severe ROP and the group who did not develop severe ROP). The result was that the difference between the mean values of the two groups is highly statistically significant with a p value <0.001 for gestational age and the birth weight.

Discussion and conclusion

In industrialised countries, two epidemics of ROP has been described. The “first epidemic” (of blindness) occurred in the 1940s and 1950s in premature babies in the USA and Europe due to unmonitored supplemental oxygen. During this epidemic the mean birth weight of affected babies was 1370 g in the UK and 1354 g in the USA. (1)

A “second epidemic” (of acute ROP) in industrialised countries started in the 1970s, due to higher survival rates in extremely premature babies. During this era, mean birth weight of babies needing treatment for threshold disease were 759 g in UK and 763 g USA. The gestational ages of the same babies being 25.6 and 25.4 respectively.

There is a Third epidemic of ROP was described in the low and middle income countries with severe ROP observed in larger and mature babies. (1) This “third epidemic” of ROP has several explanations. Firstly, rates of preterm birth tend to be higher in low and middle income countries than in high income countries, where teenage pregnancies are common. Second, in middle income countries the proportion of women who are delivered in health care facilities is high and premature babies are, therefore, likely to be admitted to neonatal intensive care. Thirdly, rates of severe ROP are higher in premature babies in low and middle income countries suggesting that babies are being exposed to risk factors such as unmonitored oxygen which are now largely controlled in industrialised countries.

Data from current study from Jaffna shows the birth weight and gestational age of the babies who developed severe ROP are in between those values from the second epidemic of ROP and the third epidemic. More recent BEAT-ROP study in USA indicates the gestational age and the birth weight of the babies who develop severe ROP are 24 weeks and 615 g respectively. Statistical analysis shows the difference between the mean gestational age and birth weight of the study samples from BEAT-ROP and Jaffna are statistically significant (Table 3). Therefore we may be having reasons for the development of severe ROP from those reasons of industrialised countries. These reasons may be similar to the explanations given to the onset of third epidemic of ROP in the other countries of the region.

	Babies who developed Severe ROP in Jaffna	Babies who did not develop severe ROP in Jaffna	BEAT-ROP Study Sample	Second epidemic (USA) ¹
Birth Weight (g)	n=12 x=958 SD=227	n=106 x=1427 SD=395	n=33 x=615 SD=139.5	n? x=763 SD?
Gestational Age (weeks)	n=12 x=27.6 SD=1.56	n=106 x=32 SD=2.39	n=33 x=24.2 SD=1.3	n? x=25.4 SD?

Table 3: Summary of data. Current study from Jaffna, BEAT-ROP (USA) and Second epidemic of ROP in USA.

This analysis shows that a small but significant number of premature babies develop severe ROP. Bevacizumab mono-therapy for Zone 1 and Posterior Zone 2 severe ROP is a complication free method which help to preserve the anatomy of the retina. The babies who develop severe ROP are the most premature and the babies born with lowest birth weight. Accurate diagnosis, timely intervention with Bevacizumab injection and prolonged follow up are essential to achieve success in this important condition. The rate of recurrence of ROP after Bevacizumab injection was low (8.3%) and comparable to BEAT-ROP result (6%).

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