Zohari Z[1,2], Chan LY[2], R Jamalia[2], Embong Z[1]

[1]Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

[2]Department of Ophthalmology, Hospital Kuala Lumpur, Kuala Lumpur, Wilayah Persekutuan, Malaysia

*Corresponding author
Zayani Zohari
zayanizohari@gmail.com

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Aggressive Posterior ROP: Unmonitored Oxygen Therapy Contributed to Blindness in Preterm Infant – A Case Report

Abstract – A subtype of retinopathy of prematurity (ROP) with aggressive behaviour is called aggressive posterior retinopathy of prematurity (APROP), which occurs in very preterm infants. We report a case of APROP in a borderline moderate preterm baby who was resuscitated with supplemental unblended oxygen. A premature baby boy was born at 31 weeks gestational age (GA) with a birth weight of 1500 grams in a rural hospital. He was intubated at birth due to respiratory distress syndrome and received unmonitored supplemental oxygen for 5 days. ROP screening at 36 weeks GA showed features of stage 4a ROP in bilateral eyes, which progressed to stage 5 ROP at 43 weeks GA. He was diagnosed to have APROP in both eyes and was treated surgically. APROP is a rapidly progressive severe form of ROP. Our report showed that a high flow of unmonitored oxygen supply could lead to severe ROP. Thus, an earlier ROP screening may be of value in this group of infants.

Keywords – *Aggressive posterior retinopathy of prematurity, premature infant, supplemental oxygen*

1 INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder that primarily affects infants of very low birth weight (<1500 gram [g]) and very preterm (<32 weeks gestational age [GA]) [1]. Retinal vascular development begins during 16 weeks of gestation. It reaches nasal ora serata by 36 weeks of gestation and temporal ora serrata by 40 weeks of gestation. ROP results from abnormal growth of these retinal blood vessels in premature infants. The early hyperoxia stage retards the vessel's growth. Retinal hypoxia subsequently promotes anomalous vascularisation by a complex interaction between vascular endothelial growth factor (VEGF) and insulin-like growth factor I (IGF-I) [2].

A rapidly progressing type of ROP is known as "aggressive posterior retinopathy of prematurity" (APROP). The clinical characteristics set them apart from the classical ROP. If untreated, the condition might quickly advance to stage 5 ROP [3]. It is characterized by severe plus disease, flat neovascularisation in zone 1 or posterior zone 2, intraretinal shunting, retinal haemorrhages, and a rapid progression to retinal detachment [3]. Based on the International Classification of Retinopathy of Prematurity, Third Edition (ICROP3), aggressive retinopathy of prematurity may occur beyond the posterior retina [4].

APROP lead to unfavourable outcome despite early laser photocoagulation, which varies from 71% to 84% [5]. In contrast, the favourable success rate for classically staged ROP is greater than 90% [5]. APROP generally occurs in infants with extreme prematurity <28 weeks GA infants, extremely low birth weight <1000 g infants, and prolonged unmonitored oxygen therapy [5,6]. However, recent reports showed that APROP develops in heavier low birth weight ≥1500 g and moderate preterm infants >32 weeks GA, particularly in countries with limited resources [4,5]. We present a case of APROP in a newborn with a heavier low birth weight of 1500 g who was resuscitated with supplemental unblended oxygen at 31 weeks GA, the borderline between very preterm or moderately preterm.

2 CASE REPORT

A premature baby boy was born via spontaneous vaginal delivery at 31 weeks GA with a birth weight of 1500 g in a rural hospital in a small town in southwestern Sabah, Malaysia. He was intubated at birth in view of respiratory distress syndrome.

There was inadequate mechanical ventilation support at the hospital, and neonatal intensive care unit (NICU) beds were unavailable at the nearest tertiary hospital. He received unmonitored supplemental unblended oxygen for 5 days with an oxygen saturation (SpO2) target of more than 95%.

He was transported for advanced neonatal care, including invasive mechanical ventilation, at a tertiary hospital for an additional 4 days. Subsequently, he was extubated and placed on nasal continuous positive airway pressure (NCPAP) ventilation for another 4 days before weaning to room air. He underwent transfusion once for anaemia of prematurity.

ROP screening at 36 weeks GA (5 weeks after birth) showed features of stage 4a ROP in both eyes. There was a prominent dilatation and tortuosity of retinal vessels, multiple retinal haemorrhages, and fibrovascular membrane with tractional retinal detachment in zone I in the right eye. The retinal detachment surrounding the optic disc extends at around 6 and 12 o'clock in zone I (Figure 1A). The left eye showed prominent dilatation and tortuosity of retinal vessels with multiple retinal haemorrhages in zone I. There was tractional retinal detachment in zone I surrounding the optic disc extending from 10 to 2 o'clock and 5 to 8 o'clock (Figure 1B). With extensive florid vessels at the posterior retina, he was diagnosed with APROP in both eyes.

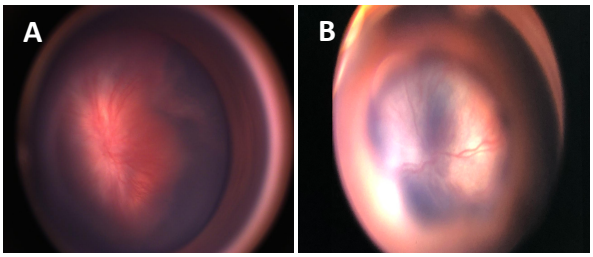

Figure 1. Fundus showed florid retinal vessels with extrafoveal retinal detachment in the right eye (A) and the left eye (B)

He underwent bilateral laser photocoagulation at the area of the flattened non-vascularised retina with weekly monitoring of the fundus. Four weeks later, at 39 weeks GA, there was iris rubeosis at 7 to 8 o'clock, vitreous haemorrhage, and tortuous vessels temporally in zone II of the right eye. The left eye showed an extension of retinal detachment inferiorly with a new vitreous haemorrhage. Repeated bilateral laser photocoagulation was performed at 39 weeks GA. At 41 weeks GA, there was a progression of ROP with an extension of fibrovascular tissue at the posterior part of the crystalline lens in both eyes. However, there was no vitreous haemorrhage. At 43 weeks GA, there were bilateral posterior capsule opacities with florid vessels and total retinal detachment in both eyes. The patient was diagnosed to have stage 5 ROP. He was transferred to the Paediatric Ophthalmology centre for further management. He underwent lensectomy, vitrectomy, and fibrosis removal with air tamponade (Figure 2) in both eyes. Postoperatively, there was partial re-attachment of the retina in both eyes.

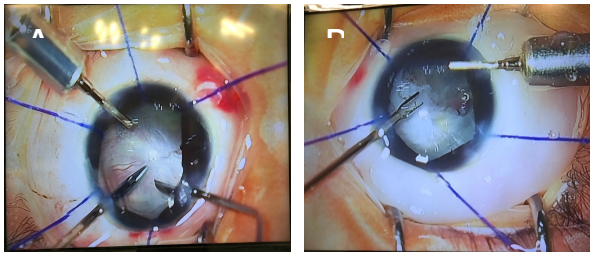

Figure 2. Intraoperative shows total retinal detachment in the right eye (A), and left eye (B) shows total retinal detachment during lensectomy

3 DISCUSSION

APROP generally occurs in extreme premature and extreme low birth weight infants [6]. Studies in Japan and India showed different predilections of infants with APROP. Developed countries in the West and Japan describe APROP in infants <30 weeks GA and <1000 g birth weight [5,6]. In a developing country like India, APROP is reported in moderate preterm infants with heavier low birth weights. In a study conducted in north India, 15.91% of infants developing APROP had a birth weight above 1500 g [7]. In our case, based on the latest ICROP3 [4], this patient may suit well into the diagnosis of advanced ROP in view of ROP occurring beyond the posterior retina and in borderline moderate preterm infants.

Other risk factors for APROP which has been reported are extreme prematurity, disruption of vasculogenesis, and a low platelet count [6]. However, these factors do not explain APROP in moderate preterm and heavier low birth weight infants. A recent study has observed supplemental unblended oxygen as one of the risks in heavier low birth weight infants developing APROP [6,8]. These infants usually had multiple comorbidities and received supplemental oxygen in a centre with poor neonatal care. Thus, early exposure to unmonitored oxygen therapy may lead to APROP

in these infants. Hartnett et al. highlight that the most important modifiable risk factor in these babies with APROP was prolonged unblended oxygen supplementation in 76.6% and ventilator dependence in 50% [9]. The hypothesis concluded that a premature infant's avascular retina becomes hypoxic once removed from high supplemental oxygen. The retinal hypoxia led to a release of angiogenic factors that caused intravitreal blood vessel growth. Since then, VEGF and other angiogenic growth factors have been essential for vascular activity in severe ROP [10].

The role of supplemental oxygen causing ROP, previously termed retrolental fibroplasia, has been studied by Terry et al. [11] since early 1940 and Campbell et al. [12] in 1950. Earlier research revealed that prolonged supplemental oxygen usage significantly increased the risk of ROP compared to restricted oxygen use, leading to fewer deaths, less respiratory failure, and decreased lung damage. Desaturation to prevent ROP was an option previously, but it increases the prevalence of cerebral palsy and death.

The American Academy of Ophthalmology's guidelines for newborn resuscitation serves as the foundation for paediatric resuscitation in Malaysia. Resuscitation started with an oxygen concentration of 21% in term and late preterm newborns >35 weeks GA. The oxygen concentration of 21% to 30% is used in preterm newborns <35 weeks GA [13]. Supplemental oxygen requires a blender to provide appropriate oxygen concentration and monitoring using a pulse oximeter sensor to maintain oxygen saturations within the target range after positive-pressure ventilation (PPV).

The oxygen saturation range varies in preterm babies and has increased based on different studies and guidelines. The European guidelines for oxygen limits have increased from 85% to 93% in 2010 to 90% to 94% in 2016 [14,15]. American Association of Paediatrics guidelines in 2012 stated that oxygen saturation in preterm babies is between 85% and 95% [14]. World Health Organization (WHO) suggests oxygen saturation in preterm babies <32 weeks GA is between 88% and 95% [16].

Few case reports have been published on uncontrolled oxygen supplementation and the outcome of ROP (Table 1). Zhou et al. reported a premature baby born at 30 weeks GA with a birth weight of 1700 g received continuous positive airway pressure (CPAP) for 26 days with a low oxygen saturation level of <40% [17]. The baby had ROP screening at 34 weeks GA and was diagnosed with stage 3 ROP in both eyes. Buksh et al. reported a premature baby born at 28 weeks GA with a birth weight of 700 g and had respiratory distress syndrome, had no ROP until 32 weeks of GA. The baby received supplemental oxygen <90% since birth until 32 weeks GA and between 90-95% at 35 weeks GA for 3 days. ROP screening showed stage 3 ROP with the plus disease at 35 weeks GA and progressed to stage 4 ROP at 37 weeks GA despite laser photocoagulation therapy [18].

Epoch I (2003-2016) and Epoch II (2010-2016) are retrospective studies done on 651 infants from 2003 to 2016, which is closest to our case study as the inclusion criteria are premature infants born at 32 weeks GA or below, with birth weight 1500 g or less [19]. In Epoch I, lower oxygen saturation was used between 88% to 92%, and Epoch II, oxygen saturation was targeted at 90 to 95% up to 99%. The incidence of ROP in Epoch I was 29.1%, and 29.3% in Epoch II. ROP progression was 11% in Epoch II, whereas only 5% in Epoch I. However, the mortality rate was 4.23% in Epoch I, and no mortality was seen in Epoch II.

There are randomized trials regarding oxygen supplementation and the outcome of ROP, such as SUPPORT [20] and BOOST II [21]. SUPPORT or Surfactant, Positive Airway Pressure, Pulse Oximetry Randomized Trial is a clinical trial to compare a range of oxygen targets between 85 to 89% and 91 to 95% in 1,316 infants born between 24 to 28 weeks GA. The study found severe ROP occurred less frequently in the lower oxygen saturation (28.3% versus [vs] 32.1%) but significantly increased mortality (19.9% vs 16.2%) [20]. The BOOST II or Benefits of Oxygen Saturation Targeting group assesses the incidence of ROP in preterm infants, comparing oxygen saturation between 85% to 89% and 91% to 95%. The study reported that the incidence of ROP is reduced in the lower oxygen saturation group (10.6% vs 13.5%). However, the death rate in infants is 23.1% in the lower oxygen saturation group compared to 15.9% in the higher oxygen level group [21].

Table 1. Reported case report and clinical studies on supplemental oxygen in preterm infants

Case Report / Clinical Study	Infant characteristics	Intervention	Outcome
Case Report Zhou et al. (2017) [17]	• GA: 30 weeks • BW: 1700 g	• ROP screening at 34 weeks GA • Received continuous CPAP with low oxygen saturation level <40% for 26 days	Stage 3 ROP
Case Report Buksh et al (2008) [18]	• GA: 28 weeks • BW: 700 g	• ROP screening at 32 weeks GA • Received supplemental oxygen <90% since birth till 32 weeks GA and between 90-95% at 35 weeks GA for 3 days	• No ROP at 32 weeks • Stage 3 ROP with plus at 35 weeks GA • Progress to stage 4A at 37 weeks GA
Clinical Study Epoch I [19] (2003-2009) Epoch II [19] (2010-2016)	• GA: ≤32 weeks • BW: <1501 g • Requiring oxygen for 1 month/ ventilation for 7 days	Epoch I (2003–2009) • Lower oxygen limit (88–92%) Epoch II (2010–2016) • Higher oxygen limit (90–95% up to 99%)	In Epoch I • ROP: 29.1%% • Mortality: 4.23% In Epoch II • ROP: 29.3% • Mortality: absent
Clinical Study SUPPORT [20] (2005-2009)	• GA: between 24 to 28 weeks	Comparing oxygen saturation: 85%-89% SaO_2 vs 91%-95% SaO_2	• Less incidence of ROP in 85%-89% SaO_2 (28.3% vs 32.1%) • Increased mortality in 85%-89% SaO_2 (19.9% vs 16.2%)
Clinical study BOOST II [21] (2006-2011)	• GA: <28 weeks	Comparing oxygen saturation: 85%-89% SaO_2 vs 91%-95% SaO_2	• Less incidence of ROP in 85%-89% SaO_2 (10.6% vs. 13.5%) • Increased mortality in 85%-89% SaO_2 (23.1% vs 15.9%)

*GA: Gestational age; BW: Birth weight; ROP: Retinopathy of prematurity; CPAP: continuous positive airway pressure

In our report, the patient needed immediate neonatal resuscitation care as he developed respiratory distress. Since he was born in a rural town hospital without the technology to blend air using a manual ventilator, the child continuously receives 100% oxygen concentration. There is also a risk of delivering breaths with a longer than desired inspiratory time if the operator does not monitor the duration of occlusion of the positive end-expiratory pressure (PEEP) cap with each breath. Thus, the risk of developing APROP was high in our patient.

Apart from prolonged unmonitored oxygen supply, other risk factors in preterm babies contributing to APROP in heavier low birth weight infants ≥1500 g include neonatal jaundice, sepsis, meningitis, respiratory distress syndrome, birth asphyxia, blood transfusion, and twin deliveries. A study in Turkey concluded that respiratory distress syndrome has a 52.3% higher risk of severe ROP in premature infants with birth weight >1500 g [22]. In our case scenario, our patient also had respiratory distress syndrome and was admitted to a hospital with an unequipped NICU backup.

Developing countries, including Malaysia, face common challenges amid the 'third epidemic' of ROP. Improvement in neonatal care facilities has increased the survival of preterm babies.

This patient underwent ROP screening following the established national clinical practice guidelines. Unfortunately, the infant showed the presence of APROP.

According to Malaysia Clinical Practise Guideline (CPG) on ROP, screening should be carried out for infants with either birth weight <1500 g or GA <32 weeks or infants with an unstable clinical course who are at high risk as determined by the neonatalogist or paediatrician. The first eye examination should be done 4 to 6 weeks after birth since a very early examination has no value if there are no signs of ROP. Infants at risk should be screened 2 to 3 weeks after birth until the retina is fully vascularised. If ROP is present in zone I, infants should be screened at least weekly because there is a high risk of disease progression. If ROP is present at zone II, the infant should be screened based on the staging. In stage 1, they are screening at 2 weekly. In stage 2, screening at 1 to 2 weekly, and in stage 3, screening at least weekly.

However, these guidelines need to be reassessed as more cases of ROP are seen in infants >1500 g with GA >32 weeks. The United Kingdom screening guidelines by the Royal College of Ophthalmologists recommend screening infants with a GA <32 weeks or a birth weight <1,501 g [23]. In China, the ROP screening guidelines recommended that infants with birth weight ≤2000 g or GA ≤34 weeks who meet the criteria to be screened [24].

The first examinations and follow-ups should be tailored individually. The screening guidelines differ considerably in countries where heavier babies with birth weight >1500 g also develop severe ROP because of poor NICU care [25]. There are no definite guidelines for screening those at risk for APROP. India guidelines recommend screening preterm infants earlier than usual, within 2 to 3 weeks after birth, rather than at 4 weeks in infants born <28 weeks GA or <1200 g to detect APROP.

In our case, based on Malaysian CPG guidelines, the recommended first ROP examination should be at 4 weeks after birth. However, in view of respiratory distress syndrome and unmonitored supplemental oxygen being given, an earlier ROP screening, such as 2 weeks after birth, may be beneficial for this patient to detect an earlier stage of ROP.

The challenges of screening ROP can be attributed to a lack of awareness and inconsistent standards of care in the growing number of NICUs and special newborn care units (SNCUs).

Lack of knowledge among doctors at district and tertiary hospitals regarding a timely diagnosis of premature infants and those with risk factors is one of the challenges. The lack of ophthalmologists at district hospitals to do ROP screening may also play a role. Delaying the screening as the infants is not stable due to medical conditions lead to delayed treatment of ROP.

4 CONCLUSION

APROP is a rapidly progressive severe form of ROP, and our case report demonstrated that a high flow of unmonitored oxygen supply could lead to APROP. We conclude that considerable ocular morbidity related to ROP can occur in heavier birth weight and moderate preterm babies. Particular geographic areas may have a different preponderance to the type of APROP progression. Future research is needed to analyze the prospective data related to the geographical area to ascertain prematurity screening criteria for ROP.

Prevention of ROP by good quality neonatal care, timely diagnosis by mandatory ROP screening in NICUs, and training doctors for laser treatment of ROP requires close collaboration between neonatologists, ophthalmologists, and policymakers. It is also crucial to upgrade NICU with more well-equipped ventilation machines and to provide medical doctors at district hospitals with yearly training in neonatal resuscitation techniques. Team approach and interdisciplinary coordination are keys to a nation's drive to fight this preventable cause of blindness. This patient underwent ROP screening following the established national CPG. Unfortunately, the infant showed the presence of APROP.

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