Rejuvenation of retinopathy of prematurity

Tracy HT Lai[1,2], MSc (Epidemiology) (Lond), FHKAM (Ophthalmology), **Paul RV Chan**[3], MD, FACS, **Kenneth KW Li**[1,2] *, FRCOphth (UK), FHKAM (Ophthalmology)

[1] *Department of Ophthalmology, United Christian Hospital and Tseung Kwan O Hospital, Hong Kong SAR, China*

[2] *Department of Ophthalmology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*

[3] *Department of Ophthalmology, University of Illinois College of Medicine, Chicago, United States*

* Corresponding author: lkw856@ha.org.hk

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In 1942, TL Terry was the first to report a condition that he termed 'retrolental fibroplasia', which developed in premature infants with low birth weight (BW)—this condition is now known as retinopathy of prematurity (ROP).[1] Insufficient retinal vasculature development can lead to abnormal blood vessel growth, typically at the junction of the peripheral vascular and avascular retina. Subsequent fibrosis onset can result in retinal detachment and fibrovascular mass formation behind the crystalline lens (ie, retrolental fibroplasia). Oxygen therapy contributes to ROP onset.[2] In the vasoconstrictive phase, oxygen can inhibit retinal vascularisation and suppress the production of vascular endothelial growth factor (VEGF). During the vasoproliferative phase, increased VEGF levels can cause neovascularisation and retinal blood vessel dilatation. Meticulous control of hyperoxia (arterial oxygen saturation >92%-93%) and avoidance of fluctuations in arterial oxygen saturation could prevent severe ROP.[3]

Appropriate treatment can protect against ROP-related blindness. Treatment largely depends on the location (zone) and severity of neovascularisation (stage), as well as a confirmed need for treatment. Historically, ROP was initially managed by avascular retina–targeted cryotherapy to reduce ischaemic drive. In the Cryotherapy for ROP (CRYO-ROP) study, adverse outcomes (retinal detachment, macula fold or retrolental mass) were reduced by almost 50% in eyes that received cryotherapy.[4] In the 2000s, laser photocoagulation largely replaced cryotherapy as conventional treatment. The Early Treatment for ROP (ETROP) trial established standard treatment recommendations for type 1 (treatment-warranted) ROP: zone II ROP, stage 2 or 3 with plus disease, and zone 1 ROP, stage 3 with or without plus disease.[5] Since then, the intravitreal injection of anti-VEGF drugs, including bevacizumab, ranibizumab, and aflibercept, has gained broad acceptance in the treatment of ROP; laser is still a popular option for primary therapy as well as rescue therapy (eg, in cases of disease reactivation and persistent avascular retina). The Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) study showed promising results when bevacizumab was used in the treatment of stage 3 ROP; the retreatment rate was 4%, compared with 22% in the laser group.[6] The ranibizumab compared with laser therapy for the treatment of infants born prematurely with ROP (RAINBOW) study also revealed excellent treatment success in 80% of infants receiving ranibizumab, compared with 66% of infants receiving laser therapy.[7] Late complications, such as high myopia (-5 dioptres or worse), were less frequent after ranibizumab (5%) than after laser therapy (16%).[8] Systemic complications did not differ between groups; the incidences of motor and hearing problems were similar.[8] However, anti-VEGF therapy is not a panacea for ROP; reactivation or delayed progression of peripheral retina vascularisation may occur after injection.[9] Therefore, recent ROP treatment guidelines from The Royal College of Ophthalmologists recommend close monitoring after anti-VEGF injection therapy.[10]

This new paradigm of ROP treatment requires an update to the classification of ROP. The International Classification of ROP, Third Edition (ICROP3) refined classification metrics such as posterior zone II, notch, and subcategorisation of stage 5; it also recognised the existence of a continuous spectrum of vascular abnormalities (ie, from normal to plus disease).[11] The term 'aggressive ROP' replaced the term 'aggressive-posterior ROP' because of increasing awareness of aggressive ROP onset in larger infants, which extends beyond the posterior retina in regions of limited resources.

Modern advances in neonatal care have greatly improved premature infant survival. However, this improvement has led to an increase in ROP incidence, especially in middle-income countries (eg, India and China).[12] In less developed countries or remote areas, telemedicine is increasingly important for ROP screening. Fundus photographs can be taken by nurses or technicians; screening can then be conducted remotely by ophthalmologists who specialise in ROP. This approach avoids the physical stress and financial cost involved in transporting high-risk infants; it also minimises screening delays. The Stanford University Network for Diagnosis of ROP (SUNDROP), a telemedicine-based screening initiative covering six satellite neonatal intensive care units in northern California of the United

States (US), has screened 608 infants over 6 years. Its screening sensitivity of 100% and specificity of 99.8% are comparable with bedside clinical examination.[13] Furthermore, the use of deep learning and federated learning for automatic diagnosis of ROP is under extensive investigation and may be important in future clinical management.[14,15] Technical, medicolegal, regulatory, and financial aspects require consideration.

Local investigators have provided valuable data regarding the incidence and visual outcomes of ROP in Hong Kong. From 2007 to 2012, the incidences of ROP and type 1 ROP were 18.5% and 3.7%, respectively, among 513 infants at Caritas Medical Centre.[16] Incidences were similar at Queen Mary Hospital in 2013 (16.9% and 3.4%, respectively).[17] However, incidences at Prince of Wales Hospital were higher (31% and 4.5%, respectively) among 754 infants from 2007 to 2012.[18] This discrepancy may be related to an increase in premature infant survival.[18] In a study of 14 infants with type 1 ROP, one (7%) developed retinal detachment, nine (64%) developed amblyopia, and nine (64%) developed strabismus.[19]

Because ROP is a leading preventable cause of childhood blindness, screening protocol adherence is essential. The 2022 United Kingdom (UK) ROP screening protocol recommends examination of all infants born at gestational age (GA) ≤31 weeks and 6 days or with BW <1501 g.[20] These thresholds differ from the US screening protocol (GA ≤30 weeks and 0 days or BW ≤1500 g).[21] Because of the GA difference, fewer infants would be screened using the US protocol. This modified screening approach would reduce stress on premature infants, limit systemic absorption of dilating eye drops, and eventually lower medical costs. Currently, most hospitals under the Hospital Authority follow the UK protocol.

In this issue of the *Hong Kong Medical Journal*, Iu et al[22] evaluated whether the use of the US protocol could reduce the number of infants screened without compromising the type 1 ROP detection sensitivity. The authors reviewed the clinical records of premature infants screened at Prince of Wales Hospital from 2009 to 2018; they found that if the US protocol had been followed, the number of infants requiring screened would have decreased by 21.1%. Using the US protocol, the investigators found that only 1.7% of cases would have been missed; all missed cases would have been mild ROP that did not require treatment.

However, conventional screening protocols have their own limitations, primarily because they are solely based on GA and BW. Many potentially unnecessary examinations are conducted to identify the approximately 20% of infants requiring treatment. To avoid unnecessary examinations, investigators are developing new screening algorithms with multiple clinical parameters (eg, postnatal weight gain and hydrocephalus status). Examples of these screening algorithms include WINROP, PINT-ROP, CHOP ROP, ROPScore, CO-ROP, OMA-ROP, G-ROP, STEP-ROP, and DIGIROP.[23,24] Various studies are underway to validate these new algorithms. The G-ROP criteria appear promising; they demonstrated greater sensitivity and specificity than the US protocol for US infants.[25] Although there is emerging evidence that up to 50% of eye examinations may be avoidable, it remains challenging to utilise the new screening algorithms in Hong Kong; postnatal weight gain is required to calculate these scores, and such data may not be readily available in our region. Until these new screening algorithms are satisfactorily validated, they are unlikely to replace conventional screening criteria. However, now may be the best time for neonatologists and ophthalmologists in Hong Kong to begin preparing for the new era of ROP by updating classification, screening, and treatment protocols.

Author contributions

All authors contributed to the editorial, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

The authors have declared no conflicts of interest.

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