Case Series

Flying baby optical coherence tomography alters the staging and management of advanced retinopathy of prematurity

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ABSTRACT. Purpose: To report the use of flying baby spectral domain optical coherence tomography (SD-OCT) on infants with advanced retinopathy of prematurity (ROP), where clinical findings alone failed to differentiate between retinoschisis and retinal detachment. Methods: Prospective, non-interventional case-series study of three premature infants with advanced ROP of clinically uncertain stage, after examination by indirect ophthalmoscopy. To confirm the diagnosis, table-mounted SD-OCT retinal imaging was performed with the infant held in the flying baby position under topical ocular anaesthesia only. Spectral domain optical coherence tomography (SD-OCT) findings were correlated with clinical examination and ultra-widefield scanning laser ophthalmoscopy to determine disease stage and appropriate management. Results: The flying baby position was well tolerated, and SD-OCT images of central and peripheral retina were successfully obtained in all three cases. Additional information provided by the SD-OCT changed the ROP staging from 3 to 4 in one case, which subsequently required surgical treatment. In two other cases, clinical suspicion of stage 4 ROP was overruled as SD-OCT revealed tractional retinoschisis rather than full-thickness retinal detachment, thereby avoiding the need for immediate surgical intervention. Conclusions: In this case-series study, flying baby SD-OCT provided a rapid and widely accessible imaging approach that overruled clinical findings and altered classification and management of infants with advanced ROP. The methodology was suitable for outpatient settings with no risks associated with systemic anaesthesia. The increased use of OCT imaging will make apparent how structural information is useful in management of ROP and may influence future classification of the disease.

Key words: OCT – ROP – tractional retinoschisis – infant – flying baby

Introduction

Retinopathy of prematurity (ROP) affects 68% of premature infants with birthweight less than 1251 g. It is characterized by immature retinal development with disrupted vascularization that in a subset of infants, progresses to fibrovascular proliferation, vitreoretinal traction and ultimately sight loss from retinal detachment (Hartnett & Penn 2012; Shah et al. 2016). Retinopathy of prematurity (ROP) screening and timely intervention with peripheral ablation of retina and more recently, intravitreal injection of antivascular endothelial growth factor (VEGF), are essential to prevent poor outcomes (Good 2004; Mintz-Hittner et al. 2011; VanderVeen et al. 2017).

Binocular indirect ophthalmoscopy with indentation remains the gold standard method for ROP screening. Over the past decade, retinal imaging techniques such as Retcam (Clarity Medical Systems, Pleasanton, CA, USA) and Optomap ultra-widefield scanning laser ophthalmoscope (Optos PLC, Dunfermline, UK) have gained popularity as more objective measures for monitoring ROP, including facilitation of telemedicine (Richter et al. 2009; Patel et al. 2013). However, image-based diagnosis of advanced ROP, and especially stage 4 and 5, remains challenging due to inability to appreciate retinal elevation on two-dimensional imaging. To this end, spectral domain optical coherence tomography (SD-
OCT) can provide highly valuable three-dimensional information (Patel 2006; Joshi et al. 2006; Chavala et al., 2009; Muni et al. 2010; Vinekar et al. 2010; Chen et al. 2019). Despite this, the use of OCT imaging in ROP remains limited due to risks associated with general anaesthesia in premature babies or the necessity to use specially adapted OCT devices that are currently only available in a few specialist centres. Herein, we investigate the use of table-mounted SD-OCT in flying baby position under topical anaesthesia in evaluating retinas of three infants with clinically equivocal stage of advanced ROP. The resulting OCT images were critical in determining the correct disease stage and formulating the appropriate management plan.

Methods

The study was conducted in accordance with the tenets of the Declaration of Helsinki at Oxford University Hospitals associated with a level-3 neonatal intensive care unit (NICU), and written informed consent was obtained for each participant. Clinical examination and ‘flying baby’ ultra-widefield ophthalmoscopy (Panoramic 200Tx System, Optos PLC, Dunfermline, Scotland, UK) were conducted post-dilation as part of the standard NICU protocol and in the presence of a specialist nurse trained in neonatal resuscitation. The eye undergoing imaging was held open with a paediatric Lieberman lid speculum (Duckworth & Kent Ltd, Baldock, Hertfordshire, UK) following topical anaesthesia (0.5% proxymetacaine hydrochloride, Bausch & Lomb, Rochester, New York, USA). The speculum was stabilized by taping its handle to the temple. The cornea was wetted with saline drops and the infant held in vertical ‘flying baby position’ (Fig. 1), with one arm supporting the chin and chest and the other hand supporting the head. The head was positioned and the eye aligned until optimal position for image acquisition by the photographers. The imaging parameters used on the Spectralis included volume scans (21 B-scans over 7.2 mm with B-scans consisting of 768 A-scans over 55 degrees or 16.3 mm) and line scans (typically 384 A-scans over 15 degrees (4.6 mm) or 768 A-scans over 30 degrees (10 mm) or 55 degrees (16.3 mm)). The procedure was repeated for the fellow eye. In our hands, image acquisition was relatively fast and took approximately 30 seconds per eye. Retinopathy of prematurity (ROP) was graded according to the modified ICROP classification.

Case 1

A male infant was born at 25 weeks postmenstrual age (PMA), weighing 770 g. Co-morbidities relating to prematurity included chronic lung disease, adrenal insufficiency and osteopenia. At 39 + 4 weeks, he was referred to the neonatal unit at Oxford University Children’s Hospital for assessment and potential treatment of stage 3 ROP. Binocular indirect ophthalmoscopy showed peripheral elevations that were suspicious of retinal detachments following Optos ultra-widefield retinal imaging (Fig. 2A and B, red arrows). Flying baby SD-OCT was thus performed showing areas of shallow subretinal fluid temporally in the right eye (Fig. 2C, blue arrows) and predominantly tractional retinal schisis in the left eye (Fig. 2D, yellow arrows) and very shallow subretinal fluid (Fig. 2D, blue arrows). Further assessment of the posterior pole demonstrated normal macula anatomy in the right eye (hence ROP stage 4a) (Fig. 2E) but shallow submacular fluid in the left eye (ROP stage 4b) (Fig. 2F–G, blue arrows). The infant underwent urgent bilateral lens-sparing vitrectomies and endolaser to relieve vitreoretinal traction and repair retinal detachments. At 2 months postsurgery, the right retina was fully re-attached with some residual dragging of the vascular arcades and a small retinal fold nasally, while the left retina had flattened with some subretinal fluid in the temporal periphery only. The condition of both retinæ remains stable under observation.

Case 2

A male infant was born at 24 + 6 PMA, weighing 800 g. His postnatal history was complicated by pulmonary haemotoma, intestinal perforation secondary to necrotizing enterocolitis, a large collection in the right lobe of the liver, right lung collapse and a haemodynamically significant patent ductus arteriosus. Standard ROP screening by indirect ophthalmoscopy was performed, and bilateral progressive ROP with plus disease (zone 1, stage 2 both

Fig. 1. Flying baby Heidelberg Spectralis spectral domain OCT. Images were acquired with the infant held in the ‘flying baby’ position with lid speculum under topical anaesthesia only. The head was stabilized by gripping the angles of the mandible and additional support to the arms, and back was provided by an assistant.
eyes) was observed at 36 weeks. The findings were confirmed by Optos ultra-widefield retinal imaging (Fig. 3A, B). The infant was treated with intravitreal injection of 0.4 mg/0.12 ml bevacizumab (Avastin, Genentech, South San Francisco, CA, USA) in both eyes and observed closely.

At 5 months of age, repeat Optos imaging showed bilaterally aberrant retinal vascularization with recurrence of plus disease and large residual areas of avascular retina temporally (Fig. 3C, D, red arrows). This was managed with repeat bilateral intravitreal injections of bevacizumab (0.4 mg/0.12 ml). At one week post-injections, indirect ophthalmoscopy detected signs of peripheral retinal elevation in the right eye, which was suspicious of retinal detachment. Further assessment using flying baby SD-OCT was performed. This demonstrated unusual schitic response without full thickness retinal detachment in the right eye (Fig. 3E-G, yellow arrows) and flat retina with epiretinal membrane in the left eye (Fig. 3H, I, green arrow). In view of recurrence of peripheral ROP with extraretinal neovascularization, bilateral diode laser photocoagulation of the avascular retina was performed. At the most recent follow-up at 10 months of age, the infant showed good visual behaviour, no nystagmus and flat retina by indirect ophthalmoscopy.

**Case 3**

A female infant was referred to the Oxford University Children’s Hospital at 39 weeks of PMA due to bilateral ROP and suspected retinal detachment. She was born at 24 + 6 PMA...
Fig. 3. Case 2 – Flying baby OCT helps to distinguish between retinoschisis and retinal detachment. Ultra-widefield optomap images (A, B) at presentation (36 weeks PMA) demonstrate bilateral ROP (zone 1, stage 2) with plus disease that was treated with intravitreal bevacizumab. At 5 months of age, repeat optomaps show recurrence of plus disease (worse on the right) and areas of avascular retina (red arrows) temporally in both eyes (C, D). Further intravitreal bevacizumab was given bilaterally and at 1-week follow-up indirect ophthalmoscopy raised suspicion of retinal detachment in the right eye (green line demarcation E on optomap shown in C). Flying baby OCT, however, through the reference green lines shown in C, demonstrated retinoschisis (yellow arrows) in the right eye without retinal detachment (E–G). OCT of the left eye confirmed flat retina with epiretinal membrane (green arrow) (H–I).
with birthweight of 625 g and suffered from chronic lung disease requiring supplemental oxygen, patent foramen ovale and mild necrotizing enterocolitis. She had a dizygotic male twin who required laser photoagulation for ROP.

Optos ultra-widefield retinal imaging and fluorescein angiography showed preplus disease with aberrant retinal vascularization in both peripheries (Fig. 4A-D, red arrows). Binocular indirect ophthamoscopy confirmed bilateral preplus disease and an area of retinal elevation, suspicious of detachment, temporally in the right eye. However, flying baby SD-OCT revealed the suspicious area to be thickened but attached schitic retina (Fig. 4F, H, yellow arrows), likely to represent a fibrovascular complex with associated tractional schisis. The angle between the superior and inferior temporal vessels is quite narrow suggesting tractional dragging. There was also evidence of epiretinal proliferation and minimal cicatrization temporally. Both retinas were treated with diode laser photoagulation, including two rows posterior to the ridge. At 42 weeks of PMA, both indirect ophthalmoscopy and Optos imaging showed that the preplus disease had resolved and the tractional schisis was walled off with intact macula in the right eye (Fig. 4I, J).

Fig. 4. Case 3 – Flying baby OCT reveals peripheral epiretinal membrane and tractional retinoschisis. Optos ultra-widefield retinal imaging and fluorescein angiography at presentation showed bilateral ROP with preplus with aberrant peripheral retinal vascularization (A–D, red arrows). SD-OCT of the right eye, through the reference green lines shown in E and G, revealed temporal peripheral epiretinal proliferation and retinoschisis (yellow arrows) but no evidence of retinal detachment (F, H). Follow-up Optomap images at 42 weeks showing laser burns and walled-off area of schisis (I, J).
Discussion

Establishing the correct diagnosis of retinal elevation in advanced ROP remains challenging and currently at large relies upon clinical examination with indirect ophthalmoscopy. In particular, differentiating retinoschisis (with or without traction) and retinal detachment and determining foveal involvement in stage 4 ROP can be difficult, even in the hands of paediatric vitreoretinal experts, where the decision whether to operate or not remains a great challenge. In this case series, we showed that flying baby SD-OCT imaging provided valuable additional information to clinicians’ clinical understanding, altering classification and management of the disease in the cases presented.

Retinal image acquisition with SD-OCT is generally a quick, straightforward procedure in co-operative adults and older children. It requires vertical alignment of the head on the scanner, with good foveal fixation and minimal eye movements. The lack of co-operation in young children and inability of non-sedated infants to maintain steady head and eye positions during image acquisition precludes the use of OCT imaging in routine ROP screening. We have previously attempted to use the standard table-mounted OCT imaging in an anaesthetized child, and faced considerable challenges in head positioning (Harris et al. 2009), an issue that has been overcome in centres with access to hand-held OCT probes (Joshi et al. 2006; Chavala et al., 2009; Muni et al. 2010; Vinekar et al. 2010; Chen et al. 2019). However, most studies have relied on OCT image acquisition in infants in supine position in operating theatres under general anaesthesia, where the risks of anaesthesia to premature infants remain substantial and preclude from frequent examination and monitoring of disease progression. Herein, we describe an alternative approach, the ‘flying baby’ approach, where non-anaesthetized infants are held by the examiner in a vertical position allowing ocular alignment with the scanner for good quality image acquisition in an outpatient setting, using a standard SD-OCT without the need for adjunct hand-held devices. The technique enabled rapid and minimally invasive retinal imaging for establishing the nature of retinal elevation observed by indirect ophthalmoscopy. In our experienced hands, the estimated success rate of obtaining good quality images was 90–100%, and thus comparable with the existing hand-held devices, despite the use of a speculum.

The possibility to readily use the OCT to aid clinical diagnosis and help interpret examination and widefield ophthalmoscopy findings is very appealing, including existing hand-held devices where available. In particular, there is currently lack of anatomical data necessary to understand the prevalence and natural history of schitic changes in ROP, which have to date not been easily visible clinically. A recent retrospective review of OCT images revealed the presence of retinoschisis without detachment in 50% of eyes with stage 4a ROP, where decision to operate remained unchanged at the time of examination under anaesthesia (Chen et al. 2019). In our prospective case series, the use of SD-OCT was critical in aiding the diagnosis and subsequent management of all three infants. In case 1, the initial diagnosis of bilateral stage 3 ROP was revised to stage 4a in the left eye and stage 4b in the right eye based on additional information from OCT. As a result, the infant underwent bilateral vitrectomies for retinal detachment with good outcome, as opposed to originally planned intravitreal anti-VEGF injections and/or laser ablation. In the second case, clinical suspicion of tractional retinal detachment in the right eye following repeat intravitreal injection of anti-VEGF was overruled following SD-OCT imaging demonstrating schitic, but flat retina. As a result, surgery was avoided and the infant underwent laser ablation for recurrence of peripheral ROP. Similarly, in case 3, clinical diagnosis of tractional retinal detachment (stage 4a) ROP was revised to stage 3 disease on the basis of OCT finding of epiretinal membrane and tractional retinoschisis, thereby avoiding the need for immediate surgery.

In case 1 of advanced ROP, traditional B-scan ultrasound could have been used for assessment and diagnosis of retinal detachment. B-scan ultrasonography has been used in evaluation of advanced ROP and in particular in evaluating stage 5 disease (Maidana et al. 2007; Muslubas et al. 2015). However, from our experience, the B-scan does not have the resolution to detect shallow retinal elevation and it is not adequate to distinguish retinoschisis from retinal detachment. Thus, in our hands we favour the use of flying baby OCT over the B-scan for rapid assessments under topical anaesthesia, to determine preclinical changes and distinguish between shallow retinal detachments and schisis. Case 2 in particular highlights an important role for the OCT in monitoring ROP response to anti-VEGF treatment. Although anti-VEGFs are becoming more widely used for the treatment of ROP, data regarding any anatomical changes, including schitic responses following the treatment, are lacking (Sankar et al. 2018). Although we cannot be sure of OCT-confirmed pre-existing retinal schisis prior to intravitreal bevacizumab, we did not observe any suspicious retinal elevations by indirect ophthalmoscopy or widefield imaging, indicating that the unusual schitic response was secondary to the anti-VEGF. The retinal scrub that potentially occurs following anti-VEGF injections in more advanced ROP where fibrosis is already present may represent a more extreme expression of the rapid organization of preretinal nascent fibrotic elements which are present in aggressive posterior ROP.

The retinoschisis usually occurs in advanced ROP, likely because of disease activity and/or increased vitreoretinal traction. Thus, following extraretinal neovascularization in stage 3 there is potential progression to elevation of retinal layers, either partial thickness (schisis) or full thickness (retinal detachment). The schitic split in the inner retinal layers is often cavity and has been observed in the periphery surrounding the neovascular elevation at the vascular–avascular junction in stage 3 ROP (Chen at al. 2018) and extending into the macula in infants with advanced ROP (Muni et al. 2010; Chen et al 2019) – the clinical significance of which remains unknown. The lucent cavities could form as part of intercommunicating cystic spaces found in the avascular retina bordered by Muller glia (Kushner et al. 1977), from fluid exudation secondary to aberrant neovascularization or from focal vitreoretinal traction leading to larger areas of retinoschisis and/or retinal detachment.
Our current practice for the use of OCT in ROP is guided by clinical suspicion of retinal elevation in advanced ROP. In this case series, we were satisfied that the information gained by indirect ophthalmoscopy and widefield imaging demonstrated stable retinae on follow-up visits without the need for further OCT imaging at the time of last follow-up. Future implementation of OCT imaging into a routine ROP management practice would allow more frequent image acquisition and thereby closer anatomical monitoring of advanced ROP progression, surgical timing and treatment response. Further longitudinal OCT studies are also needed to determine the natural history of retinoschisis and whether localized areas of fibrovascular complex formation associated with tracial retinoschisis, as observed in case 3 are progressive, if treatments such as laser barrage are necessary, and if some cases may indeed require surgical management. Recognition of tracial retinoschisis on OCT requires close monitoring (even after laser treatment) and may need incorporation into ROP grading, that is ‘stage 3s’ for stage 3 with schisis. This new stage could potentially be an indication for modern endoscopic vitrectomy (over laser alone) to prevent long-term cicatricial changes.

In summary, we present the use of flying baby SD-OCT to facilitate diagnosis in advanced stage ROP and guide subsequent management as an alternative to less widely accessible hand-held OCTs. The study highlights the need for more widespread use of the OCT for detailed monitoring of disease progression and/or response to new treatments. Obtaining longitudinal OCT data, however, will not be without its challenges. Repeating imaging in neonaates where trying to capture a specific region of the retina is likely to be limited by the difficulty to precisely direct the imaging to a region of interest. Further experience in ROP flying baby OCT imaging and using widefield optomaps as reference points to help with orientation of an area of interest will aid with speed and accuracy during image acquisition. In addition, future development of more portable and child-centric OCT technology, and eventually OCT angioigraphy, will allow more frequent acquisition of consistent and objective three-dimensional retinal imaging data that will help to better understand the clinical implications of this new information provided by the OCT, and ultimately aid the development of telemedicine and deep-learning paradigms in the future management of ROP.

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