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REVIEW ARTICLE

Retinopathy of prematurity treatment: Asian perspectives

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Abstract

Retinopathy of prematurity (ROP) is a vasoproliferative disease of developing retinal vessels that affects premature infants and can lead to severe and irreversible visual loss if left untreated. India and some other Asian countries are in the middle of a 'third ROP epidemic'. Blindness due to ROP is largely preventable if appropriate, adequate and accessible screening programmes are available. Screening of the premature babies is the first step in ROP management. With the increase in use of tele-screening techniques, more premature babies have been brought under the screening network both from urban and rural regions. Laser photocoagulation to the avascular retina using indirect ophthalmoscopy delivery system is the gold standard for ROP treatment and is usually done under topical anaesthesia in the Asian region in contrast to the western world. Use of intravitreal anti-vascular endothelial growth factors (VEGF) although controversial in management of ROP has been found to be effective in various Asian studies as well. ROP surgery in India and other middle-income Asian countries is largely performed only in few tertiary eye care centres. Poor visual prognosis, late presentation with advanced retinal detachments, lack of adequate number of trained paediatric retinal surgeons and paediatric anaesthetists also contribute to this problem. This current paper summarizes the Asian experience of ROP management.

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of developing retinal vessels that affects premature infants and can lead to severe and irreversible visual impairment or blindness if left untreated. ROP blindness is largely preventable if appropriate, adequate and accessible screening programmes are available. The World Health Organization in 2012 reported that about 15 million babies are born premature annually. Almost one in ten babies is born premature across the world [1]. As survival in these infants has increased, these babies face a lifetime risk of disability including blindness. Among various regions of the world, Southern Asia has the highest number of premature infants (13.3%) making this an important public health issue [2].

With improved neonatal care, in high-income countries, around 1.2 million premature babies have better chances of survival even with lower gestational ages (GA) [2]. Middle-income and developing countries have around 3.8 million preterm babies born each year. But progress in ROP-screening programmes have not kept pace with the progress in neonatal care [2, 3]. South Asian and Sub-Saharan African countries account for almost two-thirds of the world's preterm babies and over three-quarters of the world's newborn deaths [2, 3]. Six of the top ten countries with the highest preterm births are in Asia including India, China, Pakistan, Indonesia, Bangladesh and Philippines [3]. This makes ROP one of the major public health problems in the Asian region.

Blencowe et al. in 2010 estimated that, of the 184,700 preterm babies that developed any stage of ROP, ~20,000 became blind or severely visually impaired from ROP. Further 12,300 developed mild-to-moderate visual impairment [4]. Sixty-five percent of those visually impaired from ROP were born in the middle-income countries and 6.2% of all visually impaired infants due to ROP were born at more than 32 weeks gestation [3]. Recent studies suggest that ROP is an increasingly important cause of avoidable blindness in China, Southeast and South Asia [4].

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This current paper summarizes the Asian experience in ROP management as evident from various studies published from this area. It also highlights how the manifestation and management of ROP in Asian countries is different from that in the developed countries; thus suggesting region specific recommendations to control ROP related blindness.

Problem statement

Three epidemics have been described in ROP. The first one in the 1940s and 1950s in the western countries was attributed to poor understanding of the disease, and high concentrations of unrestricted oxygen given to the premature babies [5]. Its subsequent curtailment reduced incidence of ROP but increased the incidence of cerebral palsy and death. The second epidemic occurred in developed countries because of increased survival rates of very preterm babies. ROP occurred in these very premature babies despite attempts at titration of oxygen [6].

India and some other Asian countries are in the middle of a 'third ROP epidemic'. The hallmark of this epidemic is a variable spectrum of the disease. In tertiary care institutes which have a relatively high level of care, only the extremely premature are at risk of ROP (akin to the second epidemic of the west). However, in rural and semi-urban regions, even heavier and more mature premature infants are seen to suffer from the disease [4].

In 2010, of the estimated preterm births, number of eyes with ROP related severe visual impairment was estimated globally [4]. The problem statement in the Asian region can be summarized in Table 1, which is adapted from the study by Blencowe et al. [4]. This compares the geographic regions of Asia with high-income countries. Larger number of premature infants born, greater incidence of treatment requiring disease and fewer babies undergoing timely treatment leads to a large burden of infants becoming blind or severely visually impaired in Asian countries as compared with other regions of the world [4].

Dutta et al. [7] have suggested possible reasons for the increased ROP burden in India. These include, high rate of prematurity (in India over 13% babies are born premature); improved survival of preterm babies (survival rates of infants between 28 and 32 weeks of GA have improved from 75 to 93%); unrestricted use of oxygen; lack of adequate sensitization of care providers of these preterm babies and lack of uniform ROP-screening protocols [7]. This has resulted in 'heavier' and 'more mature' infants developing severe blinding stage 5 ROP compared to their western counterparts [8].

ROP-screening guidelines

Screening is the first step in management of ROP. This requires training, skill and appropriate equipment. Screening guidelines that are acceptable nationally can serve as a strong backbone to homogenize screening programmes in any country. Western guidelines which focus on infants born <1500 g or born at a GA of <30 weeks have been shown to be inadequate to cover the 'at-risk' infants in the middle-income countries [8, 9]. Many countries have therefore adopted different ROP-screening criteria to cater to their regional ROP profile.

In India, in 2010 the National Neonatology Forum in collaboration with the ophthalmologists released guidelines that recommended screening of premature infants of gestation <34 weeks and birth weight (BW) <1750 g and in those babies born with a BW of 1750–2000 g, if there were additional risk factors [10]. In 2015 the Ministry of Health, Government of India released a universal vision screening and ROP guidelines integrating ROP into the universal screening programme, the 'Rashtriya Bal Swasthya Karyakram (RBSK)' and the National Program for Control of Blindness (NPCB) which was followed by an Operational

Table 1 Distribution of ROP demographics in the Asian regions

	Central Asia	East and Southeast Asia	South Asia	High-income countries	Total
Live births and % of worldwide total	5.4 million (4%)	29 million (22%)	37.1 million (28%)	11.7 million (9%)	135 million (100%)
Preterm births	413,000 (3%)	2,808,000 (19%)	4,954,000 (33%)	1,064,000 (7%)	14,900,000 (100%)
Any stage ROP	17,200	64,000	16,800	32,700	184,700
Treatment requiring ROP	5200	19,900	5300	6300	53,800
Receiving treatment	1900	7800	1100	5500	22,700
Survivors with blindness/severe vision impairment	2000	7500	2200	1700	20,000
Survivors with mild/moderate vision impairment	1100	4400	900	2300	12,300

Modified from Blencowe et al. [4]

Guidelines for ROP (2017) by the National Task Force of ROP, Government of India. These guidelines suggest that preterm babies ≤2000 g BW and ≤34 weeks GA should be screened for ROP. Bigger babies born at 34–36 weeks GA can also be screened if they have high-risk factors for developing ROP. The guidelines emphasize that all these babies should have first screening within the first 4 weeks of life. Babies born with BW ≤ 1200 g and GA ≤ 28 weeks could be screened at 2–3 weeks of life [11].

Similar to India, in China the ROP-screening guidelines recommended in 2004 were GA ≤ 34 weeks and/or BW ≤ 2000 g [12]. Some Chinese studies have suggested to reduce the criteria to GA ≤ 33 weeks and BW ≤ 1750 g as this may still detect all treatable ROP [13]. In Turkey, screening of infants with a GA ≤ 34 weeks or a BW < 1700 g has been suggested to be appropriate across a prospective, multicentre study in 69 neonatal intensive care units [14]. A report from Thailand suggested screening guidelines for babies with GA < 33 weeks and/or BW < 1500 g. Using this screening criteria, they achieved a sensitivity of 100% and specificity of 18.3%, while using the American (BW < 1500 g and GA < 28 weeks) and British guidelines, the sensitivity was 93% and specificity was 35–40% [15]. However, in a prospective study from Korea, though the screening criteria were similar to that advised by the international committee (BW < 1500 g and/or GA < 30 weeks), the incidence of ROP in infants with GA ≥ 31 weeks was found to be 8.4%, thus, emphasizing the importance of screening even older infants when indicated [16]. Higher income group countries within Asia like Taiwan [17], Singapore [18] and Japan [19] follow screening guidelines similar to the UK/US. ROP screening guidelines followed in some Asian countries are summarized in Table 2.

Meanwhile tele-screening models continue to develop across the region with wider availability of wide-field digital imaging cameras (Fig. 1). The ability of experts based in tertiary hospitals or reading centres to opine regarding treatment and follow-up based on images captured by trained technicians in mobile-screening teams has enabled provision of a large coverage of ROP-screening care in the community. The 'K.I.D.R.O.P' model [20] is an example of such a successful tele-screening programme in Karnataka (India) under private–public partnership which provides ROP screening in low-resource settings, remote centres and regions with few ROP specialists. An impact assessment of the image based tele-ROP programme in India showed that in the ten high-risk ROP states with a population of roughly 680 million, over 35,000 infants were detected with ROP and over 1200-needed treatment

Fig. 1 Wide-field digital ROP screening by Retcam imaging

Table 2 ROP-screening guidelines in the Asian region compared with US/UK guidelines

Study group	Country	Year	Screening criteria		Timing of first screening (Age in weeks after birth)
			Birth weight (grams)	Gestational age (weeks)	
Fierson et al. [9]	USA	2013	1500	30	4
Wilkinson et al. [63]	UK	2009	1500	32	4–5 (GA < 27 weeks)
RBSK and NPCB [11]	India	2017	2000	34–36 (risk factors)	4 2–3 weeks (GA < 28 weeks/BW < 1200 g)
Chinese Expert group [12]	China	2004	2000	34	4–6
Bas et al. [14]	Turkey	2018	1700	34	4
Trinavarat et al. [15]	Thailand	2004	1500	33	4–6
Shah et al. [18]	Singapore	2005	1500	32	6
Chen et al. [17]	Taiwan	2015	1500	32	4–6
Al Amro SA et al. [64]	Saudi Arabia	2018	1500	32–36 (risk factors)	4–6

annually. The fiscal quantum of burden in 'blind-person-years' that could possibly be saved using this model is 108 million USD [21].

ROP treatments

Laser therapy

The gold standard for ROP treatment in the Asian region is laser photocoagulation delivered through laser indirect ophthalmoscopy (LIO), although there has been an increasing trend to use anti-vascular endothelial growth factor (anti-VEGF) agents more recently. There is again a gross lack of trained specialists to perform laser. The Indian ROP (iROP) society reported that less than 100 specialists were comfortable performing laser [22]. This gap between those requiring treatment and those receiving therapy is reflected in the increasing number of blind and visually impaired infants (Table 1).

In the UK, over 50% ophthalmologists treating ROP with laser photocoagulation used general anaesthesia and 37% use intravenous sedation [23]. In contrast, in the Asian region including India, China, Iran and Hong Kong, treatment is most commonly performed under topical anaesthesia (Table 3). Figure 2a, b shows indirect ophthalmoscopic examination and LIO by 532 nm green laser under topical anaesthesia, respectively. Sedation [24, 25], remifentanil analgesia [26] and oral pellets of sucrose or dextrose are other additional modifications used by various ophthalmologists for pain relief during laser treatment. In Japan, a study comparing topical vs general anaesthesia, showed that the former had fewer systemic complications [27]. Though inhalation anaesthesia did not affect the vital signs at all during the laser, it has its own problems in premature infants and adverse effects on neurodevelopment. Also, it increases the dependence on anaesthetists and operating room facilities which may not be widely available especially in the developing Asian countries.

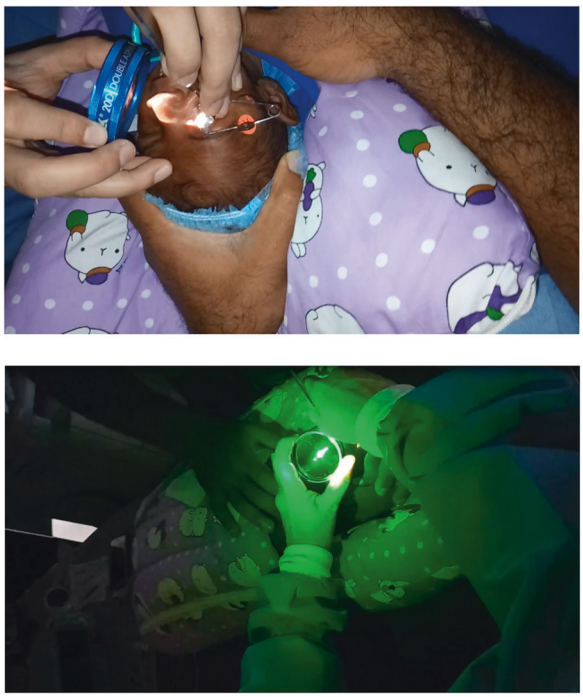

Fig. 2 **a** Indirect ophthalmoscopic examination with scleral indentation for ROP screening under topical anaesthesia. **b** Photoablation by laser indirect ophthalmoscopy using 532 nm green laser also under topical anaesthesia

Table 3 Laser treatment outcomes for ROP from Asia

Sl no.	Author	Country	Year	Study type	No. of eyes	Anaesthesia	Favourable structural outcomes (%)	Comments
1	Sanghi et al. [65]	India	2010	Retrospective	260	TA	97	Diode and green laser are similar in efficacy and safety
2.	Axer-Siegel et al. [24]	Israel	2008	Retrospective	194	Sedation	92.3	Diode laser is safe and effective
3.	Jalali et al. [66]	India	2011	Prospective	227	TA	87.5	Laser in Zone 1 ROP eyes
4	Uparkar et al. [67]	India	2010	prospective	100	TA	94–98	Laser to the ridge and posterior also safe and effective
5	Parvaresh et al. [68]	Iran	2013	Prospective	139	TA	100	Transscleral laser ablation was used. Severe chemosis, conjunctival lacerations in 8.6% eyes. Supplemental transpupillary laser for zone 1 eyes
6	Jiang et al. [25]	China	2014	Retrospective	97 infants	TA (31) Sedation (47) GA (19)	96.9	Laser under topical required more duration of treatment and was associated with more cardiorespiratory instability during and after treatment.
7	Sato et al. [27]	Japan	2015	Prospective	49	Local (L)-15 pentazocine (P)-11 I. V Fentanyl (F)-11 Inhalation (I)-12	–	L-No significant adverse side effects except *desaturation during procedure*. In group I more chances of hypothermia, apnoea, oliguria
8	Vinekar et al. [69]	India	2015	Prospective	29	TA		Compared single vs two-staged laser for APROP. Latter has fewer complications

TA topical anaesthesia, *GA* general anaesthesia, *I.V* intravenous

Laser is performed inside the neonatal unit, operating room or a facility where the infant can be monitored by a paediatrician or an anaesthetist. Diode laser has been widely replaced in many centres by the 532 nm green laser. The latter was reported to have distinct advantages such as ease of use, lower tissue penetration, less pain, less cost and better portability. Furthermore, the green laser can be utilized for diabetic retinopathy treatment as well adding a cost utility benefit in middle-income countries where resources are limited.

Dogra et al. showed that infants too sick to be transported outside the incubator can be treated successfully through the double-walled sloping incubator with either diode or green laser [28]. Posterior to the ridge laser was proposed by Ells et al. [29] when the fibrovascular proliferation is raised in the vitreous cavity (stage 3). This approach has apparently resulted in better regression of ROP, less traction and a more favourable outcome [29].

Highly favourable outcome following laser has been reported in many Asian studies. Over 96–100% of success for type 1 ROP eyes treated with laser has been reported [30]. Sanghi et al. proposed that darker retinal pigment, dense and thorough laser, close follow-up and early prompt treatment could be reasons for a higher success rate compared with western infants. Although aggressive posterior ROP (APROP) outcome following laser treatment is relatively poor (between 82.5 and 100%), few studies from India have reported good structural outcomes in these eyes [31]. GA < 29.5 weeks and presence of pre-retinal haemorrhage were found to be individual risk factors for poor outcome in eyes with APROP [31]. APROP has been reported in heavier babies in India presumably due to prolonged and uncontrolled exposure to high concentration of oxygen and other comorbid conditions [32]. A comparison of laser practices and outcomes in few Asian studies is summarized in Table 3.

Anti-VEGF therapy

After the BEAT-ROP study [33], anti-VEGF therapy has gained popularity for the treatment of ROP. In India and other Asian countries which lack adequate ROP specialists who can perform laser, this new modality has provided another alternative. However, the indications, the appropriate dosages, follow-up strategy, associated comorbidities and systemic safety remain unmet challenges. Different Anti-VEGF agents used for ROP include Bevacizumab (Avastin; Genentech Inc., South San Francisco, CA, USA), Ranibizumab (Lucentis; Genentech Inc., South San Francisco, CA, USA) and Aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY, USA). Bevacizumab and Ranibizumab are the more commonly used agents for treating ROP. There is no definite agreement regarding optimal dose of these anti-VEGF medications in ROP. Most previous studies have used 0.625 mg/0.025 ml for Bevacizumab and 0.25 mg/0.025 ml for Ranibizumab, or half of the adult doses, per eye when injected in these newborn eyes. Recent studies have found that even low-dose Bevacizumab to be equally effective with theoretically reduced risk of side effects [34].

Advantages of anti-VEGFs over laser include easier and faster administration, less structural damage, reduced refractive error, possible treatment in special scenarios like hazy media, corneal opacification, non-dilating pupil and ischaemia involving the posterior pole.

The potential disadvantages include unknown variables about the accurate dose required, the frequency and duration of follow-up, detection and management of recurrences, persistent peripheral avascularity, long-term effect on visual acuity and fields, systemic adverse effects particularly involving neurodevelopmental delay. Besides, medico-legal considerations are very important in countries like India. After the ban and subsequent reinstating of anti-VEGF agents for the use of adult retinal diseases by the Government of India, there is still no legal sanctity for the use of these agents in infants potentially exposing the treating specialist to liability. More importantly, rural patients who may not be able to follow-up indefinitely after therapy are at risk of late, undetected and untreated recurrences.

A report from Pakistan (15 eyes), in advanced stage 3 or 4 ROP, combination therapy of laser and anti-VEGF showed reduction in neovascular activity signs such as reduced tortuosity and vessel dilatation without requiring additional treatment. No systemic or ocular serious adverse events were observed [35]. Xu et al. from China investigated the use of Ranibizumab for APROP (37 eyes) associated with vitreous haemorrhage and found such approach improved fundus visibility to apply lasers at mean time of 4.8 ± 2.9 weeks and observed 92% eye had favourable anatomical outcome [36]. Shah et al. used Bevacizumab to successfully treat anterior segment ischemic Syndrome, a rare complication following laser ablation therapy in an eye with APROP [37]. In a multicentre study in Taiwan, Wu et al. reported vitreous or preretinal haemorrhage in 8% of eyes and transient venous sheathing in 4% of eyes as complications of intravitreal Bevacizumab (IVB) injection; however, vitreous or preretinal haemorrhage later resolved in all eyes, and sheathed vessels reperfused at subsequent follow-ups [38]. Serious adverse events of retinal break/s and bilateral vascular attenuation with subretinal perivascular exudates and optic atrophy were also reported after IVB in a series from India [39]. Another concern from treatment induced complication termed ‘ROP crunch’, can occur, if anti-VEGF injection was performed in eyes with preexisting significant retinal traction [40].

Table 4 Anti-VEGF therapy outcomes for ROP from Asia

Sl no.	Author	Country	Year	Study type	Eyes	Intravit therapy	Dose (mg)	Outcome	Complications
1	WU et al. [45]	Taiwan	2013	Retrospective (monotherapy)	162	IVB	0.625	New vessel regression-88% worsening-2%	VH, cataract. Systemic-none
2	Jalali et al. [39]	India	2013	Prospective (rescue therapy)	24	IVB	0.625	New vessel regression-100%	Retinal break, perivascular exudation, optic atrophy, hepatic dysfunction
3	Kusaka et al. [70]	japan	2008	Retrospective (rescue therapy in progressive ROP)	23	IVB	0.5	Reduced vascularity, decreased intra and post op. bleeding, reproliferation	Persistent high IOP
4	Yetik et al. [71]	Turkey	2015	Prospective (monotherapy)	238	IVB	0.625	Success rate by 1st inj-95.4% 2nd inj-98.2% 3rd inj-100% Worsening-0%	Subconjunctival haemorrhage
5	Huang et al. [72]	China	2017	Retrospective (monotherapy)	283	IVR	0.25	Complete regression with no reactivation-45.8% Reactivation-44.4%	VH, cataract

IVB intravitreal Bevacizumab, *IVR* intravitreal ranibizumab, *VH* vitreous haemorrhage, *Inj.* injection

Systemic complications after anti-VEGF therapy are due to the fact that VEGF levels are depressed for 2–3 months after intravitreal anti-VEGF injection in patients with type 1 ROP probably due to the leakage of the drug into the systemic circulation [41, 42]. A retrospective observational study revealed that preterm infants treated with Bevacizumab had higher odds (as compared with laser) of severe neurodevelopmental disabilities [43]. However Wu et al., did not find worse neurodevelopmental outcomes in infants who received only Bevacizumab, as compared with those treated with laser photocoagulation [44, 45]. The results of anti-VEGF therapy reports from the Asian region are summarized in Table 4.

ROP surgery

ROP surgery in India and other middle-income countries are performed only at a few tertiary care centres. Poor visual prognosis, late presentation of advanced retinal detachments (RD), lack of trained paediatric retinal surgeons, lack of paediatric anaesthetists and neonatal support after surgery, poor follow-up after surgery, and lack of vision rehabilitation and supportive therapy, all contribute to the problem.

Scleral buckling involving the placement of 240 band at the height of the tractional retinal detachment (TRD) by making scleral tunnels in all quadrants, is done only in a select group of Stage 4 eyes with only peripheral traction. Segmental scleral buckles have also been used by Chuang et al. [46] for TRD limited to the temporal quadrants, with macular attachment rates of 79% in a small series of 15 eyes.

Lens sparing vitrectomy (LSV) is the most commonly performed surgery for stage 4 ROP. Nishina et al., demonstrated using fluorescein angiography, before and after surgery that removal of proliferation tissue promptly reduced the vascular activity, limiting the progress of RD in APROP [47]. With advent of microincisional vitrectomy surgeries (MIVS), ROP surgeries now are becoming more popular. Also, intraoperative and postoperative complications appear to be much lesser with MIVS [48].

Gadkari et al. noted that eyes that have undergone prior laser have less chances of iatrogenic retinal break during surgery as compared with treatment naive eyes [49]. Bhende et al., reported an anatomical success of 96% in stage 4A and 70% in stage 4B following LSV at final visit [50]. Use of pre-operative Bevacizumab has been advocated by Xu et al. from China who found that eyes undergoing LSV with pre-operative Bevacizumab had significantly shorter surgical time (74 vs 101 min), better attachment rate (100 vs 70%), and better visual outcome (88 vs 30%) [51]. Recently, early VR surgery has been propagated in APROP eyes to prevent development of RD [52]. A combination of all possible modalities may be necessary in APROP. Figure 3a, b shows regression of stage 4A zone 1 ROP following 25 gauge LSV.

Multiple case series in India and other Asian countries have reported anatomical success ranging from 75 to 100% in stage 4A and between 62 and 100% in stage 4B ROP following LSV. The outcomes are summarized in Table 5.

Stage 5 ROP has the worst prognosis. Once retrolental fibroplasia has formed, lensectomy is done along with vitrectomy. Gopal et al. have reported almost 81% incidence of close-close configuration of RD in his series undergoing surgery for stage 5 ROP which is associated with poorer prognosis [53]. Choi et al. reported

postoperative intraocular haemorrhage using 20 gauge system in nearly 43% of cases [54], while Gonzales et al. reported postoperative vitreous haemorrhage in 13.3% of cases after 25 gauge MIVS for stage 4 and 5 ROP [48]. Gopal et al. had anatomical success with the attachment of posterior pole in 22.5% of cases with lens sacrificing closed globe vitrectomy for stage 5 ROP [53]. Recurrence of RD has been observed in 22% of cases in Stage 5 as compared with 5% in stage 4, highlighting the importance of prolonged follow-up of these eyes [55]. Plasmin assisted vitrectomy with encouraging results, for primary as well as recurrent RD in regressed ROP has been reported by Wu et al. [56]. The most important aspect of treatment for stage 5 ROP is the education of parents or guardians regarding the limited visual outcomes that may be seen in a small proportion of eyes undergoing surgery and the need for prolonged follow-up.

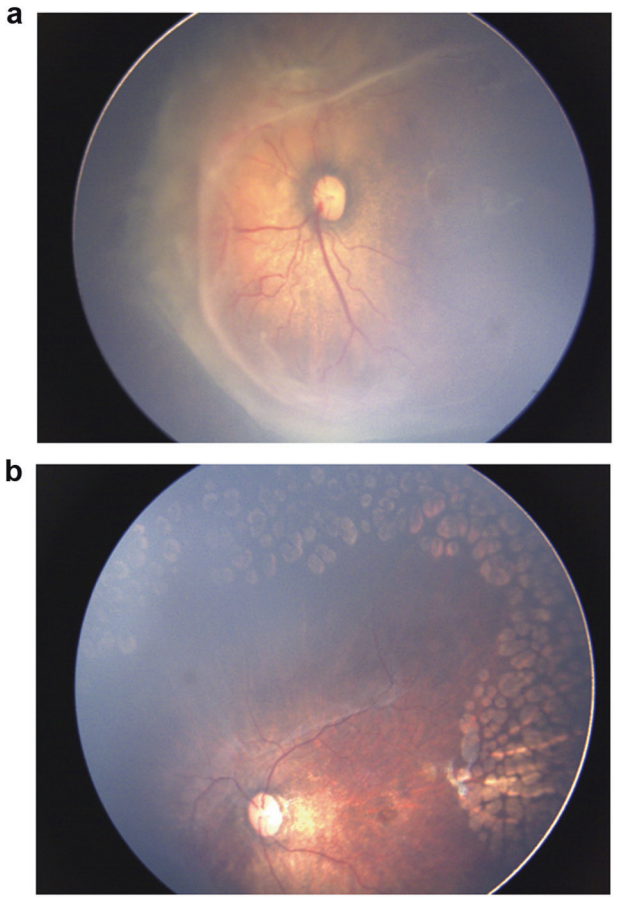

Fig. 3 **a** Left eye with circumferential Stage 4A ROP in Zone 1. **b** Left eye 4 weeks after 25G LSV showing regressed ROP

Long-term follow-up is necessary not only in postsurgery eyes but also in all premature babies because of the high incidence of refractive errors. The Asian studies are summarized in Table 6. Functional outcomes and refractive errors noted after multiple treatment modalities are summarized in Table 7.

Because of the heterogeneity in the presentation of disease in babies with similar neonatal risk factors, genetic predisposition has also been studied by the Asian researchers [57, 58].

Medico-Legal aspects of ROP

In India in 2015, a landmark judgement by the Supreme Court awarded a USD 300,000 compensation to a child who was not referred for timely ROP screening. Subsequent cases highlighted the vulnerability of the ROP problems for the infants and the caregivers. Stricter enforcement of the national screening guidelines, with increase in trained resources for screening and treatment along with strengthening preventive measures is the need of the hour. This will require stronger public and private partnerships and the use of innovative technologies to combat the ROP scourge.

Table 5 Lens sparing vitrectomy outcomes for ROP from Asia

Sl no.	Author	Country	Year	Type	Eyes	Anatomical outcome (%)	Favourable visual outcome (%)
1	Choi et al. [54]	Korea	1999–2007	Retrospective	4B-13, 5–8	4B-62, 5–13	–
2	Bhende et al. [50]	India	2000–2006	Retrospective	4A-29, 4B-10	4A-96, 4B-70	4A-86, 4B-60
3	Yu et al. [73]	Korea	1999–2003	Retrospective	4A-4, 4B-9, 5–4	4A-75, 4B-66.7, 5–25	–
4	Azuma et al. [52]	Japan	2004–2005	Retrospective	6 (APROP)	100	NA
5	Wu et al. [74]	Taiwan	2007–2010	Retrospective	4A-15, 4B-11	88	NA
6	Gadkari et al. [75]	India	2015	Prospective	4B-20, 5–11	4B-90, 5–45.5	NA
7	Shah et al. [76]	India	2018	Retrospective	4A-7, 4B-2	100	–

NA not available

Table 6 Stage 5 surgery outcomes for ROP

Sl no.	Author	Country	Year of study	Type	Eyes	Anatomical outcome (%)
1	Choi et al. [54]	Korea	1999–2007	Retrospective	8	13
2	Gadkari et al. [75]	India	2009	Prospective	11	45.5
3	Shah et al. [77]	India	2001–2006	Retrospective	14	14.3
4	Karacorlu et al. [78]	Turkey	1996–2010	Retrospective	31	42
5	Gopal et al. [53]	India	1992–1998	Retrospective	96	22.9
6	Kono et al. [79]	Japan	1989–1991	Retrospective	51	47
7	Cusick et al. [80]	USA	1977–2001	Retrospective	608	33

Table 7 Functional outcomes of ROP treatment

Sl no.	Author	Country	Year of publication	Type of study	Intervention	Eyes	ROP stage	Mean SE (Dioptres)	Myopia (%)	High myopia (%)	Follow-up (years)
1	Katoch et al. [30]	India	2011	Retrospective	Laser	69	Type 1	+0.75	26.1	1.4	1
2	Axer-Siegel et al. [81]	Israel	2008	Retrospective	Laser	134	Type 1 or threshold	1.5	55.2	23.9	2.9
3	Agarkar et al. [82]	India	2017	Retrospective	Laser + LSV	14	Stage 4A, 4B	−7.4	NA	NA	2
					Laser	14	Type 1	−6.4	NA	NA	
4	Chen et al. [83]	Taiwan	2014	Retrospective	IVB	40	5-stage 2, 52-stage 3	−0.98	47.5	10	2
					IVB + Laser	17		−2.4	82.4	29.4	
					IVB + LSV	7	Stage 4A	−14.4	100	100	
5	Yang et al. [84]	Taiwan	2010	Retrospective	Laser	60	Threshold	−3.87	60.3	16.7	7.8
6	Shah PK et al. [85]	India	2014	Retrospective	Laser	48	APROP	−6.14	4.1	NA	6.9

SE spherical equivalent, *High myopia* More than 5D of myopia, *LSV* lens sparing vitrectomy, *IVB* intravitreal Bevacizumab, *NA* not available, *Cryo* cryotherapy

The United Nation Development Programme report on the Indian tele-imaging programme and the National Health and Medical Research Council (Australia) report based on the Center for Disease Control guidelines on the KIDROP tele-ROP programme, both strongly suggest that wide-field imaging is likely to become the new gold standard in ROP screening [59], which may guard the medico-legal interest of the patients and the caregivers in countries like India and others with similar ROP demographics.

Advances in technology

Innovations in ROP management from India have been recently reported and include: (1) affordable imaging technologies—an indigenous ROP camera was developed in a collaboration between the Government, Industry and clinical partners (3Nethra Neo, Forus Health, India) [60]. This portable camera is lighter, uses a uni-body liquid lens system and is wide-field, using a light-emitting diode illumination and providing 120° of view [60]. (2) Online training and e-certification platforms such as the WISE-ROP model that allows training of remote non-physicians to capture and report images [61]. (3) Software and artificial intelligence that may help diagnose, predict and prognosticate the disease. (4) Novel service delivery models—a paediatrician led model wherein nurses screen for ROP using ROP cameras is being piloted in South India based on suggestions by Gilbert et al. [62].

Conclusion

A significant part of Asia is suffering from the third epidemic of ROP. Corrective measures need to be initiated right from the time of birth of a premature child and these include (1) increase in the availability of compressed air supply, air-oxygen blenders, trained doctors and nurses, (2) disseminate knowledge about oxygen saturation targets, (3) improve ROP screening and treatment, (4) maintain a nation-wide database of all babies who are treated and those diagnosed with ROP blindness, (5) introduce newer technology for the better and early diagnosis of ROP, (6) educating parents regarding ROP and (7) conduct research to understand the epidemiology of prematurity and translational research to minimize the known risk factors of ROP. Only combined efforts of paediatricians, neonatologists, obstetricians, ophthalmologists, nurses and parents with support from their Governments can help achieve this.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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