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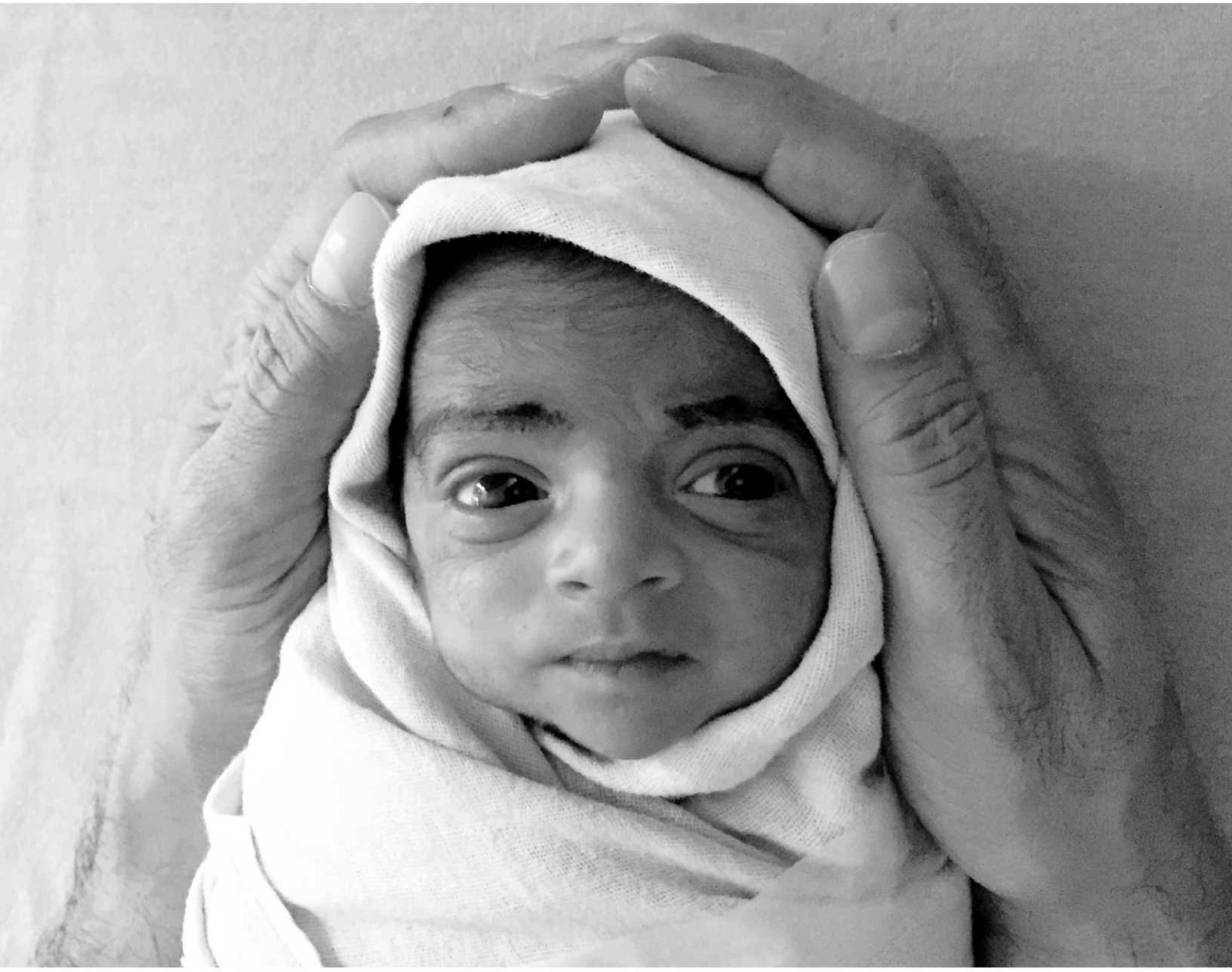

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Original Article

Neonatal Intensive Care Unit-based screening program for retinopathy of prematurity and its treatment in an Indian population

Anubhav Goyal, Ananthraman Giridhar, Mahesh Gopalakrishnan, Thomas Thachil

Purpose: The purpose was to study the incidence, risk factors, and anatomical outcomes after laser treatment in retinopathy of prematurity (ROP). **Methods:** A retrospective observational study was carried out. Infants admitted to Neonatal Intensive Care Unit of 12 referral hospitals between April 2016 and September 2017 were screened according to the latest Indian guidelines based on the International Classification of Retinopathy of Prematurity. **Results:** The incidence of ROP in 1648 eyes screened was 25.36% (418 eyes), out of which high-risk prethreshold ROP (type 1) was observed in 9.95% (164 eyes). Decreased hemoglobin ($P < 0.001$), oxygen requirement ($P = 0.008$), and number of blood transfusions ($P = 0.037$) were significant with type 1 than type 2 (low-risk prethreshold) ROP. Stages 1, 2, and 3 were observed in 82 (32.28%), 154 (60.62%), and 18 (7.08%) eyes, respectively. Aggressive posterior ROP (APROP) was observed in 20.73% eyes with type 1 ROP. Ten eyes showing APROP were treated at an early gestational age of 29 weeks. All infants with type 1 ROP were treated with laser photocoagulation only. **Conclusion:** One-fourth of the infants showed ROP and one-tenth needed laser photocoagulation, the outcome of which was excellent. Risk factors predisposing to ROP were anemia, high oxygen supplementation, increased number of blood transfusions, and septicemia. ROP screening in infants ≥1700 g birth weight associated with various systemic risk factors may be beneficial in the Indian population.

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Retinopathy of prematurity (ROP) is a disease with a wide spectrum, ranging from mild, transient changes in the retina with regression to severe progressive vasoproliferation, fibrosis, and retinal detachment, leading to blindness. It is mostly reported in preterm neonates. ROP-related vision loss is also termed as "third epidemic" in developing countries, and many of these countries are organizing screening programs for its better management. The development of retina is incomplete during the course of gestation and depends mainly on the severity of prematurity of retina at birth. In 1942, Terry first described retrolental fibroplasia with implication of oxygen therapy as the causative agent.[1] Hence, administration of oxygen therapy in premature infants was severely curtailed, resulting in increased mortality. Now, because of improved neonatal survival rate, the incidence of ROP is increasing in India, which is between 38% and 51.9% in preterm infants.[2] Today, it is well known that oxygen therapy is not the single causative factor, but several other risk factors also play a role in the pathogenesis of ROP.[3] Although current ablation treatments can reduce the incidence of blindness by approximately 25% in infants with advanced ROP, the patients often still have poor visual acuity even after treatment and the life-long impact of the disease on eye and vision development remains significant.[4] Early identification and successful treatment can reduce final visual morbidity.

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The aim of this retrospective study was to study the incidence and risk factors predisposing to ROP and to assess the outcome after laser photocoagulation for ROP performed in Neonatal Intensive Care Units (NICUs) of multiple referral hospitals and a tertiary eye center of a developing country.

Methods

Inclusion criteria

Given below are the latest Indian screening guidelines on screening ROP:[5]

- Birth weight of <1700 g
- Gestational age at birth of <34–35 weeks
- Exposure to oxygen for >30 days
- Infants born at <28 weeks and weighing <1200 g (particularly are at a high risk of developing severe form of ROP)
- Presence of other factors such as respiratory distress syndrome, sepsis, multiple blood transfusions, multiple births (twins/triplets), apneic episodes, and intraventricular hemorrhage (in these cases, screening should be considered even for babies >37 weeks' gestation or > 1700 g birth weight).

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All neonates admitted to NICU of 12 referral hospitals in Kochi, Kerala, India, were routinely screened for ROP between April 2015 and March 2016 (12 months) according to the latest Indian screening guidelines.[5] The initial examination was carried out at 4 weeks after birth or 31 weeks' postmenstrual age, whichever was later. All the infants were screened by the same ophthalmologist.

A detailed history including birth weight, gestational age at birth, and adverse events during NICU stay and ROP management was recorded. The screening was carried out with a binocular indirect ophthalmoscope and +28 D lens. Eyes were examined with an infant Barraquer Wire Speculum and a Kreissig scleral depressor, under topical anesthesia using 2% proparacaine eye drops. The pupils were dilated using 0.4% tropicamide + 2.5% phenylephrine eye drops three times till full dilatation occurred. ROP was graded into stages and zones as per the International Classification of Retinopathy of Prematurity.[6]

Type 1 or "high-risk prethreshold" ROP is defined as zone I, any stage with plus disease; zone I, stage 3 ROP without plus disease; and zone II, stage 2 or 3 ROP with plus disease. Type 2 or "low-risk prethreshold" ROP is defined as zone I, stage 1 or 2 ROP without plus disease or zone II, stage 3 ROP without plus disease. Aggressive posterior ROP (APROP) is defined as ROP with severe plus disease, flat neovascularization in zone I or posterior zone II, intraretinal shunting, hemorrhages, and a rapid progression to retinal detachment.

Eyes showing any stage of ROP were examined periodically or every week till they completely regressed or till they reached high-risk prethreshold or threshold ROP which mandates laser treatment. Any stage 3 ROP with plus disease with 5 contiguous or 8 cumulative clock hours in zone I or II was considered as threshold for treatment.[7,8] MII Ret Cam (an invention by Dr. Ashish Sharma),[9] a smartphone (with built-in camera and flash)-based fundus camera device, and +20 D lens were used only to capture fundus images for pictorial documentation in preterm infants already diagnosed to have either type 1 or type 2 ROP during the screening [Fig. 1].

Laser treatment

Laser photocoagulation was advised for infants who developed either high-risk prethreshold or threshold disease as per the Early Treatment for ROP (ETROP) classification[4] or if APROP was observed. Laser photocoagulation was performed using 810-nm transpupillary diode laser (OcuLight® SL, Iridex, USA) with a laser indirect ophthalmoscope and +28 D diopter lens as early as possible, within 1–3 days of the diagnosis of threshold plus disease. Laser treatment was performed under topical anesthesia, using an infant wire speculum and a sclera indentation under the supervision of a neonatologist in the respective NICUs only. The avascular retina beyond the ridge was ablated using near-confluent medium-intensity burns over one session in both the eyes simultaneously. Topical treatment with tobramycin and dexamethasone was given for 10–14 days to take care of ocular inflammation after the laser treatment. If regression was found to be inadequate or skip areas were observed on subsequent examination, laser was repeated after 1 week or more.

Follow-up

All children who had undergone laser therapy were reviewed periodically until all signs of threshold disease were regressed and follow-up was terminated once retinal vascularization has proceeded to the retinal periphery in all quadrants.

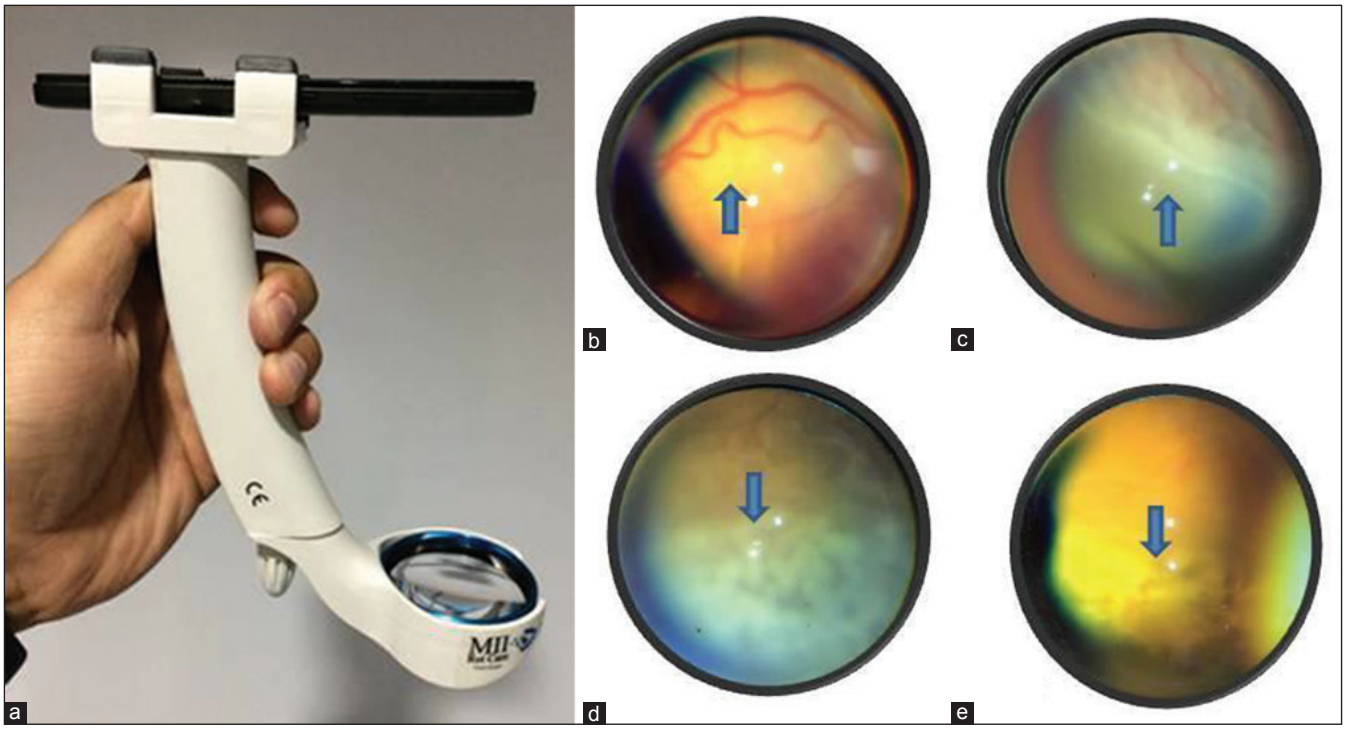

Figure 1: (a) MII Ret Cam with a smart phone. (b) Dilated and tortuous vessels suggestive of plus disease (arrow). (c) Stage 3 fibrovascular proliferation (arrow) in type 1 ROP. (d) Fresh laser marks anterior to fibrovascular proliferation (arrow). (e) Scars (arrow) with complete resolution of ROP

Statistical Package for the Social Sciences software version 16.0 (SPSS Inc.,Chicago, Illinois, USA) was used and values less than 0.05 were considered statistically significant. [** indicates a significant association ($P < 0.05$)].

Results

A total of 1648 eyes of 824 infants were screened for ROP in NICUs of 12 referral hospitals in Kochi, Kerala, from April 2016 to September 2017 (18 months). Postmenstrual age ranged from 24 to 38 weeks with a mean of 31.76 (standard deviation [SD] ±2.837) weeks. The birth weight ranged from 495 to 3000 g with a mean of 1468.37 (SD ± 454.50) g. There were 472 males and 352 females. ROP was observed in 418 eyes (209 infants), with an incidence of 25.36%. Out of the 418 eyes, type 1 ROP was found in 164 eyes with an incidence of 9.95%. Of the 418 eyes, 254 eyes showed type 2 ROP. Of these 254 eyes, Stages 1, 2, and 3 were observed in 82 (32.28%), 154 (60.62%), and 18 (7.08%) eyes, respectively. APROP or "rush disease" was diagnosed in 34 (20.73%) of 164 eyes with type 1 ROP. No ROP was found in infants with birth weight >2000 g and gestational age >36 weeks. Moreover, no type 1 ROP was seen in infants with gestational age >32 weeks and birth weight >2000 g. Incidence of type 1 ROP decreases with increase in postmenstrual age and birth weight [Figs. 2 and 3; Table 1]. None of the studied neonates initially presented with Stage 4 or 5 ROP.

Laser treatment was performed in 164 (9.95%) eyes showing type 1 ROP. Table 1 shows the number of infants who received laser treatment according to gestational age and birth weight. More than one laser treatment was performed in 12 eyes. Infant demographics and course of care correlated with the severity of ROP. However, even after appropriate laser treatment, 3 (0.18%) eyes progressed to falciform fold over macula and 1 (0.06%) eye developed blindness due to retinal detachment. These four eyes were having APROP in zone I and were treated with only laser treatment. All babies withstood laser. Five infants were born at gestational age between 24 and 25 weeks and were given laser treatment for APROP at a still early postmenstrual age of 29 weeks. All infants were screened till vascularization has proceeded to the retinal periphery in all quadrants.

Infants with type 1 ROP had statistically significant lower mean gestational age ($P < 0.001$), lower mean birth weight ($P < 0.01$), less mean hemoglobin ($P < 0.001$), higher mean oxygen requirement ($P < 0.001$), more mean hours on ventilation ($P < 0.001$), and higher mean number of blood transfusions ($P < 0.001$) compared to those with type 2 ROP [Table 2]. Considering various risk factors, initial univariate analysis showed that infants with type 1 ROP had statistically significantly decreased hemoglobin ($P < 0.001$), higher mean oxygen requirement ($P < 0.001$), mean hours on ventilation (<200 h) ($P < 0.046$), septicemia ($P < 0.041$), and higher mean number of blood transfusions ($P < 0.001$) compared to those with type 2 ROP. When these were put into multiple logistic regression analysis, only decreased hemoglobin, higher mean oxygen requirement, and higher mean number of blood transfusions were found to be significant [Table 3]. Six infants having birth weight > 1700 g developed ROP due to the presence of risk factors such as respiratory distress syndrome, septicemia, multiple blood transfusions, multiple births (twins/triplets), apneic episodes, and intraventricular hemorrhage [Table 4]. Out of these six infants having birth weight >1700 g, two infants required laser treatment for type 1 ROP.

Discussion

We screened all preterm babies admitted to NICUs according to recent Indian guidelines on ROP screening with birth weight <1700 g and gestational age <35 weeks.[5] The American Academy of Pediatrics (AAP) recommends screening of all eligible babies at 4–6 weeks' chronologic age or 31–33 weeks' postconceptional age, whichever is later.[7,8] Infants with birth weight >1700 g and gestational age >35 weeks were screened on neonatologist's discretion only if they had additional risk factors, whereas older Indian screening guidelines for ROP

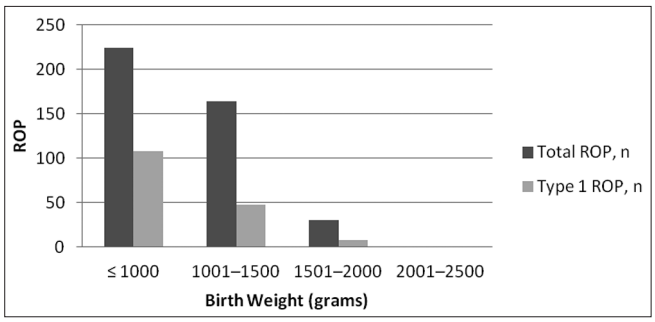

Figure 2: Incidence of Type 1 ROP according to birth weight (grams)

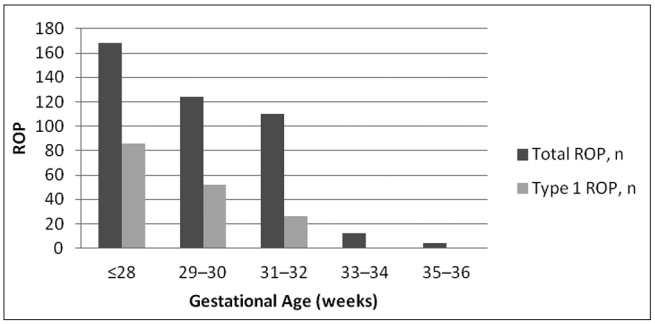

Figure 3: Incidence of Type 1 ROP according to gestational age (weeks)

Table 1: Proportion of type 1 ROP eyes treated with laser monotherapy according to gestational age and birth weight

Gestational age (weeks)	Total, *n*	Type 1 ROP, *n* (%)	Birth weight (gram)	Total, *n*	Type 1 ROP, *n* (%)
≤28	168	86 (52.43)	≤ 1000	224	108 (65.85)
29-30	124	52 (31.70)	1001-1500	164	48 (29.26)
31-32	110	26 (15.85)	1501-2000	30	8 (4.87)
33-34	12	0	2001-2500	0	0
35-36	4	0			

Table 2: Correlation of gestational age, birth weight, hemoglobin, oxygen requirement, hours on ventilator, number of blood transfusion between type 1 and type 2 ROP

	Type 1 ROP		Type 2 ROP		*P*
	Mean	SD	Mean	SD	
Gestational age	28.3	2	29.6	2.1	<0.001*
Birth weight	996.5	256.2	1110.8	290.2	0.01*
Hemoglobin (g/dl)	9	1.8	12.4	2.8	<0.001*
Oxygen requirement	40.8	13.5	31.2	9.7	<0.001*
Hours on ventilator	258.1	215.1	125.3	160.8	<0.001*
Number of blood transfusions	4.3	2.6	1.7	2.3	<0.001*
Septicemia	0.23	0.11	0.09	0.10	<0.001*

*Mann-Whitney U test

Table 3: Determinants of Type of ROP: Univariate and Multivariate analysis

Determinants	Level	Type 1 (*n*=164)	Type 2 (*n*=254)	Univariate analysis		Multivariate analysis	
		n (%)		OR (95% CI)	*P*	OR (95% CI)	*P*
Hemoglobin (g/dl)	>10	43 (26.2)	199 (78.4)	0.098 (0.047-0.207)	<0.001*	0.145 (0.061-0.342)	<0.001*
	<=10	121 (73.8)	55 (21.6)				
Oxygen requirement (%)	<35	81 (49.4)	199 (78.4)	0.267 (0.133-0.537)	<0.001*	0.309 (0.129-0.740)	0.008*
	>=35	83 (50.6)	55 (21.6)				
Hours on ventilation	<200	94 (57.4)	207 (81.5)	0.409 (0.170-0.986)	0.046*	1.863 (0.580-5.980)	0.296
	>500	35 (21.3)	16 (6.3)	2.000 (0.576-6.950)	0.275	2.608 (0.572-11.890)	0.216
	200-500	35 (21.3)	31 (12.2)				
No. of Blood transfusions	<5	86 (52.4)	220 (86.6)	0.171 (0.079-0.369)	<0.001*	0.352 (0.132-0.938)	0.037*
	>=5	78 (47.6)	34 (13.4)				
Septicemia	Yes	32 (19.5)	21 (8.3)	2.724 (1.043-7.117)	0.041*	2.438 (0.739-8.048)	0.144
	No	132 (80.5)	233 (91.7)				

**Indicates a significant association (*P*<0.05)

Table 4: Systemic associations in infants ≥1700 g

Birth weight (grams)	Gestational age (weeks)	Stage of ROP	Associated risk factors
1700	32	1	Septicemia, RDS, apneia
1710	31	1	Septicemia, Rh incompatibility
1700	29	2	Septicemia, IVH, RDS, twins birth, apneia
1900	32	2	RDS, apneia
1710	30	3+	Septicemia, RDS, apneia
1700	27	3+	Septicemia, RDS, apneia

RDS: Respiratory distress syndrome, IVH: Intraventricular hemorrhage

suggested screening of babies with birth weight <1500 g and gestational age <32 weeks.[10-12] Vinekar *et al*.[13] suggested different scenarios of ROP screening in developing countries such as India. Sen *et al*.[2] and Jalali *et al*.[5] suggested that all infants in India with birth weight <1700 g and gestational age <34–35 weeks should be screened regularly. The rate of favorable outcome and a posterior location of the disease are inversely related.

In our study, we would have missed 108 (25.83%) eyes with ROP if we had used <30 weeks criteria, as per the AAP updated recommendations,[7] and missed 16 (3.82%) eyes if we had used <32 weeks criteria, as per older Indian screening guidelines.[10-12] These findings support the validity of the latest Indian screening guidelines. We suggest that all babies with birth weight <1700 g and gestation <34–35 weeks should be routinely screened in India.[5,14] Larger and gestationally "older" infants in India can also develop ROP compared to their Western counterparts.[13] We also observed respiratory distress syndrome, septicemia, multiple blood transfusions, multiple births (twins/triplets), apneic episodes, and intraventricular hemorrhage as precipitating factors for ROP in six infants >1700 g birth weight.[5] Thus, in the Indian scenario, infants with birth weight >1700 g and gestational age >35 weeks should be screened at the discretion of the neonatologist, depending on various risk factors during the stay in the NICU.

Chaudhari *et al*.[10] treated only one affected eye in seven infants, but we aggressively treated both eyes of all infants

diagnosed with type 1 ROP. In accordance to other studies,[2,5,10] we also found that incidence and severity of ROP were closely related to lower birth weight and lower gestational age. Incidence of ROP was 25.36% in our study, which is same as shown by Chaudhari *et al*.,[10] but much lower than 38%–51.9% reported in other studies.[2,5] Incidence of APROP in our study was 20.73%, which is less than 25% documented by Jalali *et al*.[15] Improved neonatal services and better extreme preterm survival observed in our study may contribute to lower incidence of APROP in Kochi, India. We did not find any neonate initially presented with Stage 4 or 5 ROP during this study.

Many risk factors have been reported to predispose to ROP. Oxygen therapy, anemia, exchange transfusion, packed cell volume transfusion, septicemia, enhanced ventilator support, apnea, multiple births, and clinical sepsis are some important risk factors.[10,13,16] In our study, anemia, oxygen administration, hours on ventilation, septicemia, and number of blood transfusions were found to be significant risk factors for ROP, more in type 1 ROP compared to type 2 ROP.

Shift of treatment paradigm from Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study[17] to ETROP study[4] suggested that by ablating peripheral avascular retina, laser therapy significantly allows the clinician a greater precision of treatment and reduces the unfavorable effects of cryotherapy, and it has yielded successful structural results of 90% compared to 60% in eyes treated with cryotherapy.[4] BEAT-ROP study compared bevacizumab monotherapy with conventional laser therapy and showed promising results for APROP or stage 3+ ROP in zone I but not in zone II disease.[18] Studies showed that intravitreal antivascular endothelial growth factor (anti-VEGF) may cause various ocular and systemic complications such as developmental delay in other organs in these premature babies, especially with already persisting subnormal growth.[19,20] Moreover, follow-up period after anti-VEGF monotherapy is unpredictable as there can be a recurrence of neovascularization even beyond 54 weeks of postmenstrual age.[8] Still larger sample studies are needed to rule out any systemic or local side effects of anti-VEGF treatment in ROP.

Laser monotherapy can cause permanent ablation of peripheral avascular retina, resulting in permanent peripheral visual field loss[18] and very high myopia,[21] as observed in 36.4% compared to 1.7% eyes treated in bevacizumab monotherapy treatment group. The rate of recurrence (primary outcome) for zone I compared to zone 2 was significantly higher with conventional laser therapy than that with intravitreal bevacizumab, which was 26% compared to 6%.[18] Chan *et al*.[20] demonstrated similar rate of recurrence in two of the eight eyes in both the groups treated with either laser monotherapy alone or ranibizumab with or without laser treatment. Laser treatment is still a gold standard treatment for threshold ROP and practiced in most of the places. Treatment with anti-VEGF followed by laser treatment (4–5 days later) in these cases has improved the efficacy of laser along with a reduced need for extensive laser, especially in zone I ROP.[22]

Using a new lightweight, portable, handy, and inexpensive (costing only Rs. 19,999 or $380) smartphone-based fundus camera (MII Ret Cam)[9] attached with +20 D lens, we were able to capture high-quality fundus videos and images in preterm infants, documenting type 1 ROP and improvement after laser treatment [Fig. 1]. Although this smartphone-based fundus camera has only approximately 30° field of view, we were able to capture both central and peripheral retinal images, which can be used only for clinical documentation and better understanding for the treating ophthalmologist and neonatologist and counseling parents, especially in case of type 1 ROP. In the future, this portable, smartphone-based, handy fundus camera can be used as a tool for tele-ophthalmology consultation with retina specialists.

We found that five infants had gestational age between 24 and 25 weeks and were given laser treatment for APROP at a still early postmenstrual age of 29 weeks. We treated all infants with laser alone, which has its own limitations such as peripheral retinal ablation resulting in permanent peripheral visual field loss and laser-induced very high myopia. We found that the results of laser treatment were extremely satisfactory and, of all the infants who completed follow-up till complete retinal stabilization, only 4 (0.24%) eyes of three infants, having APROP, had poor outcome. Similar to Sanghi *et al*.,[23] we also observed falciform fold in macula in two eyes and stage 5 ROP in one eye treated with laser therapy. The biggest strength of our study is enrolling a large number of patients from the same geographic region and showing excellent results with laser treatment alone. Secondarily, we followed strict protocol for ROP screening and early treatment within 48 h of diagnosing type 1 ROP by the same ophthalmologist. We did not use an expensive imaging modality such as RetCam to screen ROP and none of the preterm infants were treated with anti-VEGF therapy. Still we achieved excellent results with laser monotherapy. Our study had a good sample size over a short time period.

Conclusion

A total of 418 (25.36%) eyes showed ROP, of which only 164 (9.95%) received laser photocoagulation treatment. The outcome was excellent. Of 164 (9.95%) eyes treated for type 1 ROP, only 3 (0.18%) eyes progressed to falciform fold over macula and 1 (0.06%) eye developed blindness due to retinal detachment, showing excellent structural outcomes after laser monotherapy alone. Earlier preterm infants and those with lower gestational age had higher risk of developing ROP. Birth weight and gestational age are directly proportional to hemoglobin but inversely proportional to oxygen requirement, number of blood transfusions, septicemia, and hours on ventilator. The current treatment of laser ablation therapy has limitations with regard to acute and long-term complications. A novel treatment approach of anti-VEGF therapies has not yet been sufficiently evaluated to be broadly recommended for clinical treatment. In ROP management, timing is critical in any medical or surgical intervention because both type 1 and type 2 ROP require different approaches.[24] Despite using anti-VEGF treatment in any of the treated infants in our population, we managed to get excellent outcomes of >99% anatomical success with laser monotherapy alone. In view of our findings of disease requiring early treatment, instead of 31 weeks,[7,8] we suggest starting ROP screening at a still early postmenstrual age of ≤29 weeks or 4 weeks postgestational age, whichever is later. ROP screening in infants ≥1700 g birth weight associated with systemic risk factors such as respiratory distress syndrome, septicemia, multiple blood transfusions, multiple births (twins/

triplets), apneic episodes, and intraventricular hemorrhage may be beneficial in the Indian population. Laser monotherapy can give excellent results in the treatment of ROP. It has to be noted that in a fragile neonate, careful monitoring and assessing advantages and risks of any treatment/intervention must be weighed very carefully.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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