Original Article

Real-world scenario of retinopathy of prematurity in Kerala

ABSTRACT

Objective: The objective was to study the incidence and risk factors predisposing to retinopathy of prematurity (ROP) and to assess the outcome after laser photocoagulation.

Design: This was a retrospective cohort observational study.

Materials and Methods: Infants admitted to a Neonatal Intensive Care Unit of 12 referral hospitals in Kerala between May 2015 and June 2016 were followed up till retinal vascularization completes. Preterm infants with birth weight <1700 g and gestation >34 weeks were screened for ROP at 4 weeks after birth or 31–33 postconceptional age, whichever was later. Infants with birth weight >1700 g and gestation >35 weeks were screened only on neonatologist's discretion. All infants were screened according to the Indian guidelines of type 1 and 2 ROP. We treated both eyes of all infants showing threshold ROP. Statistical analysis was done using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Results: The incidence of ROP in 622 infants screened was 158 (25.4%), of which threshold ROP was seen in 61 (9.80%). No ROP was found in infants weighing >2000 g or with a gestational age >36 weeks. Risk factors predisposing to ROP were hours on ventilator, hemoglobin%, oxygen therapy, and number of blood transfusions, which were more significant in infants with type 1 or threshold ROP than type 2 ROP. Out of 97 infants with type 2 ROP, we saw stage 1 in 31 (30.92%), stage 2 in 59 (60.82%), and stage 3 in 7 (7.21%) infants. 61 (9.80%) infants with threshold ROP were treated with laser photocoagulation. Aggressive posterior ROP or rush disease was seen in 29 (47.54%) of 61 infants with type 1 ROP. Only 2 (3.27%) infants showed falciform fold over macula and 1 (1.63%) infant was blind due to retinal detachment.

Conclusion: One-fourth of the infants showed ROP, of which one-tenth needed laser photocoagulation, the outcome of which was good. Risk factors predisposing to ROP were low hemoglobin, high oxygen therapy, increased number of blood transfusions, and hours of ventilator.

Keywords: Aggressive posterior for retinopathy of prematurity, retinopathy of prematurity, SPSS

INTRODUCTION

Retinopathy of prematurity (ROP) is a disease process mostly reported in preterm neonates with a wide spectrum, ranging from mild, transient changes in the retina with regression to severe progressive vasoproliferation, retinal detachment, and blindness. The development of retina, which proceeds from optic nerve head anteriorly during gestation, is incomplete, with the extent of prematurity of the retina depending mainly on the severity of prematurity at birth. In 1942, Terry[1] first described retrolental fibroplasia with implication of oxygen therapy as the causative agent. Hence, administration of oxygen in prematures was severely curtailed, resulting in increased mortality. Because of improved neonatal survival rate, incidence of ROP is increasing in India between 38% and 51.9% in low birth weight infants.[2] Today, it is well known that oxygen therapy is not the single causative factor, but many other risk factors play a causative role in the pathogenesis of ROP.[3] Although the current ablation treatments can reduce the incidence of blindness by ~25% in infants with late-stage ROP, the patients often still have poor visual acuity after treatment and the lifelong impact of the disease on eye development and vision remains significant.[15] If identified early, it can be treated successfully.

The aim of this retrospective study was to find incidence and risk factors predisposing to ROP and to assess the outcome

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after laser photocoagulation for ROP done in Neonatal Intensive Care Unit (NICU) of all referral hospitals by a tertiary eye center of a developing country.

MATERIALS AND METHODS

Screening guidelines

American Academy of Pediatrics (AAP) guidelines[5]

- Infants with birth weight of ≤1500 g
- Gestational age of 30 weeks or less
- Infants with birth weight between 1500 and 2000 g or gestational age of >30 weeks with unstable clinical course.

Latest Indian screening guidelines[6]

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

All neonates admitted to NICU of 12 referral hospitals in Kerala were routinely screened for ROP between May 2015 and June 2016 (14 months) according to the current Indian guidelines. The initial examination was carried out at 4 weeks after birth or 31 weeks postconceptional age, whichever was later. All the infants were screened by the same ophthalmologist.

A detailed history including birth weight, gestational age at birth, and problems during NICU stay and its management were recorded. The screening was done with a binocular indirect ophthalmoscope. Eyes were examined with an infant speculum and a Kreissig scleral depressor under topical anesthesia using 2% proparacaine drops. The pupils were dilated by using 0.4% tropicamide +1.25% phenylephrine eye drops three times till full dilatation occurred. Retinopathy was graded into stages and zones as per the International Classification of ROP (ICROP) classification.[7]

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

Those with ROP were examined periodically or every week till regression occurred or till they reached threshold for laser treatment. Any stage 3 ROP with plus disease with 5 contiguous or a total 8 cumulative clock hours in zone I or II was considered as threshold for treatment.[8]

Laser treatment

Laser photocoagulation was advised for infants who developed threshold disease as per ICROP classification.[7] Laser was done using 810 nm red laser (IRIDEX SLx) with laser indirect ophthalmoscope as early as possible, at least within 1–3 days of diagnosis of threshold plus disease. This was done under topical anesthesia, using an infant wire speculum and scleral indentation under neonatologist supervision in the respective NICUs only. The avascular retina beyond the ridge was ablated using confluent medium intensity burns over one session. Invariably, both eyes were treated in all infants in single sitting. Topical treatment with tobramycin and dexamethasone was given for 14 days. If regression was found to be inadequate or skip areas were seen 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. In general, follow-up for all babies terminated once vascularization was completed up to periphery.

Statistical analysis

Statistical analysis was done using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

RESULTS

Six hundred and twenty-two infants were screened for ROP in NICU of 12 referral hospitals in Kerala from April 2015 to June 2016 (14 months). Their gestational age ranges from 25 to 38 weeks with a mean of 31.76 (standard deviation [SD] ± 2.837) weeks. Their birth weight ranges from 495 to 3000 g with a mean of 1468.37 (SD ± 454.50) g. There were 332 males and 290 females. ROP was seen in 158 infants with an incidence of 25.4%. Out of 158 infants, type 1 or threshold ROP was seen in 61 infants with the incidence of 9.80%. Ninety-seven out of 158 infants showed type 2 or prethreshold ROP. Out of 97 infants having type 2 ROP, stage 1, 2, and 3 were seen in 31 (30.92%), 59 (60.82%), and 7 (7.21%) infants, respectively. APROP or rush disease was seen in 29 (47.54%) of 61 infants with type 1 ROP. No ROP was seen in birth

weight >2000 g and gestational age more than 36 weeks. Incidence of ROP decreases with increase in gestational and birth weight [Figures 1, 2 and Table 1].

Laser treatment was done in 61 (9.80%) infants showing type 1 ROP. Table 2 shows proportion of infants required laser treatment according to gestational age and birth weight. More than one laser sitting was needed in four infants. Even after appropriate laser treatment, 1 (1.63%) infant progressed to falciform fold over the macula in both the eyes and 1 (1.63%) infant was blind from right eye due to retinal detachment. All babies withstood laser well. All infants were screened till vascularization completed or plus disease completely disappeared with retinal stabilization.

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

Gestational age (weeks)	Total, *n* (%)	Laser, *n* (%)	Birthweight (grams)	Total, *n* (%)	Laser, *n* (%)
≤28	124	64 (52.45%)	≤1000	170	80 (65.57)
29-30	92	38 (31.14%)	1001-1500	122	36 (29.50)
31-32	86	20 (16.39%)	1501-2000	24	6 (4.91)
33-34	8	0	2001-2500	0	0
35-36	2	0			

Table 2: Correlation of gestational age, birth weight, haemoglobin, 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*
Haemoglobin (%)	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*

*Mann whitney U test

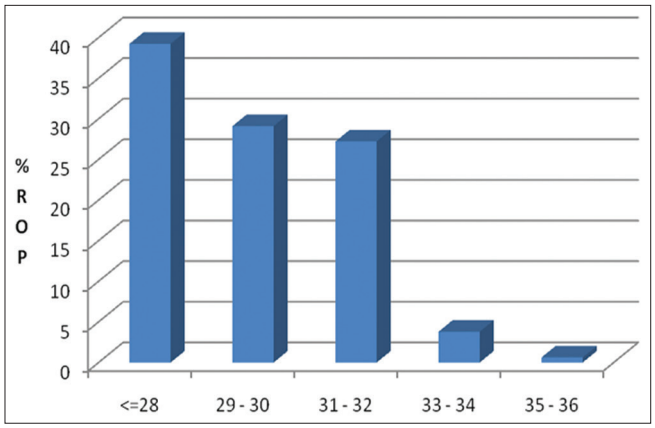

Figure 1: Incidence of retinopathy of prematurity according to gestational age

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 ($P < 0.001$), more mean oxygen% requirement ($P < 0.001$), more mean hours on ventilation ($P < 0.001$), and more mean number of blood transfusions ($P < 0.001$) as compared to infants showing type 2 ROP [Table 2].

DISCUSSION

We screened all babies admitted to NICUs according to the recent Indian guidelines of screening type 1 and 2 ROP with birth weight <1700 g and gestational age <34 weeks. The AAP recommends screening of all eligible babies at 4 weeks chronologic age or 31–33 weeks postconceptional age whichever is later.[8] Infants with birth weight >1700 g and gestational age >34 weeks were screened only if they had additional risk factors and on neonatologist discretion. While old Indian screening guidelines suggested screening in birthwight <1500gms and gestational age <32 weeks.[4,8,10,11] Vinekar *et al*.[12] suggested that the scenario in developing countries like India is quite different. Larger and gestational "older" infants are more likely to develop ROP as compared to their counterparts in Western countries.[9] Praveen Sen *et al*.[2] and Jalali *et al*.[6] suggested that all infants with birth weight <1700 g and gestational age <34–35 weeks should be screened regularly.

In our study, we would have missed 41 (25.94%) infants with ROP if we had used <30 weeks criteria, as per AAP updated recommendations,[8] and missed 6 (3.79%) infants with ROP if we had used <32 weeks criteria, as per old Indian screening guidelines.[4,10,11] Hence, we feel that all babies with birth weight <1700 g and gestation <34–35 weeks should be routinely screened. Infants with birth weight >1700 g and gestational age >35 weeks should be screened at the discretion of the neonatologist, depending on other risk factors during stay in the NICU.

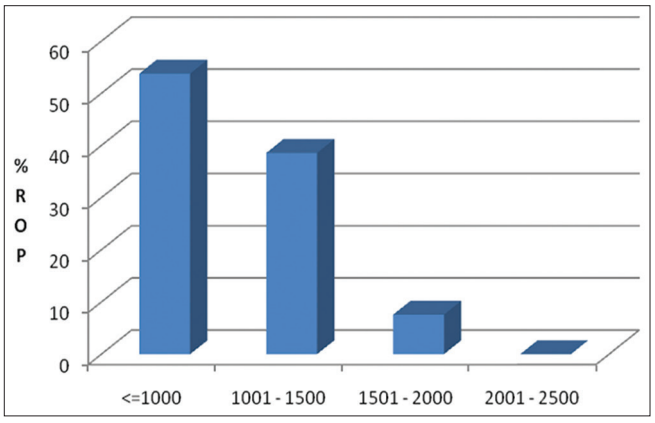

Figure 2: Incidence of retinopathy of prematurity according to birth weight

Chaudhari *et al*.[4] treated only 1 affected eye in 7 infants, but we indiscriminately treated both eyes of all infants diagnosed to have threshold ROP. In accordance with other studies,[2,4,6,9] we also find that incidence and severity of ROP were closely related to lower birth weight and lower gestational age. Incidence of ROP was 25.4% in our study which is same as Chaudhari *et al*.[4] but much lower than 38%–51.9% reported from other studies.[2,6] Incidence of APROP or rush disease in our study was 26.22%, which is approximately equal to 25% documented by Jalali *et al*.[6] Improved neonatal services and better extreme preterm survival can contribute to lower incidence of APROP. We did not find any neonate presented with stage 4 or 5 ROP during this study.

Many risk factors have been reported to predispose to the development of ROP. Oxygen therapy, anemia, double volume exchange, packed cell volume transfusion, septicemia, apnea, and clinical sepsis are important risk factors.[4,12] In our study, anemia, oxygen administration, hours on ventilation, and blood transfusion were found to be significant risk factors for ROP, more in type 1 ROP as compared to type 2 ROP.

Shift of treatment paradigm from CRYO-ROP[14] to early treatment for ROP[15] suggested that by ablating peripheral avascular retina, laser therapy significantly allows more precision of treatment as well as reduces the unfavorable side effects of the cryotherapy and has more than 90% successful results.[15] BEAT-ROP study compared bevacizumab monotherapy with conventional laser therapy showed promising results for stage 3 + ROP in zone I but not in zone II.[16] However, studies showed that anti-vascular endothelial growth factor (VEGF) systemic absorption may cause vascular development delay in other organs in these premature babies, especially with already persisting subnormal growth. Moreover, follow-up period after monotherapy is unpredictable as there can be a recurrence of neovascularization even beyond 54 weeks of postgestational age. Therefore, anti-VEGF is not recommended by many as the first-line therapy.[17]

However, in zone I ROP, especially APROP, only laser treatment results are poorer and cause permanent ablation of peripheral avascular retina, resulting in permanent peripheral visual field loss. The rate of recurrence (primary outcome) for zone I and posterior zone II combined was significantly higher with conventional laser therapy than with intravitreal bevacizumab which was 26% versus 6%.[16] Treatment with anti-VEGF followed by 4–5 days later with laser treatment in these cases has improved the efficacy of laser along with a reduced need for extensive laser, especially in zone I ROP. Still, larger sample studies needed to rule out any systemic or local side effects of anti-VEGF treatment in ROP.[16]

Three infants who had gestational age between 24 and 25 weeks were given laser treatment for APROP at a still early postconceptional age of 29 weeks. We had treated all infants with laser treatment alone which has its own limitations of peripheral retinal ablation resulting in permanent peripheral visual field loss. We found that the results of laser are extremely satisfactory and only 2 children (3.27%) had poor final anatomical outcome. The limitation of our study was the study design as we performed a retrospective, observation study of data extracted from medical records and databases.

CONCLUSION

About 25.4% of the infants showed ROP out of which only 9.8% infants needed laser photocoagulation, the outcome of which was good. Earlier the preterm and lower the gestational age, higher risk of developing ROP. Birth weight and gestational age are directly proportional to hemoglobin% while these are inversely proportional to oxygen requirement, number of blood transfusions, and hours of ventilator. The current treatment of laser ablation therapy has limitations with regard to acute and long-term complications. 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 since both type 1 and type 2 ROP require different approaches.[13] We have not used anti-VEGF treatment in any of the treated infants still we have good outcomes. We restrict use of anti-VEGF treatment especially for zone I disease or APROP and it may not be necessarily given for all stages of ROP. Finally, we recommend starting ROP screening a still early gestational age ≤29 weeks and birth weight till <1700 g. It has to be noted that in a fragile neonate, the advantages and risks of any intervention must be weighed very carefully and needs very careful monitoring due to rapid developmental changes in these infants.

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Conflicts of interest
There are no conflicts of interest.

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