RESEARCH PAPER

Retinopathy of Prematurity in a Tertiary Care Center – Incidence, Risk Factors and Outcome

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Manuscript received: April 23, 2007; Initial review completed: May 12, 2008;
Revision accepted: July 2, 2008.

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

Design: Prospective cohort observational study.

Setting: Infants admitted to a neonatal intensive care unit of a referral hospital between 2000-2006 and followed up till the age of 3 years.

Methods: Preterm infants with birthweight < 1500g and gestation ≤ 32 weeks were screened for ROP at 4 weeks after birth or 31-33 post conceptional age, whichever was later. Infants with birthweight ≥ 1500g and gestation > 32 weeks were screened only if they had additional risk factors. Those found to have threshold disease ROP had laser photocoagulation. They were recalled at 3 years and had a complete ophthalmic check up.

Results: The incidence of ROP in the 552 infants who were screened was 22.3%. No ROP was found in infants weighing ≥ 2000g or with a gestational age more than 36 weeks. Risk factors predisposing to ROP were septicemia (P<0.001), apnea (P=0.0001) and oxygen therapy (P=0.031). Out of the 123 infants who had ROP, 41 (33.6%) needed laser photocoagulation. Twenty two (53.6%) were seen at 3 years of age. Ten children had myopia, 1 had amblyopia and 9 children had completely normal structural and visual outcome. Only two (9%) children were blind due to retinal detachment.

Conclusion: One third of the infants with ROP needed laser photocoagulation, the outcome of which was good. Risk factors predisposing to ROP were septicemia, apnea, oxygen therapy and use of blood products.

Key words: *Laser photocoagulation, Follow-up, Retinopathy of prematurity, Visual outcome, Risk factors.*

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, scarring, detachment of retina and blindness. If identified early, it can be treated successfully. 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. 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(2,3).

The aim of this prospective study was to find out the incidence of ROP in a tertiary care centre in a developing country. It also attempts to identify the risk factors which predispose to ROP in a large population of Neonatal Intensive Care Unit (NICU) graduates and the long term outcome of those treated with laser photocoagulation.

METHODS

All neonates weighing <1500g and/or with a gestation ≤32 weeks admitted to our NICU were routinely screened for ROP between the years 2000-2006. The initial examination was carried out at 4

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weeks after birth or 31 to 33 weeks postconceptional age, whichever was later(4). All the infants were screened by the same ophthalmologist(VP).

Ethical clearance was obtained from the hospital ethics committee and informed consent of the parents was also obtained.

Neonates with birthweight ≥ 1500g or gestational age more than 32 weeks were screened if they had an unstable neonatal course with risk factors like ventilation, oxygen requirement, use of surfactant, septicemia, hyperbilirubinemia, intraventricular hemorrhage, patent ductus arteriosus, exchange transfusion, apnea and use of blood products. A detailed history including birthweight, gestational age at birth, weight for gestation (AGA / SGA status) 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% phenylepherine eye drops two or three times, till full dilatation occurred. Retinopathy was graded into stages and zones as per the ICROP classification(5,6).

Infants with normal vascularization upto the periphery were not examined again. Those with ROP were examined every week till regression occurred or till they reached threshold for laser treatment. Any stage 3 ROP with plus disease with 5 contiguous clock hours of disease or a total 8 noncontiguous clock hours in zone 1 or 2 was considered as threshold for treatment(4).

Laser treatment: Laser photocoagulation was advised for infants who developed threshold disease as per ICROP classification(5) or earlier, if aggressive progression was seen in zone 1 disease. Laser was done using 810nm red laser (iridex SLx) with laser indirect ophthalmoscope as early as possible, at least within 7 days of diagnosis of threshold plus disease. This was done under topical anesthesia, using an infant wire speculum and scleral indentation in the NICU. The avascular retina beyond the ridge was ablated using confluent medium intensity burns over one session. Topical treatment with tobramycin and dexamethasone was given for 5 days and an oral analgesic was given for one day. If regression was found to be inadequate or skip areas were seen on subsequent examination, laser was repeated after one or two weeks.

Follow up: All children who had laser therapy were asked to come for regular follow up. At the age of 3 years, they were called for a detailed ophthalmic examination.

Statistical analysis: Analysis was performed using SPSS version 10.0. Univariate analysis was conducted using Chi square test. Multiple logistic regression analysis was performed to study the predictors of ROP using independent variables as those variables which were significant in the univariate analysis.

RESULTS

Five hundred and fifty two infants were screened for ROP in the NICU from year 2000 to 2006. Their birthweight ranged from 550-2499g with a mean of 1306±267g. The gestational age ranged from 26-37 weeks with a mean of 31.4±2.2 weeks. There were 340 males and 212 females. ROP was seen in 123 infants and the overall incidence of ROP was 22.3%. The incidence of ROP according to gestational age is shown in ***Fig.* 1**. As the gestational age decreased, the incidence of ROP increased (P=0.003). The incidence of ROP in 58 ELBW infants was 36.2%, in the 381 VLBW infants, it was 23.6% and was 11.4% in 105 infants weighing 1500-1999g. No ROP was seen in infants with birth weight ≥2000g and gestational age more than 36 weeks. The frequency distribution of stages of ROP is shown in ***Table* I.**

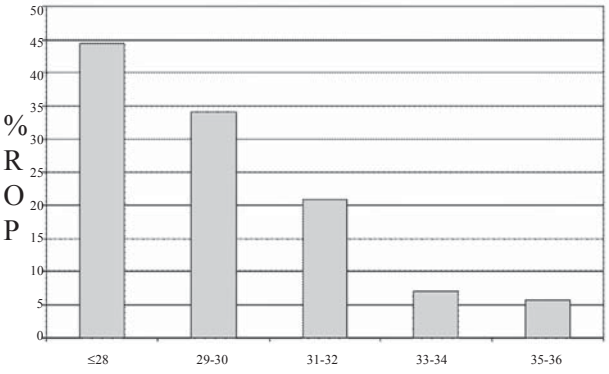

FIG. 1 *Incidence of ROP according to gestational age.*

TABLE I FREQUENCY DISTRIBUTION OF STAGES OF ROP

	Left Eye *n* (%)	Right Eye *n* (%)
I	46 (39.6)	49 (39.8)
II	40 (34.5)	43 (34.9)
III	23 (20.2)	23 (18.7)
IV	5 (4.4)	6 (4.9)
V	2 (1.7)	2 (1.6)
Total	116	123

When we looked at the year-wise distribution of the incidence of ROP, it was 24.4% in 2000 and 27.3% in 2001. It declined to 16.7, 19.5, 18.4% in 2002, 2003 and 2004, respectively. However, it rose to 26% in 2005 and 2006, as we started saving smaller babies. There was no significant difference in the incidence of ROP between males and females. There was no difference in the incidence of ROP between appropriate for gestational age (AGA) and small for gestational age (SGA) low birthweight infants.

A univariate analysis was initially done taking each risk factor. The risk factors included were oxygen therapy, seizures, ventilation, exchange transfusion, use of blood products, patent ductus arteriosus, septicemia, continuous positive airway pressure (CPAP), apnea, hyperbilirubinemia. Septicemia (P=0.003), apnea (P=0.0001), oxygen therapy (P=0.0001), ventilation (P=0.001) and use of blood products (P=0.013) were found to be significant. When these were put in a multiple logistic regression, only apnea, septicemia and oxygen therapy were found to be significant, as shown in ***Table* II.**

In 116 infants, both eyes were affected. In 7 infants, only one eye was affected. Laser photocoagulation was done in 41 (33.3%) infants out of the 123 infants having ROP. ***Table* III** shows the frequency distribution of infants requiring laser therapy according to gestational age and birth weight. More than one laser was needed in 9 infants. All babies withstood the procedure well and there were no post-laser complications other than reddening of the conjunctiva, which disappeared in 2-3 days.

An effort was made to recall all children who had undergone laser therapy at the age of 3 years. Those born in 2005 and 2006 had not completed 3 years at the end of the study. Four children were lost to follow up. Twenty two children had a complete ophthalmic checkup (53.6%). Ten children had myopia and needed glasses and one had amblyopia. Nine children had completely normal structural and visual outcome. Two children had poor outcome (9%). One girl had retinal detachment and is blind in one eye, and another boy had retinal detachment in both eyes and is totally blind.

TABLE II THE UNIVARIATE AND MULTIVARIATE (INDEPENDENT) DETERMINANTS OF ROP

Risk factor	ROP (+ve) (*n*=123) (%)	ROP (–ve) (*n*=429) (%)	Univariate analysis Odds Ratio 95% CI	Multivariate analysis Odds Ratio 95% CI	*P*-value
Seizures	2.5	0.7	3.46 0.48-24.97	1.04 0.11-9.60	0.969
Oxygen therapy	64.5	39.7	2.75 1.81- 4.19	1.89 1.06-3.39	0.031
Ventilation	41.7	24.8	1.69 1.23- 2.34	1.06 0.55-2.01	0.867
Exchange transfusion	20.2	13.5	1.62 0.93- 2.81	1.60 0.75-3.43	0.220
Blood products use	23.6	14.2	1.86 1.13- 3.06	1.68 0.86-3.28	0.125
Hyperbilrubinemia	56.1	51.0	1.22 0.82- 1.83	0.78 0.45-1.37	0.390
PDA	8.6	4.4	2.06 0.78- 5.43	1.60 0.52-4.92	0.407
Apnea	38.4	10.7	5.19 2.91- 9.23	3.75 1.98-7.09	0.0001
Septicemia	22.0	11.4	2.17 1.29- 3.66	3.13 1.56-6.29	0.001
CPAP	68.9	67.4	1.07 0.49- 2.31	0.74 0.26-2.12	0.578

TABLE III PROPORTION OF INFANTS REQUIRING LASER THERAPY ACCORDING TO GESTATIONAL AGE AND BIRTHWEIGHT

Gestational age (wks)	Total	Laser *n* (%)	Birthweight (g)	Total *n*	Laser *n* (%)
≤ 28	31	12 (38.7)	<1000	24	11 (45.8)
29-30	55	17 (30.9)	1000-1499	128	24 (18.8)
31-32	60	6 (10)	1500-1999	31	6 (19.4)
33-34	33	6 (18.2)	2000-2499	3	0
35-36	6	0	–	–	–
≥ 37	1	0	–	–	–

DISCUSSION

We screened all babies admitted to our NICU with birthweight <1500g and gestation ≤32 weeks. Infants with birthweight ≥1500g and gestation more than 32 weeks were screened only if they had additional risk factors. In a recent article, Chawla, *et al.*(7) have suggested the same screening criteria. As reported by Palmer, *et al*.(8), incidence and severity of ROP was closely related to lower birthweight and lower postconceptional age, as was seen in our study. The incidence of ROP of 22.6% in our study was much lower than that reported by Gopal, *et al.*(9) in 1995. In more recent studies, incidence of ROP reported is similar to our incidence(10,11).

There are varying screening criteria described by different authors. Maheshwari, *et al*.(12) screened all babies weighing <1500g with a gestational age <35 weeks. Gupta, *et al*.(11) screened all babies ≤1500g and/or gestational age ≤35 weeks. Vinekar, *et al.*(13) suggested that the scenario in developing countries is quite different. Larger and gestationally 'older' infants are more likely to develop ROP compared to their counterparts in Western countries. Hence, the application of Western screening guidelines for developing countries has been questioned by Jalali, *et al*.(14). As a higher cutoff limit, they recommended screening babies born at <37 weeks gestation and/or birthweight <2000g in the presence of a high sickness score, in order to prevent missing any infant with threshold ROP. Goble, *et al.*(15) felt that they were screening too many babies for ROP and recommended that babies with birthweight above 1250g should not be screened. In our study, we would have missed 12 cases of ROP needing laser if we had used <30 weeks criteria, as per American Academy of Pediatrics (AAP) updated recommendations(16).

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(10,13, 17,18). In our study, oxygen administration, septicemia, and apnea were found to be significant risk factors. Vinekar, *et al*.(13) also found that septicemia was a significant risk factor. Aggarwal, *et al*.(10) found apnea, clinical sepsis and male sex to be significant risk factors. We started using surfactant sparingly in 2001, and then more frequently in later years. Seventy one neonates received surfactant, out of which 37 had ROP and 34 had no ROP. Seiberth, *et al*.(4) found surfactant a significant risk factor, but we did not find it significant.

It has been suggested that 13% of infants would be missed if AAP criteria are applied(19). So, we feel that all babies with birthweight less than 1500g and gestation ≤32 weeks should be routinely screened. Infants with birthweight between 1500-2000g and gestational age more than 32 weeks should be screened at the discretion of the neonatologist, depending on other risk factors during the course of stay in the NICU.

Ng, *et al*.(19) and Connolly, *et al*.(20) have reported that long term structural and functional outcome using laser was superior to that obtained with cryotherapy. Favorable results were obtained in 83% eyes treated with laser as compared to only 25% treated with cryotherapy. Laser obviates the need for general anesthesia and hardly has any complications. We found that the results of laser are extremely satisfactory and only 2 children (9%) had poor outcome, out of the 22 children who were available for 3 year follow up.

Since ROP is essentially asymptomatic in the early stages, standards of practice now demand carefully timed retinal examination of at risk infants

WHAT IS ALREADY KNOWN?

- Prematurity, oxygen administration, septicemia, apnea and blood transfusion predispose to retinopathy of prematurity (ROP).

WHAT THIS STUDY ADDS?

- Bigger and gestationally more "mature" babies can develop ROP. Laser photocoagulation is a safe therapeutic procedure with good outcome.

for ROP by an ophthalmologist experienced in the examination of the retina, to minimize the risks of visual loss by these infants.

ACKNOWLEDGMENT

We gratefully acknowledge the help of Dr Vaijayanti Deodhar for doing the follow up ophthalmic examination and Ms Anjali Mote for statistical analysis.

Contributors: SC conceived the project, supervised data collection, wrote the manuscript and will be guarantor for the paper. VP did the retinal examination and laser photocoagulation and helped to write the article. UV was in charge of the clinical management in NICU and reference for ROP screening. SK was in charge of the clinical management in NICU and reference for ROP screening. AK collected data, helped in statistical analysis and writing of the article. The final manuscript was approved by all authors.

Funding: None.

Competing interest: None stated.

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