Original Articles

RETINOPATHY OF PREMATURITY: INCIDENCE AND RISK FACTORS

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Objective: *To determine the incidence of Retinopathy of Prematurity (ROP) in high risk babies admitted to the neonatal unit and to study risk factors for it's development.* ***Design:*** *Prospective cohort study.* ***Setting:*** *Level 11 Neonatal Intensive Care Unit.* ***Subjects:*** *100 babies admitted to the neonatal unit during a 4,year period who were below 1500 g or whose gestation was ≤ 34 weeks.* ***Methods:*** *Examination of the eye was done in the neonatal unit or in the neonatal follow up clinic by an Ophthalmologist by indirect Ophthalmoscopy at 4-6 weeks postnatal age.* ***Results:*** *The incidence of ROP was 46%. Of the 100 babies screened, 21 had stage 1,14 had stage II, 8 had stage III and 3 had stages IV and V. The incidence of ROP was 73.3% among < 1000 g babies and 47.3% among < 1500 g babies. The incidence of ROP among 28-29 weeks, 30-31 weeks and 32-33 weeks babies was 83%, 60% and 50%, respectively. The maximum stage of ROP developed between 37-42 weeks post conceptional age in 69% subjects. On univariate analysis, gestation ≤ 32 weeks, anemia, blood transfusions, apnea and exposure to oxygen significantly increased the risk of developing ROP. On multivariate logistic regression analysis, anemia and duration of oxygen therapy were the significant independent predictors of development of ROP. Nine of the 46 babies underwent cryotherapy for threshold ROP.* ***Conclusion:*** *The incidence of ROP among high risk babies is significant and duration of oxygen therapy and anemia are independent factors predicting the development of ROP. All high risk babies should be screened for ROP. Cryotherapy is a relatively simple procedure which can be done in the neonatal unit.*

Key words: *Retinopathy of prematurity, Prematurity, Low birth weight, Cryotherapy.*

RETINOPATHY of prematurity (ROP) is a vaso-proliferative retinopathy occurring mostly in premature babies. With improved survival of sick premature and very low birth weight babies there has been a steady increase in the incidence of ROP(l). Neonatal care in India has been improving and with this, there has been an increase in survival of very low birth weight and premature babies. Many neonatal units are now screening high risk babies for ROP but there is a paucity of published reports in this direction. This study is a follow up to our earlier report of ROP in India(2) with the objectives of determining the incidence and risk factors for ROP.

Subjects and Methods

Babies admitted to the neonatal unit

with birth weight of <1500 g and/or gestation of <34 weeks were screened for ROP. They were entered into the study if they had atleast 2 Ophthalmoscopic examinations and were followed up for atleast 6 mo. The study period was from January 1991 to December 1994. These babies were examined by an Ophthalmologist by indirect ophthalmoscopy. In the beginning, assessment was done at 4-6 wks post natal age while in the later part of the study we examined babies at 3-4 wks postnatal age. Examination was done in the nursery or in the neonatal follow up clinic.

Mydriasis was achieved by using 1% Tropicamide thrice at intervals of 5 min followed by 1-2 drops of 2.5% or 5% phenylephrine twice at intervals of 5 min. Follow up assessments were done once a week, if there was stage 1 ROP, once in 3-4 days if there was stage 2 ROP and alternate days if there was stage 3 ROP. Staging of ROP was done according to the International classification(3,4). Babies were subjected to cryotherapy if they had threshold disease *(Table I).* Subjects with non-threshold ROP were followed till there was regression. Cryotherapy was done in the neonatal ward by the Ophthalmologist under topical anesthesia. Babies were monitored during the procedure using a saturation monitor or cardio-respiratory monitor and ventilatory support was provided, if needed. Sedation and analgesia were not used during the procedure. Cryotherapy protocol used was as per earlier recommendations (5). After cryotherapy, re-examination was done after 48 h and 1 wk later and repeat cryotherapy was done if there was no regression. Favorable outcome was defined as per the Cryo-ROP study (5). Presence of retinal fold or retinal detachment, involving macula and presence of retrolental tissue was defined as unfavorable outcome. If these changes were absent, a favorable outcome was defined.

TABLE I-*International Classification of ROP*

Stage	Features
I	Demarcation line- a line seen between vascular and avascular retina
II	Ridge -(elevated demarcation line)
III	Ridge with extra retinal fibrovascular proliferation
IV	Sub total retinal detachment
	A - Not involving fovea
	B - Involving fovea
V	Total retinal detachment

PLUS DISEASE-dilatation of posterior pole vessels; Threshold disease-Stage III PLUS disease in zone 1 or zone 2, 5 contiguous clock hour involvement or 8 non contiguous clock hour involvement.

For study purposes, small for date (SFD) was defined as any baby whose weight was <3rd percentile for the gestation, anemia was defined as a hematocrit of <40, sepsis was defined as clinical and hematological evidence of sepsis and oxygen meant use of hood oxygen.

Relevant patient data was entered in a proforma and analyzed. Statistical analysis was done by't' test and chi-square test and relative risk were calculated for various risk factors. Multiple logistic regression analysis was done to assess the significance of the risk factors. The statistical packages EPI6 and SPSS were used.

Results

A total of 100 babies were screened during the 4 year period. A total of 201 babies (102 intramural, 99 extra mural) were eligible to enter the study but only 100 babies could be followed up (56 intramural and 44 extramural). The weight range was 710 to 1700 g with a mean

weight of 1236.97± 220 g. The gestation range was 28 weeks to 38 wks with a mean gestation of 32.8±2 wks. Fifty eight babies were small for date (SFD) and 42 were appropriate for date (AFD). There were 7 babies > 1500 g weight which were preterm AFD while 11 subjects > 34 wks were SFD babies whose weights were < 1500 g.

Of the 100 babies screened, 54% had no ROP and 46% had some stage of ROP; 21% had stage I, 14% had stage II, 8% had stage III, 1% had stage IV, and 2% had stage V. Most cases had similar stages of ROP in both eyes. Only 4 babies had different stages of ROP in each eye. The maximum ROP stage was taken into consideration for analysis. The incidence of ROP was 73.3% among <1000 babies and 47.3% among <1500 g babies. The incidence of ROP among 28-29 wks, 30-31 wks and 32-33 wks gestation subjects was 83%, 60% and 50%, respectively. The maximum stage of ROP developed between 37-42 wk post conceptional age in 69% cases. The mean postnatal age at examination was 4.75±1.5 wks and mean postnatal age when maximum stage of ROP was detected was 6.34±2.55 wks. The mean post conceptional age at first examination was 37.8±2.85 wks. The mean post conceptional age when maximum stage of ROP was detected was 38.8+ 2.97 wks.

On univariate analysis, significant factors were gestation < 32 wks, oxygen use,anemia, blood transfusions and apnea *(Table II).* Oxygen was one of the significant risk factors but 33% of babies not on oxygen developed ROP. Factors which did not increase the risk of ROP were sepsis, SFD, and weight <1000 g. When duration of oxygen therapy was compared in the ROP and non-ROP group, this difference was significant (p <0.001). The mean duration in the ROP group was 1.8±2.9 days and in the non-ROP group it was 0.5±.92 days. Multiple logistic regression analysis with backward stepwise selection model using SPSS identified only presence of anemia and duration of oxygen therapy in days as independent factors which could significantly predict development of retinopathy of prematurity (p = 0.005 and 0.04, respectively). Presence of anemia correlated highly with receipt of blood transfusions (r = 0.88) and hence the increased risk may be related to either anemia itself or the blood transfusions. The regression model could predict ROP in 70% of the babies.

Cryotherapy Results: Cryotherapy was done in 9 babies and 16 eyes. One subject with bilateral stage 4 disease refused surgery. This was detected at first examination at 6 weeks post natal age and 37 weeks post conceptional age. One baby had stage V disease in one eye and stage III in the other eye detected first at 4 wks

TABLE II–*Univariate Risk Factors*

Risk Factors (n)		Relative Risk (95% confidence limits)		P value
Weight <1000 g	(15)	1.53	(1, 236)	0.09
Gestation ≤32 wks	(44)	1.81	(1.17, 279)	0.006
Small for date	(58)	0.86	(.56, 1.32)	0.49
Oxygen	(46)	1.83	(1.17, 2.84)	0.005
Oxygen >3 days	(12)	1.57	(1.15, 2.13)	0.01
Anemia	(59)	2.50	(1.41, 4.45)	0.003
Blood transfusions	(62)	2.91	(1.52, 5.56)	0.001
Apnea	(32)	1.95	(1.31, 2.90)	0.001
Sepsis	(45)	0.86	(0.56, 1.33)	0.04

post natal age and 37 wks post conceptional age. One subject had stage IV bilaterally which progressed to stage V. This was first detected at 4 wks post natal age and 38 wks post conceptional age. Seven babies needed cryotherapy for both eyes and 4 babies (8 eyes) required repeat cryotherapy. When there was bilateral disease, cryotherapy was done at two sittings. Complications during cryotherapy included pre-retinal and conjunctival hemorrhages, and chemosis and edema of lids in all subjects and cryoburns of lids in 14/16 eyes. All problems were resolved promptly. Three babies developed apneic episodes and 2 of these needed ventilatory support. In one baby, there was keratinization of the palpebral conjunctiva. On follow up, a favorable outcome was evident in 14/16 eyes.

Discussion

Retinopathy of prematurity is a vasoproliferative disorder occuring predominantly in premature infants. Normal vasculature of the developing retina is interrupted due to some injury. After a latent period there is neovascularization. If this new vessel formation is abnormal, it leads to progressive retinopathy, ultimately resulting in retinal detachment and blind-ness(6-8). If this process occurs rapidly, it is called rush disease(3). The incidence of ROP in the west has been reported to be 53-88.5% in <1000 g babies and 34.9-60.1% in <1500 g babies(9-ll). In our study, the incidence seems to follow a similar pattern. The incidence of ROP has been reported to be 82.5% in babies <28 wks and 27% among 29-31 wks gestation(ll). In our study the incidence seems to be higher in 28-29 and 30-31 wks group.

The risk factors for ROP that have been mentioned include prematurity, hyperoxia, hypoxia, hypercarbia, apnea, sepsis and blood transfusions(3,12,13). The risk factors that we found significant by univariate analysis were gestation <32 wks, oxygen administration, anemia, blood transfusion and apnea. Factors which were not significant were SFD, sepsis and weight <1000 g. We found that the mean duration of oxygen was significantly higher in the ROP group. Logistic regression analysis identified anemia and oxygen therapy to be independent factors which significantly predicted the development of ROP. Since there was a high correlation between anemia and blood transfusions, this effect may be due to anemia *per se* or due to blood transfusions. Anemia may produce tissue hypoxia and hence predispose to ROP and adult blood transfusions could increase oxygen dissociation and hence cause tissue hyperoxia which could predispose to ROP.

In our study, the maximum stage of ROP developed between 37 and 42 wks post conceptional age in 69% of babies, supporting the theory that post conceptional age is an important factor in the development of ROP(13). The mean postnatal age when maximum stage of ROP occured was 6.34±2.55 wks and when first examination was done was 4.75+1.5 wks. The mean post conceptional age when maximum ROP developed was 38.8±2.97 wks and mean post conceptional age when first examination was done was 37.8+2.5 wks. We feel that the first screening should be done earlier as some of the babies developed ROP as early as 3 wks post natal age and 34 wks post conceptional age.

Nine babies and 16 eyes underwent cryotherapy for thereshold disease and the results of cryotherapy were good and complications due to procedure were minimal. Cryotherapy is the recommended mode of treatment for ROP and it is known to reduce unfavorable outcome(14). Long term follow up of untreated babies has shown that unfavorable outcome could be

as high as 43-59%(15).

To conclude, we feel that the incidence of ROP in our study is significant and the risk factors are also similar to those mentioned in other studies. Appropriate screening of high risk babies has been shown to be cost effective(16). We recommend that first assessment be done as early as 3-4 weeks postnatal age or 34-35 weeks post conceptional age and stress the need to follow up till term gestation. Cryotherapy is a relatively safe procedure which can be done in the neonatal unit itself and should be done when there is threshold disease.

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