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Literature Review

Retinopathy of Prematurity (ROP): Analysis of Screening, Incidence and Risk Factors (FP 1343)

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Abstract

This is a prospective, observational and unmasked study. Two hundred and seven premature babies were screened for incidence of ROP and foetal and maternal risk factors to design an effective screening program for ROP. Preterm neonates with birth weight ≤ 1500 grams (gms) and/or gestation age ≤ 32 weeks and selected patients with birth weight between 1500 to 2000 grams or gestational age > 32 weeks but ≤ 35 weeks with unstable clinical course or neonatologist's over high risk factors were included in the study. The incidence of ROP (any stage) in this study was 21.26% (37/207 neonates). Majority of patients (88.70%) develop mild form of ROP (stage 1 and 2). Low gestation age low birth weight were significant risk factors for developing ROP. Other risk factors predisposing to development of ROP were unmonitored oxygen supplementation, respiratory distress, sepsis, blood transfusion, surfactant use, metabolic acidosis and intraventricular haemorrhage. Maternal risk factor was pregnancy induced hypertension (PIH). On multivariate analysis unmonitored oxygen exposure was the only independent risk factor for developing ROP.

Keywords: *Low Birth Weight; Low Gestation Period; Oxygen Supplementation; Preterm Neonate; Risk Factors; Retinopathy of Prematurity*

Introduction and Review of Literature

Retinopathy of prematurity (ROP) is one of the leading causes of blindness and marked visual impairment among premature and low birth weight neonates. The rate of blindness caused by ROP varies greatly among countries and different regions within countries depending on their level of development, standard of neonatal care, neonatal outcomes and whether effective screening and treatment programs exist. That is why, screening guidelines must 'not be generalized' and must take into account 'regional differences'. As screening criteria differ across different units and time-periods, overall incidence of ROP varies from 20% to 52% with more recent studies reporting lower rates of ROP ranging from 20% to 30% [1-5]. An important lesson is learnt from units reporting ROP in different time periods. Initial low incidence of ROP rises with better screening protocols, availability of assisted ventilation services and survival of sicker, smaller neonates. In this phase even sick but relatively mature (late preterm) neonates have been reported to develop ROP. This period is followed by gradual decline in incidence of ROP especially of more severe variety.

Different studies have reported various risk factors. Some of them are debatable, but most established among them are low gestation age, low birth weight and unmonitored supplemental oxygen administration [6-8]. Treatment includes cryotherapy/laser photocoagulation of avascular retina and recently intravitreal injections of anti-VEGF agents for threshold disease and vitreoretinal surgery for advanced stages with variable visual outcomes.

Considering so much of diversity in incidence, risk factors and treatment outcomes of this disease, we realised that guidelines and screening programs that take into consideration the characteristics of local populations should be designed. So, we decided to conduct a prospective study in our region, in order to design a better and more efficient screening program and analyse risk factors and efficacy of latest treatment modality using anti VEGF agent.

Materials and Methods

This prospective, unmasked study was conducted in a tertiary care hospital in Northern India among the premature neonates admitted in Neonatal intensive Care Units (NICU), from September 2009 to August 2010. Patients with birth weight ≤ 1500 grams and/or Gestational age ≤ 32 weeks and selected patients with birth weight between 1500 and 2000 grams or gestational age > 32 weeks but ≤ 35 weeks with unstable clinical course or neonatologist's concern over high risk factors were included. Patients with major congenital malformations, chromosomal anomalies, ocular anomalies and patients who died or lost to follow up were excluded from the study. All subjects underwent thorough history taking from parents, data recording from available records. Complete Ophthalmologic examination including fundus examination was done with Binocular Indirect Ophthalmoscope using +20 D or +30 D lens and scleral indentation using a small muscle hook.

Standard procedure and precautions described in literature were employed for fundus dilatation, local anaesthesia and examination.

For each infant with ROP, the age at which it was first detected, the location (zones), severity and extent of ROP, exposure to any risk factors were recorded on a prescribe format and analysed statistically regarding factors such as gestation age, birth weight, gender, period of supplemental oxygenation, Apgar score, history of blood transfusion, total parenteral nutrition, surfactant used, respiratory distress, documented sepsis, metabolic acidosis, seizures, neonatal jaundice, intracranial haemorrhage, apnoeic attacks, necrotizing enterocolitis, multiple gestation and some prenatal maternal factors such as mother's age at the time of conception, diabetes, smoking, preeclampsia and maternal bleeding etc. ETROP recommendations were adhered to whenever treatment was necessary.

Results

In total 207 surviving preterm neonates who met inclusion criteria were screened. Subjects were finally divided in two groups. In group I: ROP was present while in group II: ROP was absent. At the completion of follow-up, 44 (21.26%) were diagnosed to have developed some degree of ROP in at least one eye on at least one occasion. Gender was not found to significantly influence the frequency of ROP in the study ($p = 0.124$). The mean birth weight of group I was 1284.66 ± 209.144 grams and of group II was 1396.04 ± 188.237grams. This difference was statistically significant using independent sample t-test (p-value = 0.001). The mean period of gestation in group I was 31.095 ± 1.856 weeks and of group II was 32.207 ± 1.545 weeks. This was highly significant using independent sample t-test ($p < 0.001$). Among the 44 ROP patients, 2 (4.54%) cases of unilateral and 6 (13.62%) cases of bilateral stage 3 with plus disease, extending over > 6 contiguous/8 cumulative clock hours were found. Bilateral cases underwent nonconfluent green laser peripheral retinal ablation using the indirect ophthalmoscope. The 2 cases with U/L disease were treated with intravitreal injection of 125 µg (0.05 cc) of Intravitreal Bevacizumab (Avastin, Zentech) once in involved eye. Regression occurred in all cases. We observed 16 cases (36.32%) of stage 2 retinopathy occurring in zone III or zone II and 20 cases (45.40%) of stage 1 retinopathy in zone III or zone II, all of which regressed during without any intervention during the observation period.

Although 37.3% of neonates with a birth weight ≤ 1,250g had ROP, only 14.9% of neonates with a birth weight > 1,250g had ROP. This was statistically significant ($P = .001$). The rate of ROP between neonates with a birth weight ≤ 1,500 g and those with a birth weight > 1,500 g, was also statistically significant ($P < .001$). The rate of ROP was also higher in neonates with a gestational age of 32 weeks or less (29.9%) compared to neonates with a gestational age > 32 weeks (10.0%) ($P = 0.001$). The mean gestational ages were 31.31± 1.692 weeks for mild disease and 29.40 ± 2.408 weeks for severe disease. This difference was statistically significant (p=0.028). While, on univariate analysis Respiratory distress, use of Surfactant, Sepsis, low Apgar score, metabolic acidosis, Blood transfusion and Pregnancy Induced Hypertension were found to be significant, only exposure to unmonitored oxygen was significant on multivariate analysis.

Discussion

In our study, incidence of ROP (21.26%) is similar to more recent studies.[5] Our incidence of 14.9% in babies with birth weight >1250 gm. is greater than a report from USA (2006) in which Yanovitch., *et al.* found 4.2% in babies weighing between 1250 - 1800 grams [9]. Our study has revealed 10 risk factors that portend the development of ROP in preterm babies in our region. This is comparable to other studies [2,10,11]. When these significant factors were analysed using multivariate logistic regression, it was found that oxygen exposure ($p < 0.001$) was the only independent risk factor, which is a well-established risk factor in the development of ROP including severe ROP, in VLBW and LBW babies [8].

A recent study in India with similar screening criteria and similar overall incidence (22.3%) found that 33.6% babies with ROP required treatment [5]. This was greater than that found in our study (11.36%). This difference may be explained by better NICU facilities in our institute. Though the incidence of ROP is significantly greater below the 1500 mark but the fact that 8.1% of high risk babies weighing > 1500 grams have ROP, cannot be ignored. The need of the hour is to establish 'sickness criteria' so that only those with significant risk factors in the heavy cohort are screened.

Conclusion

Incidence of ROP was inversely correlated with low birth weight and gestation age. The incidence of ROP in neonates with birth weight of ≤ 1500 grams and those with greater than 1500 gms was statistically significant. Of 37 babies weighing > 1500 gms 8.1% develop ROP. Eight % of high risk babies weighing > 1500 gms having ROP is a considerable figure. So, babies with birth weight > 1500 gms should also be screened. The population of infants who develop severe ROP in developed countries differs from those in developing countries. That's why the screening guidelines must 'not be generalized' but should take into account 'regional differences'.

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