

THRESHOLD STAGE OF RETINOPATHY OF PREMATURITY: MATERNAL AND NEONATAL RISK FACTORS

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Background: The aim of this study was to review the maternal and neonatal risk factors associated with retinopathy of prematurity (ROP) and the threshold stage of the disease.

Patients and Methods: In this prospective cohort study, all preterm infants of less than 1501 g birth weight were screened for ROP between January 1996 and December 1997 at the neonatal unit of the Maternity Hospital in Kuwait. The rate of the threshold stage of ROP, as well as risk factors associated with the disease, were identified.

Results: A total of 234 babies were screened for ROP, of which 151 (64.5%) developed the disease and 34 (14.5%) had the threshold stage of ROP. Several factors were found to be associated with ROP and threshold ROP. Stepwise regression analysis revealed that low birth weight ($P<0.002$) and exposure to high oxygen concentration ($P<0.0001$) were independently associated with ROP. In addition, low birth weight ($P<0.006$), high oxygen concentration ($P<0.003$), and culture-proven sepsis ($P<0.04$) were found to be independent predictors of threshold ROP.

Conclusion: Apart from low birth weight and exposure to high oxygen therapy, which are well-documented risk factors of ROP, septicemia was also found to be associated with the threshold stage of ROP.

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Key Words: Retinopathy of prematurity, threshold stage, low birth weight, perinatal risk factors.

Retinopathy of prematurity (ROP) is a disorder of the blood vessels in the developing retina of premature infants,¹⁻³ and is one of the major causes of blindness and impaired vision among children.^{1,2,4,5} Since many premature and extremely low birth weight babies survive, the disease has become a challenge to neonatologists and ophthalmologists. The incidence varies in different neonatal units,^{3,6-13} and low birth weight has been the only risk factor uniformly identified.^{1,3,4,6-11,13-17} The rate of the threshold form of the disease has been measured in different neonatal units,^{6,7,9,13} however, its association with risk factors has not been fully identified. We present the rate of and risk factors associated with the threshold stage of ROP in a cohort of preterm babies born in our units over a two-year period.

Materials and Methods

Two hundred and thirty-four infants with a birth weight of less than 1501 g were admitted to the neonatal unit of the Maternity Hospital of Kuwait, from 1996 to 1997. Our unit

has secondary and tertiary neonatal care levels with a capacity of about 80 beds, and the hospital has an annual delivery rate of about 13,000.

Infants were screened for ROP by an ophthalmologist using indirect ophthalmoscope, after dilating the pupils with 2.5% phenylephrine and 0.5% tropicamide eye drops instilled into each eye three times, at intervals of 15 minutes prior to examination. We follow the protocol of examining the preterm infants at four weeks of postnatal age, and/or at 32 weeks of postmenstrual age, with those above 32 weeks of gestation examined in the first week of birth. If no ROP was detected at the initial examination, the infants were re-evaluated once every two weeks until discharge, and then every four weeks until three months of postnatal age. If ROP was detected, the examinations were performed every week until the disease started to regress. The changes of ROP were classified according to the International Classification of Retinopathy of Prematurity.¹⁸⁻²²

Patients' data were collected prospectively, and the following neonatal risk factors were identified: birth weight, gestational age, Apgar score of less than 5 at five minutes, and maximum concentration of inspired oxygen. We usually aim to keep the oxygen saturation above 91% most of the time despite the difficulties involved. In addition, surfactant therapy (Survanta[®]), reception of blood transfusion, phototherapy, and total parenteral nutrition, presence of patent ductus arteriosus, intraventricular

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TABLE 1. Neonatal risk factors associated with ROP.

	ROP (n=151)	No ROP (n=83)	P-value
Birth weight in grams (Mean±SD)	1087.3±208.1	1250.6±175.3	0.0001
Oxygen therapy (Mean±SD)	60.23±12.12	50.12±9.85	0.0001
Presence of patent ductus arteriosus	96 (63.6%)	25 (30.1%)	0.0001
Presence of intra-ventricular hemorrhage	62 (41.1%)	13 (15.7%)	0.0001
Blood transfusion	134 (88.7%)	58 (69.9%)	0.002
Surfactant therapy	108 (71.5%)	26 (31.3%)	0.0001
Phototherapy	144 (95.3%)	71 (85.5%)	0.008
Apnea	67 (44.4%)	15 (18.1%)	0.0001
Apgar score <5 at 5 min	54 (35.8%)	21 (25.3%)	0.11
Proven sepsis	95 (62.9%)	23 (27.7%)	0.0001
Undergone surgery	16 (10.6%)	1 (1.2%)	0.008
Total parenteral nutrition	135 (89.4%)	64 (77.1%)	0.01

TABLE 2. Maternal risk factors and ROP.

	ROP (n=151)	No ROP (n=83)	P-value
Antepartum hemorrhage	31 (20.5%)	7 (8.4%)	0.016
Chorioamnionitis	7 (4.6%)	8 (9.6%)	0.165
Gestational diabetes	16 (10.6%)	13 (15.7%)	0.26
Maternal hypertension	50 (33.1%)	26 (31.3%)	0.72
Premature rupture of membranes	25 (16.6%)	18 (21.7%)	0.33

TABLE 3. Neonatal risk factors associated with threshold stage of ROP.

	Threshold ROP (n=34)	Others (n=200)	P-value
Birth weight in grams (Mean±SD)	1002.1±222.31	1169.55±200.5	0.0001
Oxygen therapy (Mean±SD)	65.6±10.85	55.1±12.01	0.0001
Presence of patent ductus arteriosus	24 (70.6%)	97 (48.5%)	0.017
Presence of intra-ventricular hemorrhage	15 (44.1%)	60 (30%)	0.1
Blood transfusion	32 (94.1%)	160 (80%)	0.26
Surfactant therapy	26 (76.5%)	108 (54%)	0.05
Phototherapy	34 (100%)	181 (90.5%)	0.06
Apnea	19 (55.9%)	63 (31.5%)	0.006
Apgar score <5 at 5 min	13 (38.2%)	62 (31%)	0.4
Proven sepsis	23 (67.6%)	95 (47.5%)	0.03
Undergone surgery	7 (20.6%)	10 (5%)	0.001
Total parenteral nutrition	32 (94.1%)	167 (83.5%)	0.11

TABLE 4. Maternal risk factors and threshold stage of ROP.

	Threshold ROP (n=34)	Others (n=200)	P-value
Antepartum hemorrhage	6 (17.65%)	32 (16%)	0.5
Chorioamnionitis	3 (8.8%)	12 (6%)	0.46
Gestational diabetes	3 (8.8%)	26 (13%)	0.5
Maternal hypertension	8 (23.5%)	68 (34%)	0.43
Premature rupture of membranes	8 (23.5%)	35 (17.5%)	0.4

hemorrhage of all grades collectively, apnea and proven sepsis, and ongoing abdominal surgery were also considered.

The following maternal factors were also identified: gestational or maternal diabetes, gestational or maternal

hypertension, antepartum hemorrhage, chorioamnionitis and premature rupture of membranes. The risk factors were then related to the presence of the disease and its threshold form in order to establish an association. Threshold ROP was defined as the presence of at least eight cumulative 30° sectors (clock hours) of stage 3, or at least five contiguous 30° sectors of stage 3 of extraretinal neovessels in the presence of disease. This is also defined as the presence of dilated tortuous vessels in the posterior pole.¹⁸⁻²²

Cryotherapy or laser treatment for threshold ROP was done under general anesthesia in another center after transporting the infants. Those infants were then followed up weekly until the regression of the disease.

The data was then entered in the SSPS database program and analyzed statistically, using Student's *t*-test for continuous variable and chi-square test for categorical variables. Stepwise logistic regression analysis was used to determine the predictor variables associated with the development of ROP.^{10,23}

Results

Over the two-year study period, a total of 234 babies of less than 1501 g were screened for the presence of ROP. The mean birth weight was 1145.64±211.24 g (range 600-1500), and that for the gestational age was 30.20±1.96 weeks (range 26-35). There were 115 males and 119 females, 171 singleton infants, 47 infants who came from sets of twins, four sets of triplets and four infants who were part of a set of quintuplets. There were nine deaths.

The total number of documented ROP cases was 151 (64.5%), of whom three had become blind. The mean birth weight was 1087.3±2 and that of the gestational age was 29.7±1.8. There were 74 males and 77 females. The disease occurred in 32 twins, in three infants of the 12 triplets, and in four of the quintuplets. A total of 148 infants had the disease in both eyes, one had it in the right eye, and two infants in the left eye only. The neonatal and maternal risk factors associated with the disease are shown in Tables 1 and 2.

After stepwise logistic regression analysis, only low birth weight (odds ratio 1.03, 95% confidence interval 1.01 to 1.05, *P*=0.002) and oxygen therapy (OR 0.94, 95% CI 0.91 to 0.97, *P*=0.0001) were found to be independently associated with the development of ROP.

Severe (threshold stage) ROP was found in 34 infants (14.5%), consisting of 12 males and 22 females. They comprised 21 singleton babies, nine twin babies, two babies of a set of triplets and two babies of a set of quintuplets. The left eye was involved in 30 babies and the right eye in 28 babies. There was one death among this group. The neonatal and maternal risk factors associated with the threshold stage of ROP are shown in Tables 3 and 4.

After stepwise logistic regression analysis, low birth weight (OR 1.02, 95% CI 1.001 to 1.04, *P*=0.006), high concentration of oxygen therapy (OR 0.92, 95% CI 0.87 to 0.97, *P*=0.003), and presence of culture-proven sepsis (OR 3.5, 95% CI 1.02 to 12.2, *P*=0.04) were independently

associated with the development of the threshold stage of ROP.

Of the 32 infants who received cryotherapy, two failed the treatment and became blind, while one of the two babies who had laser treatment also became blind.

Discussion

Our study showed a high incidence of ROP among the 234 babies of <1500 g birth weight. These findings were similar to a previous report by the authors,¹¹ and to a study by Ng et al.⁶ However, the incidence of the threshold disease in this report was even higher (14.5%) than in our previous article (8.3%) and in Ng's report (6.3%).

Establishing an association between retinopathy of prematurity and perinatal factors surrounding the infant remains a big challenge to neonatologists and ophthalmologists. Low birth weight is constantly associated with the disease, as, to a lesser extent, is oxygen therapy.^{3,5,11-13,15-22,26} Regression of the disease without treatment occurs in the majority of preterm babies who have the disease.²⁶ However, the threshold stage of ROP is the severe form of the disease, and the recommended treatment is either cryotherapy or laser treatment.¹⁸⁻²²

Reports of an association between the threshold stage of ROP and perinatal factors are lacking. In our study, we were able to establish this association, as we found that low birth weight, oxygen therapy, and culture-proven sepsis could all be considered as risk factors for the threshold disease. This does not mean that the lower the birth weight, the higher the risk of sepsis and abdominal surgery, since the logistic regression analysis identified these to be independent predictors. None of the maternal risk factors reported were associated with ROP or its severe form, a finding which is consistent with other studies.^{9,12}

Our study showed a success rate of 93.7% using cryotherapy, which used to be the standard treatment of retinopathy of prematurity. The current standard is laser treatment, which has been used in different trials with a high success rate, although many centers lack the facilities to use this and so rely on cryotherapy.

We had two infants who received laser treatment. Our experience with laser treatment for retinopathy of prematurity is limited so far, although we are building it up. Of the two babies who received the treatment, we had one failure.

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