Original Research Paper

Volume - 12 | Issue - 10 | October - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Ophthalmology

EFFECT OF ANTENATAL STEROID AND OTHER RISK FACTORS ON RETINOPATHY OF PREMATURITY AT TERTIARY CARE CENTRE.

Dr. Shruti A Patel	3rd Year Resident Doctor Ophthalmology SMIMER, Surat.
Dr Karishma D Desai	M.B.B.S., SMIMER, Surat.
Dr. Khushnood M Sheikh	Professor Department of Ophthalmology SMIMER, Surat.
Dr. Manisha N Patel	Professor and Head of Department of Ophthalmology SMIMER, Surat.
Dr Swati Patel	Assistant Professor in Community Medicine

ABSTRACT **Purpose:** This study aims at identification of various risk factors and effect of antenatal Betamethasone on severity of ROP. **Methodology:** Retrospective observational study done at Tertiary care centre in Ophthalmology department . Prior ethical committee approval and consent from parents were taken. Babies with BW <1.75kg and preterm <34 weeks were screened for ROP after one month and Babies born with <28 weeks were screened after two weeks post partum. The ROP was graded as per guideline given by Government of India under RBSK. The severity of ROP is graded as Non Severe ROP (NO ROP, and stage 1 ROP) and Severe ROP (stage 2,3,4,5 and plus disease) .Their associated risk factors and use of antenatal steroid were noted. All the babies were dilated with short acting cycloplegics and mydraitics and examined by VR surgeon .Babies were followed up as per their maturity of retina till it attains maturity and if require intervention done .In this study data from January 2021 to June 2022 were taken for the purpose of analysis. Statistical analysis done by chi square test and logistic regression for various perinatal factors. **Results:** In this study 113 babies were screened for ROP out of which 41 were having severe ROP and 72 were having non severe ROP. 67 patients were given antenatal betamethasone in that group 18 patients were having severe ROP and 49 having Non severe form(Pvalue 0.01).89 babies were given humidified O2 from that 32 developed severe and 49 Non severe form whereas lower gestational age is more significantly associated with severe form (p Value0.008).ROC curve indicates the probability of development of severe ROP among infants having weight <1.62kg and for GA it showed43.1% sensitivity of severe ROP. **Conclusion:** Study concludes that low gestational age with low birth weight are acting as risk factors for development of severity of ROP. Independently low birth weight (<=1.75kg) is not significantly associated with severity of ROP. Whereas humidified oxygen does not have any effect on severity of ROP. Antenatal steroid independently has a protective role in development of severity of ROP, which requires further exploration.

KEYWORDS : Gestational age (GA) Low birth weight (LBW) Retinopathy of prematurity (ROP)Antenatal steroid

1.INTRODUCTION

Retinopathy of prematurity is a potentially blinding eye disorder that primarily affects premature infants. ROP is a preventable cause of irreversible total blindness in preterm babies. Nowadays with advances in neonatal care, smaller and more premature infants are saved. These babies are at a much high risk for ROP. Babies with ROP are at higher risk for developing retinal detachment, high myopia, strabismus, amblyopia and glaucoma. In the womb a baby's retinal blood vessels begin to grow at 16 weeks and finish growing until after the baby is born. Babies born earlier <=34 weeks of gestation or weight is <=1.75 kg at birth are at risk. ROP occur when abnormal blood vessels grow and spread throughout the retina. These abnormal vessels are fragile and can leak, scarring the retina and pulling it out of position causing retinal detachment. Other risk factors are respiratory distress, type of delivery, blood transfusion, sepsis and apnea. Few western studies have found antenatal steroid to be protective for severe form of ROP but it's impact on ROP is still not clear[3]. Hence, retrospective analysis is done to find the perinatal factors (like oxygen supply and antenatal steroid) associated with severity of ROP.

2.MATERIALS AND METHODS

It is retrospective observational study. Prior ethical committee approval taken and informed consent were taken from parents. The record of data was done at tertiary care hospital in ophthalmology department for duration of 18 months (from Jan.2021 to June 2022). All preterm babies were dilated with combination drop of tropicamide 0.8% and phenylephrine hydrochloride 5%. All the preterm babies less than 34weeks and low birth weight babies of <=1.75 kg weight were examined after 4 weeks postpartum and babies with less than equal to 28 weeks were examined at 2 weeks postpartum using 20D lens with indirect ophthalmoscopy by vitreoretinal surgeon.

Paediatric speculum was used to spread eyelids and wire Vectis was used as a depressor. Babies were examined for retinal development till up to orra serrata and followed up till complete development of retina. The mothers were given injection Betamethasone at the time of delivery were noted from history records. Data were recorded and analysed by following way:

ROP was classified by following screening guidelines of government of India [RBSK guidelines][4] The retina is divided into three concentric circles, each centred on the optic disc. The retinal vessels grow out from the optic disc to the periphery and the designation of zones corresponds to the vascular developmental pattern.

Zone1: Defined by a circle whose radius is twice the distance from the centre of the optic disc to the centre of macula (Fovea).

Zone 2: Defined by a circle whose radius is the distance from the centre of the optic disc to the nasal margin of the retina (ora serrata)

Zone3: The remainder of the retina. This is crescent-shaped zone that largely involves temporal retina

Disease severity (Staging). Vascularization of the retina is incomplete or immature prior to the development of ROP. Disease severity is determined by staging. More than one stage may be present in the same eye.

Stage 1. Demarcation line , A thin but definite structure separating the avascular retina anteriorly from the posteriorly vascularized retina.

Stage 2. Ridge , A ridge arising from the demarcation line which has 3 dimensions (height and width) and extends above the retina.

Stage 3. Extra retinal fibro vascular proliferation Extra retinal fibro vascular proliferation or neovascularization extends into the vitreous from the ridge. The posterior aspect of the ridge appears irregular as the proliferation becomes more extensive.

Stage 4. Partial retinal detachment , Retinal detachments are generally concave and most are circumferential. Stage 4A ROP with Nasal Retinal Detachment , They are divided into 2 stages: 4A: extra foveal, and 4B: foveal.

Stage 5. Total retinal detachment , Retinal detachments are generally tractional but may occasionally be exudative. They are usually funnel-shaped.

Plus disease:
It is characterized by: Significant level of venous dilation, Arteriolar tortuosity of the posterior retinal vessels. Arteriolar tortuosity of the posterior retinal vessels. Two quadrants of the eye retina must be involved for the changes to be characterized as plus disease.

Pre-plus disease: 1. Pre-plus disease indicates posterior pole tortuosity and dilatation that are not sufficiently abnormal to reach the criteria of plus disease, but is nevertheless greater than that regarded as normal. 2. Pre-plus disease may or may not progress to plus disease.

Aggressive posterior ROP (AP-ROP): This is an uncommon, rapidly progressive, and severe form of ROP that has previously been referred to as "Rush disease". Untreated, it usually progresses to Stage 5 ROP. Characteristic features are: the posterior location, prominence of plus disease. Haemorrhages may be present at the junction between vascularised and avascular retina.

All ROP babies were classified in non-severe and severe form for purpose of analysis.

Non-severe ROP	Mature Retina (NO ROP)
	Stage -1 ROP
Severe ROP	Stage -2ROP
	Stage -3ROP
	Stage-4ROP
	Stage-5ROP

Inclusion Criteria:
1: All the premature babies which are less than or equal to 34 weeks.
2: All the low birth babies (<=1.75 kg irrespective of gestational age)
3: Babies with GA 34-36 weeks and given oxygen therapy with other risk factor (antenatal steroid and low birth weight).

(4) Exclusion Criteria (All / any of the following)-
1: Neonate who dies before 4 weeks postpartum.
2: Infant with congenital anomalies
3: Chromosomal abnormalities
4: Congenital metabolic disease

Statistical Method :
Various Perinatal factors were analysed by bivariate analysis and logistic regression. Where as ROC curve was used to analyse relationship between GA, birth weight with severity of ROP.In bivariate analysis, factors associated with severe ROP development were investigated using the chi-square test. A significance level of 5% was used. For Comparison of mean difference of Quantitative risk factors related with severe and no severe ROP were checked using independent t-test. Logistic regression is used to estimate the association of one or more independent (predictor) variables (i.e GA & Steroid) with a binary dependent (outcome) variable severe and non-severe ROP.

A logistic regression was performed to estimate the effect of GA and Steroid given to mother on the likelihood that infant have Severe /Non sever ROP. Receiving Operating Curve (ROC) used to find out the cut-off value of Birth weight and GA for prediction of development of severe and non-severe ROP.

RESULTS:
Table.1 Details of association of severity of ROP and risk factors.

Risk Factors	Severe ROP	Non severe ROP		P- Value
Steroid not taken	23(50%)	23(50%)	46	0.01
Steroid taken	18(26.86%)	49 (73.13%)	67	
Total	41	72	113	
HumidifiedO2 not given	9(37.5%)	23(50%)	24	0.99
Humidified O2 given	32(35.95%)	49 (73.13%)	89	
Total	41	72	113	
Birth Weight	1.499+/-0.336	1.621+/-0.397		0.079
GA	32.627+/-2.461	33.935+/-2.586		0.008

Table 1 reveals the details of association of various risk factors with severity of ROP. Total 67 mothers who were given the steroids and 46 did not given at the time of premature delivery . The percentage of non-severe ROP (73.13%) is higher among the infants whose mother given the steroid as compared to those infants whose mothers were not given and this difference is statistically significant (P value =0.01).

Antenatal administration of steroids can reduce the chance of developing severe ROP among the infant whose mother given steroids. ($OR_{(unadjusted)}$ =2.722,95%CI (1.234,6.004)). Total 89 infants administered with humidified O_2 among them 57(64.04%) developed non severe ROP. No significant difference has been observed in development of severity of ROP in infant to whom humidified O_2 was given and not given. (P- value = 0.99). Birth weight of infants was not found to be significantly associated with development of severe and non-severe ROP (P- value =0.079) whereas lower GA was significantly associated with development of severity of ROP (P- value = 0.008).

Table.2 Multi variate Analysis of Risk factors associated with development of Severe ROP.

	B	P- value	Adjusted OR Exp(B) with 95% CI
GA	-.221	.019	0.801(0.666,0.964)
Steroid	-.925	.048	0.397(0.159,0.991)
Constant	7.042	.026	0.0001144

A logistic regression model was statistically significant Chi-square (3) = 36.390, P < 0.005. The model explained 33.7% (Nagelkerke R^2) of the variance in Severity of ROP and correctly classified 76.1% cases.

The Mother who took Steroid in their infant 0.397 time less chance of development the severe ROP. It showed 0.801 times higher chance of development of severe ROP in preterm infant with lower gestational age.

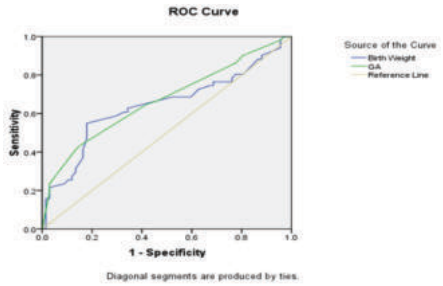

Table.3 Receiver operator characteristics curve

Test Result Variable(s)	AUC	P- Value	Cut-Off Value	Sensitivity	Specificity
Birth Weight	0.643	P<0.05	1.62	54.9%	82.1%
GA	0.668	P<0.05	34.5	43.1%	85.1%

Area Under the Curve represents the degree or measure of separability. It tells how much the model is capable of distinguishing between classes. By analogy, the Higher the Area Under the Curve, the better the model is at distinguishing between patients with the disease and no disease Here in this Area Under the Curve for birth weight and GA is 0.643 & 0.668 Which indicates model is good predictor.

By cut-off value of 1.62kg, Birth weight predicted risk of development of severe ROP with sensitivity 54.9% and specificity 82.1%. It indicates that the probability of development of severe ROP among infants having weight < 1.62 kg is 54.9%. For GA with cut-off point of 34.5 weeks showed sensitivity of development of sever ROP is 43.1% and specificity 85.1%.

DISCUSSION:
ROP is a serious disease if left undetected and not screen on time it would be progress and reach to the last stage of severity of ROP which results in total blindness. In order to decrease this type of severity screening guidelines were made and followed. These guidelines are strictly followed in the developed countries but it lacks in developing country like India which have the highest number of preterm deliveries in the world. This burden will increase in future if corrective steps are not taken immediately. [8]

In this study out of 113 babies, 67 babies were given antenatal steroid and 49 babies had non-severe stage of ROP. Which on analysis is statistically significant. (p-value 0.01). In contrast, the study which was done by Rosemary D. Higgins [2] in New York city ,47 out of 63 babies had non-severe ROP p-value is 0.04. Similarly, Baljeet Maini et

al [3] in new Delhi did study , ROP : risk factor and role of antenatal betamethasone in Indian preterm new born babies in total 148 babies in which 48 had non-severe ROP and 31 had severe ROP p-value is 0.0435.They found that antenatal steroid (betamethasone) may be preventive for severe ROP. [3].

Worldwide, nearly 10% of all births are premature (before 37 weeks gestation) [5]. In this study babies born before <=34 week are more to develop severe form of ROP than the term babies, which is statistically proven. 67 babies born with 1.75kg with Gestational age 32+/-2 having severe ROP for which p-value is 0.008 .47 babies born with weight 1.6>=kg with gestational age 34+/- weeks where develop non-severe ROP for which p-value 0.08 is not significant. The study on The influence of gestational age on the dynamic behaviour of other risk factors associated with retinopathy of prematurity was done by Joao Borges fortes filho et al [6] also found that out of 467 new born infants Mean BW and GA in the total cohort were 1,216.5 g (±278.3) and 30.3 weeks (±2.2), respectively. This study indicates that the probability of development of severe ROP among infants having weight < 1.62 kg is 54.9%. For GA with at cut-off point of 34.5 weeks showed sensitivity of development of severe ROP is 43.1% and specificity 85.1%. But independently low birth weight (<=1.75kg) is not significantly associated in severity of ROP. A study from Australia and New Zealand [13] of infants with a gestational age of less than 29 weeks at birth reported severe retinopathy of prematurity in 10% (203/2105).[13] Similarly study in Norway [18] of infants with a gestational age of less than 28 weeks at birth, retinopathy of prematurity (at any stage) was reported in 33% (95/290).[14]

The oxygen was given in these babies was humidified oxygen as per babies maturity of lungs. Humidified oxygen was given by various method like cannula, hood, ventilator, c-pap. Total of 113 babies' oxygen was given to 89 babies, in which 32 had severe ROP and 49 had non-severe ROP. p-value is 0.99 which indicates that humidified oxygen support is statistically not associated with ROP. The Neonatal Research Network Of The Eunice Kennedy Shriver National Institute Of Child Health And Human Development performed study of 1,316 infants born at 24 to 28 weeks gestational age who received intubation and surfactant within 1 hour of birth or on positive airway pressure. Infants were assigned to target oxygen saturation of 85% to 89% or 91% to 95%. Among survivor, they found that low saturation group were less likely to develop ROP p-value <0.001[7]. Several studies have provided evidence of oxygen fluctuation are now a risk factor for ROP. [9-11]. The best oxygen levels for reducing ROP is still yet to identified.

CONCLUSION:

Premature babies with ROP if not screen timely they are more prone to develop blindness in future which has impact on society and their own life. Therefore, to prevent it, early screening and immediate treatment is needed in initial stage of life. This study concludes that low gestational age with low birth weight are acting as risk factors for development of severe form of ROP. Independently low birth weight (<=1.75kg) is not significantly associated with severity of ROP. Whereas humidified oxygen does not have any effect on severity of ROP. Antenatal steroid independently has a protective role in development of severity of ROP, which requires further exploration. In developing country like India with high rate of premature births, need urgent screening for ROP in all preterm babies.

REFERENCES:

1. Padmani Karna, Jyotsna muttineni, Linda angell and wilfried Karmaus: Retinopathy of prematurity and risk factors:A prospective cohort study.BMC Pediatrics 2005,5:18
2. Rosemary D.higgins,Alan L. Mendelsohn,MD;Michael J. DeFeo,MD;Raif Ucsel,MD;Karen D. Hendricks-Munoz,MD,MPH:Antental dexamethasone and decresed severity of Retinopathy of Prematurity.Arch Ophthalmol.1998;116:601-605
3. Baljeet Maini,Harish Chellani,Sugandha Arya,B.P.Guliani:Retinopathy of prematurity:Risk factors and Role of Antenatal Betamethasone in Indian Preterm Newborn Babies:;jan-march 2014
4. Guidelines for universal eye screening in new borns including retinopathy of prematurity by Ministry of Health and Family welfare Government of India June 2017..
5. Goldenberg RL,Culhane JF,Lams JD,Romero R.Preterm birth 1:Epidemiology and causes of preterm birth.Obstet Anesth Dig.2009;29;6-7.
6. Joao Borges Fortes filho,Gabriela Unchalo Eckert,Fabiana Borba Valiatti,Paula Gabriela Batista dos santos,Marlene Coelho Da Costa,Renato Soibelmann procianoy:The influence of gestational age on the dynamic behavior of other risk factor associated with retinopathy of prematurity(ROP).
7. M. Elizabeth Hartnett,MD and Robert H. Lane,MD,MS.:Effect of oxygen on the development and severity of retinopathy of prematurity.
8. Parag K Shah,vishma Prabhu,Smita S Karandikar,Ratnesh Ranjan,Venkatapathy Narendran,Narendran Kalpnana:Retinopathy of Prematurity :Past,present and future.
9. McColm JR,Fleck BW.Retinopathy of prematurity-causation.Semin Neonatol.2001;6: 453-60.[PubMed:12014886]
10. Cunningham S,Fleck BW,Elton RA,Mclntosh N.Transcutaneous oxygen levels in retinopathy of prematurity.Lancet.1995;346:1464-5.[PubMed:7490994]
11. Saito Y, Omoto T, Cho Y, Hatsukawa Y, Fujimura M, Takeuchi T. The progression of retinopathy of prematurity and fluctuation in blood gas tension. Graefes Arch Clin Exper Ophthalmol. 1993;231:151–6. [PubMed] [Google Scholar]
12. Tin W, Milligan DWA, Pennefather PM, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonat Ed. 2001;84:106–10. [PMC free article] [PubMed] [Google Scholar]
13. Darlow BA, Hutchinson JL, Henderson-Smart DJ, Donoghue DA, Simpson JM, Evans NJ for the Australian and New Zealand Neonatal Network. Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. Pediatrics. 2005;115:990–96. [PubMed] [Google Scholar]
14. Markestad T, Kaaresen PI, Rønnestad A, et al. Early death, morbidity, and need of treatment among extremely premature infants. Pediatrics. 2005;115:1289–98. [PubMed] [Google Scholar]