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Original Article

Paediatrics Section

Perinatal Factors Associated with Spontaneous Regression of Retinopathy of Prematurity One Year Experience from a Tertiary Care Hospital

P KUMAR[1], K S KUMARAVEL[2], D SATHEESHKUMAR[3], S GOBINATHAN[4], P SAMPATHKUMAR[5], K VELMURUGAN[6]

ABSTRACT

Introduction: Spontaneous regression of Retinopathy of Prematurity (ROP) usually happens without serious residual sequelae in most neonates, while in some, blindness or serious visual impairment results from severe ROP.

Aim: The aim of the study was to estimate the incidences of ROP that spontaneously regress and ROP that requires intervention and to identify the perinatal factors that are associated with spontaneous regression of ROP.

Materials and Methods: This is a one year prospective descriptive study done in the Special Newborn Care Unit of a tertiary care hospital. All neonates diagnosed to have ROP of any stage on screening were included in the study. All these neonates were followed-up weekly for progression or regression of ROP. Data collected from case records included demographic, perinatal and neonatal profile of the study participants. The study group was divided into two groups – those neonates with spontaneous regression of ROP (Group 1) and those neonates who had severe ROP requiring intervention (Group 2).

Results: The incidence of ROP was 22.89%. The incidences of ROP spontaneously regressing and ROP requiring intervention were 93.5% and 6.5%, respectively. The univariate analysis of the factors showed a positive Odds Ratio (OR) for spontaneous regression for male gender, multiparity, lower segment caesarian section delivery and increasing gestational age. The OR was negative for factors like maternal anaemia, neonatal Respiratory Distress Syndrome (RDS), neonatal sepsis, phototherapy usage, neonatal blood transfusion, neonatal Intraventricular Hemorrhage (IVH) and increasing oxygen days. The Chi-square test revealed a significant p-value (<0.05) for the factors including IVH (p=0.002), gestational age (p=0.01), birth weight (p=0.01) and oxygen days (p=0.003).

Conclusion: The present study reiterates the need to develop a statistical model or a scoring system to predict the need for intervention in neonates with ROP by doing a larger multi-centric study.

Keywords: Low birth weight, Neonate, Oxygen, Preterm, Risk factors

INTRODUCTION

The ROP is an important cause of blindness in children across the globe [1-4]. It has been closely associated with prematurity, although other factors like oxygen administration, sepsis, blood transfusion and Low Birth Weight (LBW) were also implicated in its development [5]. India has witnessed a great improvement in the survival of premature and LBW neonates in the last few years under the National Rural Health Mission [6]. Most developed countries screen neonates born before 30 weeks or having a birth weight of less than 1,500 grams for ROP [7]. While developing countries like India, gestational age of less than 34 weeks or birth weight less than 1,750 grams were taken as cut-off values [8]. In India every year about 2 million children are estimated to be at risk for developing ROP [8]. Though ROP can cause serious blindness, fortunately, it carries a good prognosis by spontaneous regression in the vast majority [9]. Spontaneous regression of ROP usually happens without serious residual sequelae in neonates with stages 1,2 and early stage 3 of ROP. On the other hand, blindness or serious visual impairment results from progression to complete retinal detachment or severe damage to the posterior retina in some neonates [10]. Continuous Positive Airway Pressure (CPAP), active stage 3 disease and anaemia were associated with delayed regression of ROP [11]. The factors associated with spontaneous regression in some and progression to blindness in some neonates is poorly understood in most instances [3].

The aim of the study was to estimate the incidences of ROP that spontaneously regress and ROP those requiring intervention and to identify the perinatal factors that were associated with spontaneous regression of ROP.

MATERIALS AND METHODS

This was a prospective descriptive study done in the Special Newborn Care Unit of the hospital between April 2018 to March 2019. All the neonates admitted to this hospital were screened for ROP if they were: 1) less than 34 weeks of gestation; 2) less than 1,750 grams; or 3) if they had any of risk factors like sepsis, RDS or prolonged oxygen usage (more than 14 days) irrespective of gestational age and birth weight. Informed consent was taken from the parents. The screening was done by high definition RETCAM (Shuttle RX-6454) and reporting was done by retina specialist by tele screening. Institutional ethical committee clearance (4341/2018) was obtained.

The findings of the RETCAM examination were documented as per the International Classification for Retinopathy of Prematurity (ICROP) recommendations specifying the location (Zone i-iii) and severity of the disease (Stage 1-5) with or without plus component and the extent of clock hours [12]. All neonates diagnosed to have ROP of any stage on screening were included in the study. All these neonates were followed-up weekly for progression or regression of ROP. The neonates who expired or left against medical advice before complete follow-up evaluation were excluded. Threshold disease was taken as Stage 3 ROP or Stage 2 in Zone ii with plus disease and taken for intervention with either laser pan retinal photo coagulation or intra vitreal injection of Bevacizumab.

The study group was divided into two groups: those neonates with spontaneous regression of ROP (Group 1) and those neonates who had severe ROP requiring intervention (Group 2).

Data collected from the case records included gender, weeks of gestation, place of birth, mode of delivery, birth weight, parity, singleton or multiple gestation, maternal antenatal steroids administration, presence of gestational diabetes, Pregnancy Induced Hypertension (PIH) and anaemia, usage of oxygen and its days, presence of RDS and culture positive sepsis, usage of surfactant, blood transfusion or phototherapy, the maximal stage of ROP in the worst affected eye and its treatment.

STATISTICAL ANALYSIS

All data was entered into a spread sheet and analysed using R software version 3.6.3. Clinical characteristics of the two groups were described by percentage and median values. The factors which on univariate analysis found to be statistically significant between the two groups were then subjected to a logistic regression analysis to determine the strength of association between the variables and spontaneous regression of ROP. The resultant estimates were then expressed as OR with 95% confidence intervals. A p-value of less than 0.05 was taken as statistically significant. A positive OR implies that the factor is positively associated with spontaneous regression of ROP and a negative OR implies that the factor is associated with the need for intervention.

RESULTS

The perinatal profile of the study group is tabulated in [Table/Fig-1]. During the study period there were 4,288 admissions in the neonatal care unit. ROP screening was done for 611 neonates. About 155 neonates were found to have ROP of various stages. Thus, the incidence of ROP was 25.4%. Group 1, the spontaneous regression group had 145 neonates and the Group 2, the intervention group had 10 neonates. The incidences of ROP spontaneously regressing and ROP requiring intervention were 93.5% and 6.5%, respectively.

S. no	Perinatal factor	Group 1 (Spontaneous regression) (n=145)	Group 2 (Requiring intervention) (n=10)	Total (n=155)
1	Male	78 (54%)	8 (80%)	86 (55%)
	Female	67 (46%)	2 (20%)	69 (45%)
2	Intramural birth	105 (72%)	4 (40%)	109 (70%)
	Extramural birth	40 (28%)	6 (60%)	46 (30%)
3	Natural delivery	82 (57%)	9 (90%)	91 (59%)
	LSCS delivery	63 (43%)	1 (10%)	64 (41%)
4	Birth weight <1 kg	6 (4%)	3 (30%)	9 (6%)
	1-1.5 kg	68 (47%)	3 (30%)	71 (46%)
	1.5-2 kg	57 (39%)	4 (40%)	61 (39%)
	>2 kg	14 (10%)	0	14 (9%)
	Median	1,569 grams	1,289 grams	
	Range	850-2,500 grams	800-1,800 grams	
5	Gestational age <28 week	6 (4%)	3 (30%)	9 (5%)
	29-32 week	69 (48%)	5 (50%)	74 (48%)

	33-36 week	70 (48%)	2 (20%)	72 (47%)
	> 37 week	0	0	0
	Median	32.37 weeks	30.7 weeks	
6	Primiparous mother	94 (65%)	7 (70%)	101 (65%)
	Multiparous mother	51 (35%)	3 (30%)	54 (35%)
7	Singleton gestation	122 (84%)	8 (80%)	130 (84%)
	Multiple gestation	23 (16%)	2 (20%)	25 (16%)
8	Antenatal steroids administered	18 (12%)	0	18 (12%)
	Not administered	127 (88%)	10 (100%)	137 (88%)
9	Gestational diabetes present	2 (1%)	0	2 (1%)
	Absent	143 (99%)	10 (100%)	153 (99%)
10	Maternal PIH present	30 (21%)	2 (20%)	32 (20%)
	Absent	115 (79%)	8 (80%)	123 (80%)
11	Maternal anaemia present	26 (18%)	3 (30%)	29 (19%)
	Absent	119 (82%)	7 (70%)	126 (81%)
12	Oxygen administration present	95 (66%)	10 (100%)	105 (68%)
	Absent	50 (34%)	0	50 (32%)
13	No. of days of oxygen administration <5 days	59 (62%)	3 (30%)	62 (40%)
	5-10 days	20 (21%)	5 (50%)	25 (16%)
	11-30 days	16 (17%)	1 (10%)	17 (11%)
	> 30 days	0	1 (10%)	1 (0.6%)
14	Presence of RDS	52 (36%)	9 (90%)	61 (39%)
	Absence of RDS	93 (64%)	1 (10%)	94 (61%)
15	Administration of surfactant	14 (10%)	1 (10%)	15 (10%)
	Not administered	131 (90%)	9 (90%)	140 (90%)
16	Culture positive sepsis	47 (32%)	6 (60%)	53 (34%)
	No sepsis	98 (68%)	4 (40%)	102 (66%)
17	Phototherapy given	81 (56%)	6 (60%)	87 (56%)
	Not given	64 (44%)	4 (40%)	68 (44%)
18	Blood transfusion given	36 (25%)	5 (50%)	41 (26%)
	Not given	109 (75%)	5 (50%)	114 (74%)
19	USG cranium Normal	141 (97%)	7 (70%	148 (95%)
	Intra Ventricular Hemorrhage	4 (3%)	3 (30%)	7 (5%)
20	ROP stages Stage 1	140 (97%)	0	140 (91%)
	Stage 2	5 (3%)	0	5 (3%)
	Stage 3	0	1 (10%)	1 (0.6%)
	APROP	0	8 (80%)	8 (5%)
	Plus disease	0	1 (10%)	1 (0.6%)

[Table/Fig-1]: Clinical Profile of the study group.
LSCS: Lower segment caesarian section; PIH: Pregnancy Induced Hypertension; RDS: Respiratory distress syndrome; USG: Ultrasonography APROP: Aggressive Posterior ROP

The male:female ratio of the study group was 1.25:1. About 70% were intramural admissions and 59% were born by natural labour in the study group. On analysis of the birth weight distribution of the study group, about 6%, 46%, 39% and 9% were seen in the <1 kg, 1-1.5 kg, 1.5-2 kg and >2 kg groups, respectively. On analysis of the gestational age distribution of the study group, about 5%, 48%, and 47% were seen in the <28 weeks, 29-32 weeks and 33-36 weeks group, respectively.

About 65% neonates were born to primiparous mother and 35% were born of multiple gestation. On analysis of usage of antenatal corticosteroids, it was found that only 12% of neonates had received four complete doses of steroids. Gestational diabetes, PIH and Anaemia were seen in 1%, 20% and 19% of the mothers of the neonates in the study group, respectively. About 68% of neonates had received oxygen therapy for various conditions and about 11.6% of neonates received oxygen for more than 10 days. About 39% of the neonates had RDS and 10% received surfactant therapy. About 34% had culture positive sepsis, 56% neonates received phototherapy and 26% received blood transfusion. Ultrasound cranium showed IVH in 5% of neonates.

On analysis of various stages of ROP, about 91% of neonates had stage 1 disease, 3% had stage 2 disease and 0.6% had stage 3 disease. Aggressive Posterior ROP (APROP) was seen in 5% of the study population and 1 neonate had plus disease which denotes abnormal dilatation and tortuosity of blood vessels during examination. All the 10 neonates in Group 2 received intervention – four neonates were treated with laser therapy (Pan-Retinal Photo-coagulation) and six neonates were treated with intra vitreal injection of Bevacizumab (Avastin). All the 10 neonates are under regular follow-up.

The statistical comparison of the two study groups was difficult as the Group 2 had a very smaller sample size of 10 neonates only. The dichotomy between the sample size and the homogeneity of the sample population was common in many ROP studies, as increasing the sample size requires the inclusion of infants with dissimilar characteristics. With the advent of newer neonatal strategies for prevention of ROP, the incidence of ROP and ROP requiring intervention will eventually come down making it further difficult for analysis. The incidence of ROP requiring intervention in this study was about 6.5%. In the intervention group there was a female preponderance with male:female ratio of 1:4. In contrast to Group 1, the Group 2 had more proportion of extramural neonates, neonates with RDS, sepsis and blood transfusion and neonates with IVH. The median birth weight of Group 1 was 1,569 grams and of Group 2 was 1,289 grams. The median gestational age of Group 1 was 32.37 weeks and of Group 2 was 30.7 weeks.

All the 10 neonates in the intervention group had not received antenatal steroids. The univariate analysis of the factors showed a positive OR for spontaneous regression for male gender, multiparity, LSCS delivery and increasing gestational age. The positive OR implies that the spontaneous regression was most likely to occur in the neonates with the above factors. The OR was negative for factors like maternal anaemia, neonatal RDS, neonatal sepsis, phototherapy usage, neonatal blood transfusion, neonatal IVH and increasing oxygen days. A negative OR implies that these factors are negatively associated with spontaneous regression. The Chi-square test performed on these factors revealed a significant p-value (<0.05) for the factors including IVH (p=0.002), gestational age (p=0.01), birth weight (p=0.01) and oxygen days (p=0.003) [Table/Fig-2].

DISCUSSION

The ROP is a dynamic disease and most ROP regresses spontaneously by the process of involution or by evolution from vasoproliferative phase to fibrotic phase [13]. The overall incidence of ROP among the neonates screened in the present study was 22.89%. The incidences of ROP spontaneously regressing and ROP requiring intervention were 93.5% and 6.5%, respectively. There are only a few studies available in the literature which describe the factors associated with

Sl. no	Factor	Odds ratio	Standard error	Z value	p-value	95% Confidence interval
1	Male gender	3.43	2.77	1.53	0.127	0.70-16.73
2	LSCS delivery	6.91	7.38	1.81	0.07	0.85-56.01
3	Multiparity	1.26	0.90	0.33	0.74	0.31-5.10
4	Pregnancy induced hypertension	1.03	0.85	0.05	0.95	0.15-5.17
5	Maternal anaemia	0.50	0.36	-0.93	0.35	0.12-2.10
6	RDS	0.06	0.06	-2.60	0.09	0.007-0.50
7	Surfactant administration	0.96	1.04	-0.04	0.97	0.11-8.16
8	Sepsis	0.31	0.21	-1.70	0.08	0.08-1.18
9	Phototherapy	0.84	0.56	-0.25	0.799	0.22-3.11
10	Blood transfusion	0.33	0.21	-1.68	0.09	0.09-1.20
11	IVH	0.06	0.56	-3.17	0.002	0.01-0.35
12	Birth weight	1.00	0.001	2.48	0.01	1.00-1.00
13	Gestational age	1.52	0.25	2.47	0.01	1.09-2.12
14	Oxygen days	0.88	0.03	-3.00	0.003	0.82-0.95

[Table/Fig-2]: Logistic regression analyses of perinatal factors associated with spontaneous regression of ROP.

spontaneous regression of ROP [11]. The small sample size of the ROP requiring intervention is the reason for the paucity of studies. Various other studies have demonstrated an incidence of ROP ranging from 24-47% [9,14,15].

The incidence of ROP regressing spontaneously in the present study was 93.5%. In a study done in China by Ju RH et al., the incidence was 69.6% [15]. Repka MX et al., also reported a similar incidence and demonstrated that acute phase ROP began to involute at a mean of 38.6 weeks post menstrual age [16]. Prost M in the year 1995 to 2002 studied 168 premature neonates with active stages 1-3 and 91 neonates with stages 4-5 ROP and showed spontaneous regression of ROP in 85% of neonates with stage 1, in 56% in stage 2 and in 25% in stage 3 of disease [17].

The Group 1 in a study had male preponderance while Group 2 had female preponderance. The other studies did not demonstrate any such gender preponderance [15]. All the mothers of the 10 neonates in Group 2 requiring intervention had not received antenatal corticosteroids in the present study. The association of ROP with antenatal steroids was documented in other studies also. Console et al., demonstrated that the corticosteroid prophylaxis significantly reduced the risk of developing ROP (OR 0.35; 95% confidence interval 0.17-0.71, logistic regression analysis), and that of severe ROP (OR 0.07; 95% confidence interval: 0.02-0.34) [18].

The other factors that were associated with spontaneous regression in the present study were multiparity, increasing gestational age and LSCS delivery. The median birth weight in the intervention group was 1,289 grams in the present study. A similar study done in China had a mean birth weight of 1,376 grams in the severe ROP group [15]. The median gestational age for the intervention group in the present study was 30.7 weeks. The other study had a mean gestational age of 29.86 weeks for the severe ROP group [15]. Extreme prematurity was demonstrated to be significant for all of the ROP outcome measures by Owen LA et al., [19]. This was supported by many other studies also [20,21].

A negative OR was obtained for factors like RDS, sepsis, blood transfusion, IVH and increasing oxygen days. A negative OR suggests the negative association for spontaneous regression of ROP with these factors. A logistic regression analysis for the intervention group could not be performed as the sample size was very small. In a study done in China, Continuous Positive Airway Pressure (CPAP), active stage 3 ROP and severe anaemia were statistically associated with delayed regression of ROP [11]. In the present study all the three neonates who had IVH, required intervention. The association between IVH and ROP was well documented in many studies [22].

Limitation(s)

The comparison between two disproportionate groups – Group 1 with 145 neonates and Group 2 with only 10 neonates was statistically difficult and is the major limitation of this study.

CONCLUSION(S)

In the present study, the spontaneous regression was significantly associated with male gender, LSCS delivery and advancing gestational age. The intervention for ROP was closely associated with lack of antenatal steroids for the mother, IVH, sepsis, RDS, blood transfusion and increased number of oxygen days.

Recommendation(s): From the present study it can be recommended that a larger multi-centric study should be developed to derive a statistical model or a scoring system to predict the need for intervention in neonates with ROP. Such a model will help the treating pediatrician to stratify the neonates with those risk factors and address them more efficiently and early to prevent those neonates from developing severe ROP.

REFERENCES

[1] Tasman W. Retinopathy of Prematurity. Do we still have a problem? The Charles L. Schepens lecture. Arch Ophthalmol. 2011;129:1083-86.

[2] Azad R, Chandra P. Retinopathy of prematurity. J Indian Med Assoc. 2005;103:370-72.

[3] Coats DK, Miller AM, Hussein MA, McCreery KM, Holz E, Paysee EA. Involution of retinopathy of prematurity after laser treatment: factors associated with developed of retinal detachment. Am J Ophthalmol. 2005;140:214-22.

[4] Munoz B, West SK. Blindness and visual impairment in the Americans and the Caribbean. Br J Ophthalmol. 2002;86:498-504.

[5] Alajbegovic-Halimic J, Zvizdic D, Alimanovic-Halilovic E, Dodik I, Duvnjak S. Risk factors for retinopathy of prematurity in premature born children. Med Arch Sarajevo Bosnia Herzeg. 2015;69:409-13.

[6] Kumaravel KS, Ganesh J, Balaji J, Pugalendhiraja KV, Ramesh Babu B. A study on impact of NRHM on neonatal care and clinical profile of neonates admitted in a SNCU of a rural medical college. Journal of Evolution of Medical and Dental Sciences. 2015;4(82):14335-47. DOI: 10.14260/jemds/2015/2039.

[7] Fierson WM. American Academy of Pediatrics Section on O, American Academy of O, American Association for PediatricO, Strabismus, American Association of Certified O. Screeningexamination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131(1):189-95.

[8] Pejawar R, Vinekar A, Bilagi A. National Neonatology Foundation's Evidence-based Clinical Practice Guidelines. Retinopathy of Prematurity, NNF India, New Delhi 2010:253–62.

[9] Kumaravel KS, Molugan M. Clinical profile and risk factors leading to retinopathy of prematurity. Pediatr Oncall J. 2018;15:11-14. doi: 10.7199/ped.oncall.2018.11.

[10] Quinn GE, Gilbert C, Darlow BA, Zin A. Retinopathy of prematurity: anepidemic in the making. Chin Med J (Engl). 2010;123(20):2929-37.

[11] Ni Y-Q, Huang X, Xue K, Yu J, Ruan L, Shan H-D, et al. Natural involution of acute retinopathy of prematurity not requiring treatment: factors associated with the time course of involution. Invest Ophthalmol Vis Sci. 2014;55:3165–70. DOI: 10.1167/iovs.13-13744.
[12] International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123:991-99.
[13] Schulenburg WE, Prendiville A, Ohri R. Natural history of retinopathyof prematurity. Br J Opthalmol. 1987;71(11):837-43.
[14] Mets MB. Childhood blindness and visual loss: An assessment at two institutions including a "new" cause. Trans Am Ophthalmol Soc. 1999;97(34):653.
[15] Ju RH, Zhang JQ, Ke XY, Lu XH, Liang LF, Wang WJ. Spontaneous regression of retinopathy of prematurity: incidence and predictive factors. Int J Ophthalmol. 2013;6(4):475-80.
[16] Repka MX, Palmer EA, Tung B. Involution of retinopathy of prematurity. Cryotherapy for Retinopathy of Prematurity Cooperative Group. 2000;118(5):645-49.
[17] Prost M. Possibilities of spontaneous regression in active phase of ROP. Klin Oczana. 2003;105(1-2):57-59.
[18] Console V, Gagliardi L, De Giorgi A, De Ponti E. Retinopathy of prematurity and antenatal corticosteroids. The Italian ROP Study Group. Acta bio-medica de L'Ateneo Parmense: Organo Della Società di Medicina e Scienze Naturali di Parma. 1997;68 Suppl 1:75-79.
[19] Owen LA, Morrison MA, Hoffman RO, Yoder BA, DeAngelis MM. Retinopathy of prematurity: A comprehensive risk analysis for prevention and prediction of disease. PLoS One. 2017;12(2):doi:10.1371/journal.pone.0171467.
[20] Good WV Hardy RJ, Dobson V, Palmer EA, Phelps DL, Quintos M, et al., The incidence and course of retinopathy of prematurity: findings from the early treatmentfor retinopathy of prematurity study. Pediatrics. 2005;116(1):15-23.
[21] Lundgren P, Kistner A, Andersson EM, Pupp IH, Holmstrom G, et al. Low birth weight is a risk factor for severe retinopathy of prematurity depending on gestational age. PloS One. 2014;9(10):e109460.
[22] Le C, Basani LB, Zurakowski D, Ayyala RS, Agraharam SG. Retinopathy of prematurity: Incidence, prevalence, risk factors, and outcomes at a tertiary care center in Telangana. J Clin Ophthalmol Res. 2016;4(14):119.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Paediatrics, Govt Mohan Kumaramangalam Medical College, Salem, Tamil Nadu, India.
2. Professor, Department of Paediatrics, Govt Mohan Kumaramangalam Medical College, Salem, Tamil Nadu, India.
3. Assistant Professor, Department of Paediatrics, Govt Mohan Kumaramangalam Medical College, Salem, Tamil Nadu, India.
4. Associate Professor, Department of Paediatrics, Govt Mohan Kumaramangalam Medical College, Salem, Tamil Nadu, India.
5. Professor, Department of Paediatrics, Govt Mohan Kumaramangalam Medical College, Salem, Tamil Nadu, India.
6. Junior Resident, Department of Paediatrics, Govt Mohan Kumaramangalam Medical College, Salem, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
S Gobinathan,
Govt Mohan Kumaramangalam Medical College, Salem.30, Tamil Nadu, India.
E-mail: drsgobinathan92@gmail.com

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