A prospective observational study of retinopathy of prematurity in a tertiary care centre with respect to its incidence, risk factors and short term outcomes

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Abstract

Introduction: Retinopathy of prematurity (ROP) is an important cause of blindness in children. Early detection and timely intervention decreases the morbidity associated with it.

Objectives: To determine the incidence, risk factors and short term outcomes of ROP in a tertiary care centre and compare it to unpublished data from the same centre from 2010-2012.

Method: Newborns admitted to the neonatal intensive care unit (NICU) of Bharati Hospital and Research Centre, Bharati Vidyapeeth Deemed University Medical College (BVDUMC), Pune, Maharashtra, India, with gestational ages <32weeks or birth weights <1500g were included in the study and followed up. Newborns admitted with gestational ages 32 weeks or more or birth weights 1500g or more were also included when associated with risk factors such as sepsis, mechanical ventilation more than 24 hours, oxygen therapy / non-invasive ventilation more than 1 week, surfactant therapy, exchange transfusion, intra ventricular haemorrhage (IVH), patent ductus arteriosus (PDA), packed cell transfusion therapy, bronchopulmonary dysplasia (BPD) or necrotising enterocolitis (NEC). Enrolled babies, as per protocol, were examined regularly and in cases diagnosed with ROP, treatment was given accordingly. A total of 186 babies was screened for ROP from January 2015 to September 2016 and this data was compared to 374 babies screened for ROP from January 2010 to July 2012. Ethical clearance for the study was obtained from the BVDUMC, Pune, Maharashtra, India.

Results: ROP incidence in BVDUMC, Pune, Maharashtra, India has increased from 12% in 2010-2012 to 19.9% in 2015-2016. Ten (27%) babies with ROP required laser photocoagulation in 2015-2016 in comparison to 27 (40%) babies with ROP who needed laser photocoagulation in 2010-2012.

Conclusions: Gestational age, birth weight, mechanical ventilation, oxygen therapy, packed cell transfusion, surfactant administration and bronchopulmonary dysplasia had statistically significant associations with ROP in BVDUMC, Pune, Maharashtra, India.

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(Key words: Retinopathy of prematurity, ROP, incidence, risk factors, outcomes, oxygen therapy)

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Introduction

Retinopathy of prematurity (ROP) can, if untreated, lead to blindness due to retinal detachment, macular folds, refractive-amblyopia and strabismic-amblyopia[1]. Early detection of severe ROP and assessing risk factors allows specific treatment and intervention time, decreasing severity of ROP sequelae and unfavourable outcomes[1]. WHO Vision 2020 programme identifies ROP as an important cause of blindness in both high and middle income countries[2]. From 2002-2006, a study was done at a tertiary care centre, Pune, India, where 552 infants were screened for ROP. The incidence in their study was 22.3% and the risk factors predisposing to ROP were septicaemia, apnoea, oxygen therapy and use of blood products[3]. From July 2006-July2010, a study was conducted in Canada, where 423 infants were screened for ROP. In this study, the incidence of ROP was 40.4% and gestational age and birth weight were the most significant risk factors for developing ROP[1]. In December 2009 and January 2010, a study was done at Cape Town, South Africa. A total of 356 infants was screened and the overall prevalence of ROP was 21.8%. The risk factors with statistically significant association with development of ROP were severe apnoea and low birth weight[4]. Various studies have documented many associated risk factors for ROP such as gestational age, birth weight, oxygen supplementation, intraventricular haemorrhage, sepsis, blood transfusion, mechanical ventilation, and surfactant therapy[1,2,3,4].

Objectives
To determine the incidence, risk factors and short term outcomes of ROP in a tertiary care centre and compare it to unpublished data from the same centre from 2010-2012.

Method
This is a prospective observational study conducted in the neonatal intensive care unit (NICU) of Bharati Hospital and Research Centre, Bharati Vidyapeeth Deemed University Medical College (BVDUMC), Pune, Maharashtra, India, a tertiary care centre. One hundred and eighty six babies were screened for ROP from January 2015 to September 2016 and this data was compared to 374 babies screened for ROP from January 2010 to July 2012. Newborns admitted in the NICU with gestational age (GA) <32 weeks or birth weight <1500g were included in the study and followed up. Newborns admitted with GA 32 weeks or more or birth weight 1500g or more were included when associated with risk factors such as sepsis, mechanical ventilation more than 24 hours, oxygen therapy / non-invasive ventilation more than 1 week, surfactant therapy, exchange transfusion, intraventricular haemorrhage (IVH), patent ductus arteriosus (PDA), packed cell transfusion therapy, bronchopulmonary dysplasia (BPD) or necrotizing enterocolitis (NEC). Infants with major congenital anomalies and genetic defects were excluded. Ethical clearance for study was obtained from BVDUMC, Pune, Maharashtra, India.

Demographic data were collected from case records which included date of birth, place of delivery, birth weight, sex, mode of delivery, GA, antenatal steroid usage, maternal risk factors like pregnancy induced hypertension, pre-eclampsia and eclampsia or premature rupture of membranes. GA assessment was done by first trimester ultrasonogram (USG), if available or last menstrual period (LMP), if 1st trimester USG not available, or modified Ballard's score if LMP not known.

All babies were managed as per NICU protocol. Details of risk factors were collected prospectively. All neonates admitted in our NICU, who satisfied inclusion criteria had undergone first screening for ROP based on chronological age as per American Academy of Paediatricians guidelines of ROP screening. All of them were screened by the same ophthalmologist to reduce inter observer variation. Screening was done with a binocular indirect ophthalmoscope. Eyes were examined with an infant speculum and sclera depressor, under topical anaesthesia using 0.5% proparacaine drops. The pupils were dilated using 0.4% tropicamide and 1.25% phenylephrine eye drops, two to three times every 15 minutes till full dilatation. ROP, if present, was classified as per international classification of ROP (ICROP) and were managed accordingly. Follow up examinations were done as recommended by the ophthalmologist. Infants were followed up till completion of peripheral vascularization.

The data on categorical variables is shown as n (cases) and the data on continuous variables is shown as mean, standard deviation along with median, minimum and maximum values. The inter-group statistical significance of difference of categorical variables was tested using Chi-square test or Fisher's exact probability test. The entire data was entered and cleaned in MS Excel before statistical analysis. Multiple logistic regression analysis was performed to study the predictors of ROP using independent variables, which were significant in the univariate analysis. *P* less than 0.05 was considered to be statistically significant. All the hypotheses were formulated using two tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data was statistically analysed using Statistical Package for Social Sciences (SPSS version 17.0, Inc. Chicago, USA) for MS Windows.

Results
The present study was conducted over a period of twenty-one months in the NICU of a tertiary care hospital attached to BVDUMC. One thousand four hundred and seventy-six neonates were admitted to the NICU during the study period. One hundred and eighty six infants were screened for ROP. ROP incidence in our present study was 19.9%. The baseline characteristics of the 186 newborns are shown in Table 1.

Table 1: ***Baseline characteristics of neonates***

Characteristic	**No. (%) or ±SD** *(n=186)*
Gender	
Male	114 (61.3)
Female	72 (38.7)
Mean gestational age (weeks)	31.61 ± 2.76
Weight for gestational age	
Small for gestational age	54 (29.0)
Appropriate for gestational age	132 (71.0)
Birth weight (g)	
2500 or >	07 (03.8)
1500-2499 (LBW)	43 (23.1)
1000-1499 (VLBW)	101 (54.3)
<1000 (ELBW)	35 (18.8)
Mean birth weight (g)	1344.3 ± 413.5
Mean length at birth (cm)	39.57 ± 3.96
Mean head circumference at birth (cm)	27.95 ± 2.66
Place of birth	
Inborn	93 (50%)
Outborn	93 (50%)

LBW-Low birth weight, VLBW-Very low birth weight, ELBW-Extremely low birth weight

The male: female ratio was 1.58:1. The birth weights ranged from 714g to 3200g. GA ranged from 26 weeks to 40 weeks. Baseline maternal characteristics are shown in Table 2.

Table-2: ***Baseline maternal characteristics***

Maternal characteristic	No. (%)
Gestation	
Singleton	141 (75.8)
Twins	44 (23.7)
Triplets	01 (0.5)
Mode of delivery	
Vaginal delivery	70 (37.6)
Caesarean section	116 (62.4)
Maternal age	
< 20 years	02 (01.1)
20 – 24 years	78 (41.9)
25 – 29 years	60 (32.3)
30 – 35 years	31 (16.7)
> 35 years	15 (08.1)
Maternal risk factors	
Pre-eclampsia	66 (35.5)
Premature rupture of membranes	31 (16.6)
Eclampsia	08 (04.3)
Others	11 (05.9)
Antenatal steroids	87 (46.8)

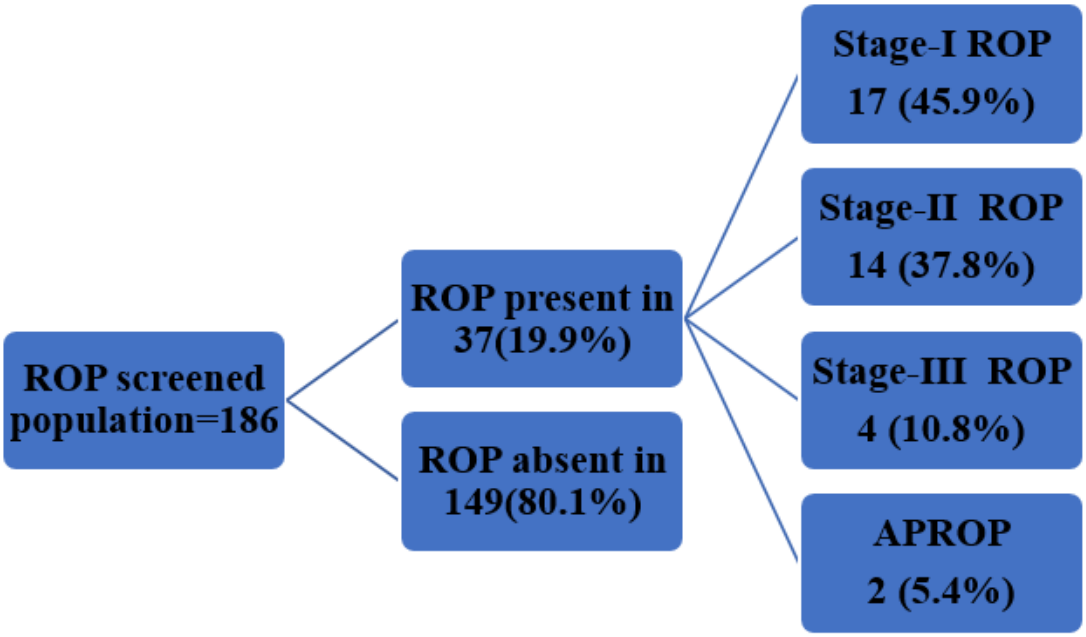
As shown in table 2, one hundred and thirty-eight babies (74.1%) were born to mothers 20 to 29 years of age. Maternal risk factors were present in 116 (62.3%) infants. ROP characteristics are showed in a flow diagram.

Classification of ROP cases is shown in Table 3.

Table 3: ***Classification of ROP cases***

Parameters	No. (%)
ROP with Plus disease	06 (16.2)
Pre-Plus disease	0 (0.0)
ROP resolution without intervention	27 (73.0)
Need for laser photocoagulation	10 (27.0)

Univariate analysis of risk factors to ROP is shown in Table 4.



Flow Diagram: ***ROP characteristics***

Table 4: ***Univariate analysis of risk factors to ROP***

Parameter	Any ROP (n=37)	No ROP (n=149)	*p* value	Odds ratio (CI)
Weight for gestational age				
Small for gestational age	09	45	0.481	0.743
Appropriate for gestational age	28	104		(0.324 – 1.701)
Gestation type				
Single	28	113		1.047
Twins	09	35	0.879	(0.451 – 2.428)
Triplets	0	01		
Sex distribution				
Male	18	96	0.078	0.523
Female	19	53		(0.253 – 1.082)
Place of birth				
Inborn	15	78	0.199	1.611
Outborn	22	71		(0.776 – 3.346)
Use of antenatal steroids				
Not used	20	79		0.959
Dexamethasone	12	46	0.925	(0.466 – 1.975)
Betamethasone	05	24		

Fifty four (29%) infants were small for gestational age (SGA) and of them 9 developed ROP. There was no statistically significant difference in the incidence of ROP among SGA and appropriate for gestational age (AGA) babies. There was no significant difference in incidence of ROP between males and females. Though population was equally distributed between inborn and outborn, incidence of ROP was 22 (59.5% of ROP diagnosed) in outborn infants compared to 15 (40.5% of ROP diagnosed) in inborn infants. This was not statistically significant. Individual risk factors and their role in ROP are shown in Tables 5, 6 and 7.

Of the 14 neonates who belonged to the 26-27 completed weeks' GA group, 57.1% had developed ROP while 23.4% of 28-29 completed weeks' GA group developed ROP. Similarly, in the 30-31 completed weeks GA group, ROP was diagnosed in 27.3% and in the remaining population of 87 neonates who were more than 32 weeks GA, 8% were diagnosed with ROP. GA has an association with development of ROP on univariate analysis.

In the extremely low birth weight (ELBW) population of 35 infants, 48.5% developed ROP. Out of 101 infants belonging to birthweight of 1000-1499g, 14.9% developed ROP. On univariate analysis low birth weight has an association with development of ROP. Twelve out of 53 (22.6%) infants with proven sepsis developed ROP. Sepsis is not a risk factor for development of ROP on univariate analysis. The association of ROP and respiratory parameters is shown in Table 6. Association of mechanical ventilation ($p<0.05$), oxygen therapy ($p<0.05$), use of surfactant ($p<0.05$) and bronchopulmonary dysplasia ($p<0.05$) with ROP had statistical significance on univariate analysis (Table 7).

Table 5: Association of ROP with gestational age, birth weight and sepsis

Characteristic	Any ROP No. (%)	No ROP No. (%)	*p* value	Odds ratio (CI)
Gestational age (weeks)				
26.0 – 27.0	08	06	0.001	4.969
28.0 – 29.0	07	23		(2.054 -12.021)
30.0 – 31.0	15	40		
≥32.0	07	80		
Birth weight				
<1000 g	17	18	0.001	0.662
1000-1499g	15	86		(0.077 – 5.674)
1500-1999 g	04	33		
2000 g or >	01	12		
Sepsis				
No	09	65	0.084	2.407
Suspected	16	43		(1.063 – 5.454)
Proven	12	41		

Table 6: Association of ROP with respiratory parameters

Respiratory parameter	Any ROP (n=37)	No ROP (n=149)	*p* value	Odds ratio (CI)
Mechanical ventilation				
No	03	36	0.006	3.611
Yes	34	113		(1.046 – 12.460)
Oxygen therapy				
No	07	67	0.006	3.502
Yes	30	82		(1.447 – 8.474)
Use of surfactants				
No	23	108	0.012	1.603
Yes	14	41		(0.753 – 3.413)
Bronchopulmonary dysplasia				
No	25	145	0.001	17.400
Yes	12	04		(5.196 – 58.267)

Table 7: ***Association of ROP with exchange transfusion, intraventricular haemorrhage, patent ductus arteriosus, necrotising enterocolitis and packed cell transfusion***

Characteristic	Any ROP (n=37)	No ROP (n=149)	*p* value	Odds ratio (CI)
Exchange transfusion				
No	37	146	0.999	0.0
Yes	0	03		
Intraventricular haemorrhage				
No	27	115	0.885	1.253
Grades 1 & 2	09	30		(0.552 – 2.845)
Grade 3 & 4	01	04		
Patent ductus arteriosus				
No	30	129	0.302	1.505
Medical	07	17		(0.583 – 3.884)
Surgical	0	03		
Necrotising enterocolitis				
No	35	143	0.195	1.362
Yes	02	06		(0.264 – 7.038)
Packed cell transfusion				
Not given	21	124	0.001	3.779
Given	16	25		(1.733 – 8.240)

Exchange transfusion, PDA, IVH and NEC had no association with ROP on univariate analyses. Ten ROP cases (27% of diagnosed ROP) had history of IVH. Packed cell transfusion had a statistically significant association with ROP. Multivariate analysis using logistic regression is shown in Table 8.

Table 8: ***Multivariate analysis using logistic regression***

Variable in the model	Odds Ratio (OR)	95% CI of OR	*p* value
Prematurity:			
Yes	3.01	1.87 – 5.23	0.001^{***}
No (Reference)	1.0	-	-
Mechanical ventilation			
Given	3.45	2.02 – 5.66	0.001^{***}
Not given (Reference)	1.0	-	-
Oxygen therapy			
Given	0.92	0.61 – 1.81	0.224^{NS}
Not given (Reference)	1.0	-	-
Blood component therapy			
Given	2.65	1.43 – 5.04	0.001^{***}
Not given (Reference)	1.0	-	-
Surfactant			
Given	0.79	0.94 – 2.39	0.188^{NS}
Not given (Reference)	1.0	-	-
Bronchopulmonary dysplasia			
Yes	2.35	1.19 – 3.74	0.031^{*}
No (Reference)	1.0	-	-

$p < 0.05$ is statistically significant. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, NS: Statistically non-significant.

On multivariate analysis prematurity, mechanical ventilation, packed cell transfusion and bronchopulmonary dysplasia had statistically significant associations with ROP.

Discussion

Our present study was conducted in a tertiary care hospital attached to BVDUMC. One hundred and eighty-six neonates fulfilling the preformed inclusion criteria were screened for ROP during the study period of 21 months. We screened all babies admitted in our NICU with birth weights <1500g and GA ≤32 weeks. Infants with birth weight ≥1500gm and gestational age >32 weeks were screened only if they had additional risk factors. Chawla *et al*[5] and Chaudhari[3] *et al* have used the same screening criteria. Screening criteria vary among institutes with respect to GA and birth weight[7-14]. The incidence of ROP in these studies from South India varied from 21.6% to 53.4%[7-14]. The incidence of ROP globally varied from 11.8% to 68.0%[1,4,15-20] . In the present study the incidence of ROP was 19.9%. Incidence of ROP during 2010 to 2012 was 12% in our previous unpublished data.

In our study, the mean GA was 31.61±2.76 weeks and mean birth weight was 1344.3±413.5g. Similar mean birth weight (1306±267g) and mean GA (31.4±2.2 weeks) were taken in a study by Chaudhari et al.[3]. This mean birth weight and GA is lower compared to our unpublished data from 2010 to 2012 in which mean birth weight was 1444±408.3g and mean GA 32.4±2.8 weeks. This means more premature babies are getting admitted now. In our unpublished data, we had more outborn babies as compared to inborn babies (1.3:1) and current data had equal number of inborn and outborn babies.

Out of 37 infants diagnosed with ROP, in the present study, the number of cases of stage I, stage II, stage III and APROP were 17 (45.9%), 14 (37.8%), 04 (10.8%) and 02 (05.4%) respectively. Among ROP cases 06 (16.2%) developed plus disease. During the present study, Stage I ROP incidence has increased and this can be explained by more number of premature and VLBW babies. This ROP incidence in present study among different stages, was comparable to the study by Aggarwal et al[10] where combined incidence of stage I and II was 79% and stage III was 21% cases. Charan et al[6] have documented similar incidence among I, II, III, IV stages respectively, i.e. 35.9%, 37.2%, 24.4% and 2.5%.

Of the 37 diagnosed cases of ROP, in our study, 10 (27%) needed laser photocoagulation and in the rest ROP resolved without any intervention. From our unpublished data from 2010-2012, 18 (40%) of 45 ROP diagnosed infants needed laser photocoagulation which implies that, though there was an increase in incidence of ROP, it is basically increase in incidence of stage I ROP and not the need for laser photocoagulation. Need for laser photocoagulation requirement in other studies was 33.3% by Chaudhari *et al*[3] and it was 15.2% cases by Port DA *et al*[19].

There is an increase in the incidence of ROP over a period but this may be due to increase in number of premature and VLBW babies. Similar findings have been reported in other studies. Chaudhari *et al*[3] in their study documented ROP incidence of 24.4% in 2000 and 27.3% in 2001. It later declined to 16.7%, 19.5% and 18.4% in 2002, 2003 and 2004 respectively but the incidence again rose to 26% in 2005 and 2006 in view of better survival rates among smaller babies. Aggarwal and co-workers from New Delhi, India included neonates who satisfied any one of the following three criteria i.e., gestation <35 weeks or birth weight <1500g or preterm neonate who required supplemental oxygen for more than 24 hours, for ROP screening. They noted an increase in the overall incidence of ROP from 20% (1993-1994) to 32% (1999-2000) over a period of 8 years, but this rise was not statistically significant ($p>0.05$). A striking fact that was observed in this comparison was that a decreasing trend in proportion of severe ROP (stage III) from 46% to 21% in later period was noted. The need for cryotherapy also dropped significantly from 46% to 8% which is statistically significant ($p<0.05$)[10]. Similar study was reported by Painter et al; regarding incidence and treatment of ROP in England from 1990-2011 using English national hospital episode statistics of babies born <1500g and eligible for ROP screening. Incidence of ROP rose from 12.8/1000 low birth weight (LBW) babies in 1990 to 125.5/1000 LBW babies in 2011. This ten-fold rise in ROP incidence, as per author, may be secondary to factors like increasing numbers of ELBW born with in 1500gms group, increasing survival of LBW babies, increased recognition of ROP and increased use of guidelines for screening and treatment. Treatment rates for ROP using either cryotherapy or laser rose from 1.7 to 14.8/1000 LBW babies between 1990 and 2011. In 1990, 13.3% of babies with ROP were treated with cryotherapy which fell to 0.1% in 2011. Rates for laser treatment increased from 1.8% in 1999 to 11.7% in 2011 to babies with ROP.[22]

There was no significant difference between incidence of ROP among males and females in present study ($p=0.078$) as well as in our previously unpublished data ($p=0.98$). Similarly there was no significant difference in the incidence of ROP between males and females in studies by Chaudhari et al[3], Goncalves E et al[15] ($p=0.430$) and Shah et al[18] ($p=0.3$). There was no difference between incidence of ROP in AGA and SGA (p value -0.481) in present

study (p=0.078) as well as in our previously unpublished data. Similar findings have been reported by Chaudhari et al[3] and Shah et al[18] (p=0.47).

Fifteen (16.1%) of 93 inborn neonates developed ROP compared to 22 (23.6%) of 93 outborn neonates. No statistical significance was seen between inborn and outborn infants in present study (*p*=0.199). Similar findings were noted in our previously unpublished data (*p*=0.78) regarding inborn and outborn. No previous studies documented ROP incidence between inborn and outborn babies.

ROP in our present study showed significant statistical correlation with prematurity and low birth weight. The current study population, if categorized into <32 weeks & ≥ 32 weeks and ROP incidence calculated corresponds to 30.3% and 8.04% respectively. Results from our unpublished data suggest that incidence in <32 weeks was 18.3% while that of ≥32 weeks was 4.6%. Among ELBW (birth weight <1000gms) babies, ROP incidence in present study was 48.5% while the previous unpublished data showed incidence of 34.5%. If VLBW (birth weight <1500gms) babies are considered ROP incidence in current study was 23.5% while from unpublished it was 15.9%. Similarly in the group with birth weight between 1500-1999gms, current showed ROP incidence of 10.8% while the previous unpublished data showed 6%. These ROP incidence in corresponding groups of ELBW, VLBW and 1500-1999g babies is comparable to data published by Chaudhari et al[3] i.e., is 36.2%, 23.6% and 11.4% correspondingly.

In our study, maternal risk factors like singleton or multiple gestation (*p*=0.879) and antenatal steroids (*p*=0.925) had no association with ROP. Similar findings have been reported by Rao AK et al i.e. multiple gestation (*p*=0.510) and use of antenatal steroids (*p*=0.104)[13] had no association with ROP. 28 out of 37 neonates diagnosed with ROP in our present study had proven or suspected sepsis (i.e. 75.6 % of ROP diagnosed neonates). There was no statistical significance between ROP and sepsis in present study (*p*=0.084). Findings noted in our previous unpublished data showed 46.7% of cases with ROP had a history of sepsis and there was statistical significance achieved on univariate analysis (*p*=0.0003). Chaudhari et al, from Pune, India reported statistical significance between ROP and sepsis (*p*=0.003); 22% of their ROP diagnosed cases had a history of sepsis[3]. Similar findings were noted by Aggarwal et al, from New Delhi, India where 67% (i.e.16/24) of diagnosed cases of ROP had history of sepsis which is statistically significant (*p*<0.01)[10]. Goncalves E et al, from Brazil, have observed association between ROP and sepsis, in their study with similar inclusion criteria of ≤1500g and/or ≤32 weeks GA. Ninety eight percent (i.e. 48/49) of diagnosed cases of ROP had a history of sepsis (*p*=0.001).[15]

In our present study, 34 (91.8%) of 37 diagnosed cases of ROP needed mechanical ventilation (invasive or non-invasive), for more than a period of 24 hours. Mechanical ventilation is observed to be a risk factor in development of ROP in the present study and that was proven statistically significant (*p*=0.006) on multivariate analysis. Similar findings were noted by Aggarwal et al[10], where 13 (54%) of 24 infants diagnosed with ROP had history of mechanical ventilation. (*p*<0.01). Chaudhari et al, from Pune, India reported statistical significance between ROP and mechanical ventilation (*p*=0.001). 41.7% of their ROP diagnosed cases had a history of mechanical ventilation[3]. Port DA et al, from USA have reported statistical significance between ROP and mechanical ventilation (*p*=0.006), 54.9% of their ROP diagnosed cases having previous history of mechanical ventilation[19].

In our present study we have collected data of all neonates who received oxygen therapy with either high flow nasal cannula (HFNC) or nasal cannula (NC) for more than one week and later observed for development of ROP. Results in the present study are consistent with the earlier studies that oxygen is a risk factor for ROP incidence (*p*=0.006). Thirty (81%) of 37 ROP diagnosed cases were on oxygen therapy in comparison to 82 (55%) of 149 infants with no ROP had a history of oxygen therapy. Chaudhari et al[3], in their study regarding ROP reported similar findings in relation between ROP and oxygen therapy. 64.5% in their study population diagnosed with ROP had a history of oxygen therapy while only 39.7% infants with no ROP were previously on oxygen therapy. (*p*=0.001)

Role of surfactant in development of ROP is widely studied by various researchers. Rao A K et al,[13] from south India, have observed 28 (45.9%) of 61 ROP diagnosed population had a history of use of surfactant which was statistically significant (*p*=0.03). Similar findings were noted by Goncalves E *et al*, where 59.2% of their study population with ROP had a history of use of surfactant during NICU stay which was statistically significant (p=0.006)[15]. In our present study, surfactant had been used in 14 (37.8%) of 37 infants diagnosed with ROP and there was a statistically significant association (*p*=0.012). Previous unpublished data from our centre also showed similar statistically significant association between ROP and surfactant therapy (*p*=0.012) and 44.4% of ROP diagnosed cases received surfactant therapy. Statistically significant association between bronchopulmonary dysplasia and development of ROP had been observed in present study (*p*=0.001)

as well in our previous unpublished data (p<0.0001). Similar findings were observed by Goncalves E et al[15] and Port et al[19] in their studies regarding bronchopulmonary dysplasia and ROP. Goncalves E et al reported 53.1% of diagnosed cases of ROP with development of bronchopulmonary dysplasia (p=0.002)[15]. Port et al, also have documented a statistical significance (p<0.001) in their study between ROP and bronchopulmonary dysplasia[19]. No statistical significance proved between exchange transfusion and ROP, either in the present study (p=0.999) or in previous unpublished data from same centre (p=0.61). Chaudhari et al in their study found no statistical significance between ROP and exchange transfusion (p=0.220)[3]. No statistical significance was proved between IVH and ROP in the present study (p=0.885). Findings noted in our previous unpublished data showed 44.4% of cases with ROP had a history of IVH and there was statistical significance achieved on univariate analysis (p<0.0001) but not on multivariate analysis. Rao A K et al.[13] & Goncalves E et al.,[15] in their studies have observed no statistically significant association between ROP and IVH. In study by Rao A K *et al*, 8.2% of ROP documented cases had history of IVH with p value of 0.19[71] while in study by Goncalves E et al, 20.4% population has an affection between ROP and IVH with a p-value of 0.589[15]. PDA and its association with ROP has been studied by many investigators. In our present study no statistical significance was observed (p=0.302) between PDA and ROP. Findings noted in our previous unpublished data showed 53.3% of cases with ROP had a history of PDA and there was statistical significance achieved on univariate analysis (p<0.0001). Findings of no association between ROP and PDA were documented by Chaudhari *et al*,[3] Rao A K *et al*[13] and Goncalves E *et al*[15]. in their studies and p-values documented were 0.407, 0.52 & 0.589 respectively in regards to association between ROP and PDA. 43.2% (i.e. 16/37) diagnosed cases of ROP had a history of packed cell transfusion in the present study while only 16.8% (i.e. 25/149) population without ROP had a history packed cell transfusion and this association was statistically significant (p=0.001) on multivariate analysis. Chaudhari *et al* had shown similar association between ROP and packed cell transfusion in their study (p=0.013) where 23.6% of diagnosed cases of ROP had previous history of packed cell transfusion[3]. Though NEC has been proven as a risk factor for ROP in certain studies, no statistical significance was observed in the present study (p=0.195). Port *et al*, in their study documented that 10.6% of ROP diagnosed population has an association with NEC while in population without ROP only 3.4% were affected with NEC and this association between ROP and NEC in their study was statistically significant[19].

There were some limitations in the study. The sample size is small and may not represent all premature babies in the region. Hence, a large multicentric study is required to establish the true incidence and causal relationship of risk factors associated with ROP.

Conclusions

- ROP incidence has increased from 12% in 2010-2012 to 19.9% in 2015-2016.
- Gestational age, birth weight, mechanical ventilation, oxygen therapy, packed cell transfusion, surfactant administration and bronchopulmonary dysplasia had statistically significant associations with ROP in the present study.
- No association was proven with other maternal and neonatal risk factors.

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