Original Research Article

Evaluation of SpO\textsubscript{2}, PaO\textsubscript{2}, FiO\textsubscript{2} levels in developing retinopathy of prematurity

Porimal Kumar Das\textsuperscript{1*}, Shubhra Prakash Paul\textsuperscript{2}, Md Shamim Parvej Ibne Halim\textsuperscript{1}, Mohammad Abdullah Al Mamun\textsuperscript{3}, Mohammad Monir Hossain\textsuperscript{4}, Mahfuza Shirin\textsuperscript{4}, A. H. M. Enayet Hossain\textsuperscript{5}, Puspanjali Biswas\textsuperscript{6}

\textsuperscript{1}Department of Paediatrics, Mugda Medical College Hospital, Mugda, Dhaka, Bangladesh
\textsuperscript{2}Department of Community Medicine, Raj Shahi Medical College, Raj Shahi, Bangladesh
\textsuperscript{3}Department of Paediatrics Cardiology, BICH and Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh
\textsuperscript{4}Department of Neonatal Medicine and NICU, BICH and Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh
\textsuperscript{5}Paediatric Ophthalmology, National Institute of Ophthalmology, Dhaka, Bangladesh
\textsuperscript{6}Dhaka Community Hospital, Dhaka, Bangladesh

Received: 30 August 2020
Revised: 01 March 2021
Accepted: 02 April 2021

*Correspondence:
Dr. Porimal Kumar Das,
E-mail: poridas@yahoo.com

ABSTRACT

Background: Retinopathy of prematurity (ROP) is a potentially blinding disease affecting the retinas in premature infants. In the treatment procedure of ROP, oxygen inhalation as well as the SpO\textsubscript{2}, PaO\textsubscript{2}, FiO\textsubscript{2} levels analysis are some major concerns.

Methods: This was a prospective COHORT study which was conducted at the special care baby unit (SCABU) and intensive care unit (ICU) of Dhaka shishu (children) hospital, Dhaka, Bangladesh from July 2012 to December 2014. Total one hundred (100) neonates of both sexes were finalized as the study population. Data were processed and analyzed using statistical software SPSS version 17, EPI info 7.

Results: We found statistically significant risk for ROP, RR 3.48 (2.61-4.64) but there was no risk associated with FiO\textsubscript{2} (24-32)% or 33-40% in inhaled air. SpO\textsubscript{2} (95-99)% was present in 25 (78.13%) of ROP (positive) neonates and 16 (23.53%) in ROP (negative) neonates. The difference was statistically significant (p<0.05) between the groups and RR 4.8 (2.51-9.28) for saturation of 95-99%. Partial pressure of oxygen >150 mm of Hg present in 12 (37.50%) cases of ROP (positive) neonates and 6 (8.82%) in ROP (negative) neonates. The difference was statistically significant (p<0.05) between the groups and RR 2.90 (1.83-4.5) for partial pressure of oxygen (>150) but there was no risk for partial pressure of 70-99 and 100-150 mm of Hg.

Conclusions: During oxygen therapy FiO\textsubscript{2} value, SpO\textsubscript{2} value and more precisely the PaO\textsubscript{2} value on neonate should be maintained within a target range.

Keywords: SpO\textsubscript{2}, PaO\textsubscript{2}, FiO\textsubscript{2} levels, Retinopathy, Prematurity, ROP

INTRODUCTION

ROP has been identified by the WHO as a priority eye disease in the vision 2020 statement for the global initiative for the elimination of avoidable blindness.\textsuperscript{1} It is a major cause of blindness in children in the developing and developed world despite current surgical treatment in the late-stage of the disease.\textsuperscript{2} In 1942, Terry first described ROP as a disease of prematurity characterized by retinal neovascularization.\textsuperscript{3} In the 1940s, there was an
epidemic of blindness resulting from ROP, exposing the need for research focused on the identification and characterization of the pathogenesis of the disease. In 1951, Campbell proposed that the incidence of ROP was tied to the supplemental oxygen administered to premature infants with under-developed pulmonary function. The second epidemic occurred in the 1970s and 1980s which was because of increased survival rate of very low birth weight infants. With the institution of carefully timed screening examinations and treatment with cryotherapy, pan retinal photocoagulation and advanced surgical techniques, the rate of blindness from ROP has dropped substantially in developed countries. As developing countries began to adopt modern neonatology techniques in the 1980s and 1990s, increasing the survival of preterm neonates, ROP began to emerge as the third epidemic in middle-income countries, where it can account for as much as 60% of childhood blindness. While the widespread implementation of vitamin A supplementation and measles immunization programs have led to a reduction in vitamin A deficiency-related blindness in many poor countries, ROP is now undergoing a third wave of endemicity, particularly in newly industrializing countries in Latin America and Asia. In these countries, close oxygen monitoring is not always possible and screening for ROP is not routine. ROP occurs due to abnormal proliferation of retinal vessels. The most important risk factors which predispose to development of ROP include oxygen therapy, anemia requiring blood transfusion, sepsis and apnea. In spite of extensive research and progress in the understanding of this disease in recent years, an explosive increase in severe ROP is seen in low-income countries. In the US and other industrialized nations O2 therapy for neonates was introduced in the 1930’s and early 1940’s. Its use then became widespread throughout the world. The use of oxygen was implemented in neonatal practice in the absence of any randomized studies. The dose was (and still is in some places) not measured well. Additionally, the newborns oxygenation levels were not measured routinely until arterial blood gases (ABG’s), capillary samples, transcutaneous PO2 (TeP02) and more recently, monitoring of oxygen saturation by pulse oximetry (SpO2) became available. However, it is one of the drugs most frequently used in NICU’s, many times without any limits or control. Oxygen was discovered more than 200 years ago and it has been administered to more infants in the world than any other neonatal treatment. However, we still do not fully know how much is wise to give or how much infants actually need in relation to variations in illness and gestational and postnatal age. But we have known for many years that too much oxygen damages the retina. Many neonatal units have adopted new oxygen saturation policies to reduce the amount of supplemental oxygen given to premature infants. Technological advances have allowed continuous monitoring of arterial oxygen saturation levels. The question today is which among the factors related to hypercarbia, hyperoxia and significant and rapid oxygen fluctuation has a greater or lesser impact on ROP. Oxygen is a drug and it is essential in some condition in NICU. It should be administered in quantity that is absolutely necessary. Both hypoxia and hyperoxia are detrimental to the baby. Ophthalmological examination of preterm babies is not routinely done in Bangladesh, despite the common occurrence of multiple risk factors for ROP among hospitalized, preterm infants. As survival of preterm infants in low resource settings increases, ROP will be increasingly important as a potential cause of blindness, emphasizing the critical importance of ophthalmic examination in premature infants from as early as two weeks after birth, with urgent initiation of treatment when ROP is diagnosed. In Bangladesh, study regarding use of supplemental oxygen and oxygen profile has been evaluated properly but scant data are available and there is no definite protocol of oxygen use in local neonatal intensive care units. The aim of this study was to evaluate the SpO2, PaO2, FiO2 levels in developing ROP.

METHODS

It was a prospective cohort study which was conducted at the SCABU and ICU of Dhaka shishu (children) hospital, Dhaka, Bangladesh during the period from July 2012 to December 2014. In total one hundred (100) neonates of both sexes having the possibilities of development of ROP were finalized as the study population. Data were processed and analyzed using statistical software SPSS version 17, EPI info 7. Ophthalmological examinations of this study have been performed at the paediatric ophthalmology department of national institute of ophthalmology, Dhaka during July 2012 to December 2014. Sample size has been estimated with EPCALC 2000 software by assuming differences in the mean in the healthy and disease (having ROP) group with 80% power and 95% significant level. Sampling method was non probability convenient and purposive sampling. A standard questionnaire including cardinal points of the history, examination findings and investigation results prepared by the investigator was used to collect data. The ethics review board of Bangladesh institute of child health approved the protocol of the study. Informed written consent/finger print was obtained from all the parents or guardians after they were thoroughly briefed about the nature, interest and purpose of the study. Reassurance was given to parents as there was no harmful effect for babies or economic loss. According to the inclusion criteria babies with birth weight ≤2500 g, babies born at <34 weeks of gestation and selected preterm babies with a birth weight between 1500 g and 2500 g with sickness like need of cardiorespiratory support, prolong oxygen therapy, apnea of prematurity, anemia needing blood transfusion and neonatal sepsis were included in the study. On the other hand, according to the exclusion criteria of this study neonate who had congenital anomalies, syndromic manifestations or suspected inborn errors of metabolism, neonates who had congenital eye problems like cataract, glaucoma or
corneal opacities and neonates who did not get supplemental oxygen were excluded from the study. Photographs were taken with due permission of the parents. The adequate facilities to manage any risk or adverse condition developed by the participants during the study were ensured. For collecting and displaying data and the findings MS excel were used.

A flowchart for cohort study should be included.

![Flowchart](chart.png)

**RESULTS**

In this prospective COHORT study after third and final screening of ROP we found 32 neonates positive for ROP patients which was 32% among total participants and 68 ROP (positive) patients which was 68% among the total 100 study people. In gender distribution of our study we found among all the participants 61.67% were male whereas 38.33% were female. So male were dominating in this study. Among 32 ROP (positive) patients 63.16% was male and 36.84% was female. On the other hand, among 68 ROP (negative) patients 60.98% was male and 39.02% was female. In this study, thirty (36.59%) neonates got oxygen up to 72 hours did not developed ROP. Only one 1 (3.13%) ROP (positive) neonates received oxygen for duration of 170-218 hours and >218 hours developed ROP, RR was 2.01 (1.17-3.48) and 4.67 (2.71-8.03) respectively and (p<0.05). On the other hand, five neonates (13.16%) of ROP (positive) got percentage of oxygen in inhaled air (41-60)% and this concentration was found statistically significant risk for ROP, RR 3.48 (2.61-4.64) but there was no risk associated with FiO$_2$ (24-32)% or (33-40)% in inhaled air. SpO$_2$ (95-99)% was present in 25 (78.13%) of ROP (positive) neonates and 16 (23.53%) in ROP (negative) neonates. The difference was statistically significant (p<0.05) between the groups and RR 2.90 (1.83-4.5) for partial pressure of oxygen (>150) but there was no risk for partial pressure of 70-99 and 100-150 mm of Hg.

**Figure 1:**

| Calculated FiO$_2$ | ROP (+ve) (N=32) (%) | ROP (−ve) (N=68) (%) | RR (95% CI) | P value |
|-------------------|----------------------|----------------------|-------------|---------|
| 24-32$^1$         | 16 (50)              | 51 (75)              | 0.48 (0.28-0.80) | 0.005   |
| 33-40$^1$         | 12 (37.50)           | 17 (25)              | 1.47 (0.87-2.49) | 0.159   |
| 41-60*            | 4 (12.50)            | 0 (0)                | 3.48 (2.61-4.64) | 0.001   |
| Total             | 32                   | 68                   |             |         |

*Fisher’s exact test; $^1$Chi square test; p<0.05 is significant.

---

International Journal of Contemporary Pediatrics | August 2021 | Vol 8 | Issue 8 | Page 1345


### Table 2: Oxygen saturation (SpO₂) and association with ROP (N=100).

| SpO₂ (%) | ROP (+ve) (N=32) (%) | ROP (–ve) (N=68) (%) | RR (95% CI) | P value |
|----------|----------------------|----------------------|--------------|---------|
| 85-89*   | 1 (3.13)             | 8 (11.76)            | 0.26 (0.04-1.76) | 0.09    |
| 90-94†   | 6 (18.75)            | 44 (64.71)           | 0.25 (0.12-0.51) | 0.001   |
| 95-99†   | 25 (78.13)           | 16 (23.53)           | 4.8 (2.51-9.28)  | 0.001   |
| Total    | 32                   | 68                   |              |         |

*Chi square test; †Fisher’s exact test; p<0.05 is significant.

### Table 3: Distribution of partial pressure of oxygen (PaO₂) and association with ROP (N=100).

| PaO₂ (mm of Hg) | ROP (+ve) (N=32) (%) | ROP (–ve) (N=68) (%) | RR (95% CI) | P value |
|----------------|----------------------|----------------------|--------------|---------|
| 70-99*         | 2 (6.25)             | 30 (44.12)           | 0.11 (0.30-0.47) | 0.001   |
| 100-150†       | 18 (56.25)           | 32 (47.06)           | 1.23 (0.72-2.09) | 0.43    |
| >150‡          | 12 (37.50)           | 6 (8.82)             | 2.90 (1.83-4.5)  | 0.001   |
| Total          | 32                   | 68                   |              |         |

*Fisher’s exact test; †Chi square test; p<0.05 is significant.

### DISCUSSION

After completing first screening of 100 participants 32 (32%) were found abnormal whereas 68 (68%) were normal. Among total participants, 61.7% were male and 38.3% were female. Most of the neonates had their first screening examination within a chronological age of 4-6 weeks. In total 10 (10%) neonates were unable to be present to the ophthalmologist in due time. The failure to attend to the ophthalmologist was probably due to the parent’s fatiguability after a long stormy hospital stay or due to long distance of the residence and financial constraints. Accumulating all the results of screening examinations 8 (8%) neonates could be labeled as having stage 1 ROP and 13 (13%) neonates had stage 2 ROP, 11 (11%) infants had stage 3 ROP. The incidence of ROP in this study is similar to studies done in India, Pakistan and Nepal. However, the inclusion criteria differ in some of these studies. In this study 14 significant factors have been found to be related with the occurrence of ROP on univariate analysis. Those were gestational age (GA), extreme low birth weight (ELBW), very low birth weight (VLBW), clinical sepsis, culture positive sepsis, oxygen by head box, mechanical ventilation, oxygen flow ≥4 liter/min, duration of oxygen for 170-218 hours, duration of oxygen ≥218 hours, FiO₂, SpO₂, PaO₂, blood volume >40 ml/kg. Multivariate logistic regression analysis was done including all of these factors. Finally, ELBW, mechanical ventilation, duration of oxygen ≥218 hours and SpO₂ >95% was found to be most significant. The role of oxygen therapy as a predictor of ROP has been reported in several other studies. In the present study multivariate logistic regression analysis found that SpO₂ is a major risk factor for ROP. Among the 32 ROP (positive) neonates 25 (78.13%) neonates had SpO₂ (95-99)% RR 4.8 (CI 2.51-9.28). Many studies have proven the role of hyperoxia or high SpO₂ (>95%) in the pathogenesis of ROP. Case-control study by STOP-ROP multicenter study group have revealed that infants who developed severe ROP, compare with infants of similar gestation and birth who do not have ROP, have hospital courses characterized by more complex medical problems, prolong oxygen requirements, lower overall arterial oxygenation levels and more episodes of fluctuating blood oxygen levels with hyperoxia. Other observational studies have reported the beneficial effects of lower target oxygen saturation levels on the incidence and severity of ROP. A randomized study reported that a target range of oxygen saturation of 85 to 89% increased mortality while substantially decreasing severe ROP among survivors as compared with a target range of oxygen saturation of 91 to 95%. PaO₂ values above 80-90 mm Hg may be considered hyperoxemiae. Haupert at el found that infant exposed to high PCO₂, low PH and high PaO₂ appear to be at increased risk of more severe ROP. In the current study PaO₂ was measured intermittently as per advised by consultant neonatologist. It was found that 12 (37.50%) neonates of ROP (positive) found to have PaO₂ >150 mm of Hg and the RR 2.90 (CI...
1.83–4.5). The high PaO₂ of this group may be due to blood sample were taken while the neonates on oxygen therapy. When duration of oxygen therapy was compared in the ROP (positive) and ROP (negative) group, this difference was significant (p<0.05). The mean duration of supplemental oxygen in the ROP (positive) neonates 299 hours and in ROP (negative) neonates it was 128 hours. Multiple logistic regression analysis using SPSS identified, duration of oxygen as an independent factor which could significantly predict development of ROP (p=0.001). Teioh at el found that the duration of exposure to oxygen therapy increase, the risk of development of ROP; in their study the mean duration of oxygen therapy among 32 infants with ROP was 9.4 days.25 In India, Rekha et al reported that duration of oxygen therapy and anemia were independent factors predicting the development of ROP.26 On the contrary Patil et al in their study did not demonstrate any significant association between ROP and length of time in supplemental oxygen or the mean maximum concentration required.26 In this study the FiO₂ was measured indirectly according to Guha et al the FiO₂ was not measured directly as lack of oxygen analyzer this is the limitation of the study.27 In the current study four neonates (12.50%) of ROP (positive) got percentage of oxygen in inhaled air (41-60)% and this concentration was found statistically significant risk for ROP, RR 3.48 (2.61-4.64). In 1954 a large trial was performed to investigate the risk of supplemental oxygen therapy. The conclusion of this trial was that it was safe to give oxygen to newborn infants as long as the FiO₂ was below 40%.28 From this study it has been known that overall ROP incidence is 32%, studies in larger scale and with enough logistic support should be undertaken to know the exact incidence and risk factors in this country. As described by vision 2020, to reduce the incidence of ROP some strategies like routine fundus examination of premature neonates <34 weeks’ gestation and/or birth weight <1500 g, provision of carefully monitored levels of supplemental oxygen and screening by well trained and well-equipped ophthalmologist are urgent necessities.29 During oxygen therapy FiO₂ value, SpO₂ value and more precisely the PaO₂ value on neonate should be maintained within a target range. For getting more specific information we would like to recommend for conducting more studies regarding the same issue with larger sized sample.

Limitations

This was a single centered study with a small sized sample. So, the findings of this may not reflect the exact scenario of the whole country.

CONCLUSION

For getting more specific findings we would like to recommend for conducting more studies regarding the same issue with larger sized sample.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. World Health Organization. Global Initiative for the Elimination of Avoidable Blindness: action plan 2006-2011.
2. Walter JR. Retrolental Fibroplasia: a modern parable. J Pediatr Ophthalmol Strabismus. 1980;17(5):347.
3. Terry TL. Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens: I, preliminary report. Am J Ophthalmol. 2018;25:203-4.
4. Campbell K. Intensive oxygen therapy as a possible cause of retrolental fibroplasia; a clinical approach. Med J Aust. 1951;2(2):48-50.
5. Gilbert C. Retinopathy of prematurity: Epidemiology. Comm Eye Health J. 1997;10(22):22-4.
6. Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev. 2008;84(2):77-82.
7. Courtright P, Hutchinson AK, Lewallen S. Visual impairment in children in middle- and lower-income countries. Arch Dis Child. 2011;96(12):1129-34.
8. Gilbert C, Rahi J, Eckstein M, O'Sullivan J, Foster A. Retinopathy of prematurity in middle-income countries. Lancet. 1997;350(9070):12-4.
9. McClom JR, Fleck BW. Retinopathy of prematurity: causation. Semin Neonatol. 2000;5(6):453-60.
10. Saugstad OD. Oxygen and retinopathy of prematurity. J Perinatol. 2006;26:46-50.
11. Sola A, Chow L, Rogido M. Retinopathy of prematurity and oxygen therapy: a changing relationship. An Pediatr (Barc). 2005;62(1):48-61.
12. Sola A, Rogido MR, Deulofeut R. Oxygen as a neonatal health hazard: call for détente in clinical practice. Acta Paediatrica. 2007;96(6):801-12.
13. McGregor ML, Bremer DL, Cole C, McClead RE, Phelps DL, Fellows RR, et al. Retinopathy of Prematurity outcome in infants with prethreshold retinopathy of prematurity and oxygen saturation >94% in room air: the high oxygen percentage in retinopathy of prematurity study. Pediatrcs. 2002;110(3):540-4.
14. The STOP-ROP multicenter study Group. Supplemen tal therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized controlled trial. I: primary outcomes. Pediatrics. 2000;15(2):0: 295-310.
15. Ahmed AS, Muslma H, Anwar KS, Khan NZ, Chowdhury MA, Saha SK, et al. Retinopathy of prematurity in Bangladeshi neonate. J Trop Pedi atr. 2008;54(5):333-9.
16. Akter S, Shirin M, Hossain MM. Retinopathy of prematurity: are we prepared to face the third epidemic? Bangladesh J Child Health. 2006;30:25-8.
17. Muhit MA, Shah SP, Gilbert CE, Foster A. Causes of severe visual impairment and blindness in Bangladesh: a study of 1935 children. Br J Ophthalmol. 2007;91(8):1000-4.
18. Chaudhari S, Patwardhan V, Vaidya U, Kadam S, Kamat A. Retinopathy of prematurity in a tertiary care centre-incidence, risk factors and outcome. Indian Pediatr. 2009;46(3):219-24.
19. Wheatley CM, Dickinson JL, Mackey DA, Craig JE, Sale MM. Retinopathy of prematurity: recent advances in our understanding. Arch Dis Child Fetal Neonatal Ed. 2002;87(2):78-82.
20. Wright KW, Sami D, Thompson L, Ramanathan R, Joseph R. A physiologic reduced oxygen protocol decrease the incidence of threshold retinopathy of prematurity. Trans Am Ophthalmol Soc. 2006;104:78-84.
21. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, et al. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010;362(21):1959-69.
22. Flynn JT, Bancalari E, Snyder ES, Goldberg RN, Feuer W, Cassady J, et al. A COHORT study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. N Engl J Med. 1999;340:77-92.
23. Hauspurg AK, Allred EN, Vanderveen DK, Chen M, Bednarek FJ, Cole C, et al. Blood gases and retinopathy of prematurity: the ELGAN study. Neonatology. 2011;99(2):104-11.
24. Teioh SL, Boo NY, Ong LC, Nyein MK, Lye MS. Duration of oxygen therapy and exchange transfusion as risk factors associated with retinopathy of prematurity in very low birth weight infants. Eye. 1995;9:733-7.
25. Rekha S, Battu RR. Retinopathy of prematurity: Incidence and risk factors. Indian Pediatr. 1996;33(10):999-1003.
26. Patil J, Deodhar J, Wagh S, Pandit AN. High risk factors for development of retinopathy of prematurity. Indian Pediatr. 1997;34(11):1024-7.
27. Guha DK, Guha R, Srivastava RD. Manual of Neonatal critical care medicine. 1st ed. New Delhi: Jaypee Brothers Medical Publisher; 2006.
28. Kinsey VE, Jacobus JT, Hemphill F. Retrolental fibroplasia: cooperative study of retrolental fibroplasias and the use of oxygen. Arch Pediatr Adolesc Med. 1956;92(4):395.
29. Gilbert C, Foster A. Childhood blindness in the context of VISION 2020-the right to sight. Bull World Health Organ. 2001;79(3):227-32.

Cite this article as: Das PK, Paul SP, Halim MSPI, Mamun MAA, Hossain MM, Shirin M, et al. Evaluation of SpO2, PaO2, FiO2 levels in developing retinopathy of prematurity. Int J Contemp Pediatr 2021;8:1343-8.