Association of Oxygen Therapy Concentration and Duration with Retinopathy of Prematurity Incidence at Naresuan University Hospital

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ABSTRACT

Objective: This study aimed to evaluate the association between the concentration and duration of oxygen therapy and the development and severity of retinopathy of prematurity (ROP). Additionally, it sought to examine the incidence of ROP at Naresuan University Hospital.

Materials and Methods: A retrospective observational cohort study was conducted, utilizing data from the medical records of infants admitted to the Neonatal Intensive Care Unit at Naresuan University Hospital, Phitsanulok, Thailand, from January 1, 2016, to December 31, 2022. The duration of various oxygen therapies was recorded in hours, and the concentration of oxygen administered per hour was calculated as the average fraction of inspired oxygen for each infant. These data were subsequently analyzed using STATA version 11.0.

Results: Out of 100 eligible infants, 27 (27%) were diagnosed with ROP at different severity levels: 17 infants (62.96%) with ROP stage 1, 9 infants (33.33%) with stage 2, and 1 infant (3.70%) with stage 3. There were no cases of Stage 4 or 5 ROP. The adjusted risk ratio revealed that infants receiving an average FiO2 of 0.3 or higher had a 1.64 times greater risk of developing ROP [95%CI 1.03-2.62], (P-value=0.038). Further analysis using mean difference regression showed a significant correlation between the duration of oxygen therapy and the severity of ROP.

Conclusion: This study suggests that regulating oxygen therapy to not exceed an FiO2 of 0.3 and administering it strictly as needed may mitigate the risk of developing ROP and its severe manifestations.

Keywords: Retinopathy of prematurity; severity of retinopathy of prematurity; premature infant; oxygen concentration; duration of oxygen therapy (Siriraj Med J 2024; 76: 160-166)

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder affecting the retina of premature infants, with a potential progression to retinal neovascularization.[1,2] In aggressive cases, this disease can progress to a severe stage, resulting in permanent visual impairments unless early diagnosis and appropriate treatment are provided.[3] Infants previously diagnosed with ROP remain at risk for developing other vision abnormalities, such as strabismus, amblyopia, and cataracts, even after treatment with laser photocoagulation or cryotherapy.

Das et al. conducted a prospective cohort study to evaluate the effect of supplemental oxygen on the development of ROP at Dhaka Shishu Hospital, Bangladesh from July 2012 to December 2014.[4] The study included infants with a birth weight ≤2500 g or born at <34

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weeks of gestation, as well as selected premature infants weighing between 1500 g and 2500 g with conditions requiring cardiorespiratory support, prolonged oxygen therapy, apnea of prematurity, anemia requiring blood transfusion, and neonatal sepsis. Following the third and final ROP screening, 38 of the 120 participants (31.67%) were diagnosed with ROP. Among 35 participants who received oxygen for more than 218 hours, 25 of them developed ROP, indicating a relative risk (RR) of 4.67 [95%CI 2.71- 8.03], p=0.0001. Five participants exposed to 41-60% oxygen concentration in inhaled air (FiO2 0.4-0.6) developed ROP, a concentration found to be a statistically significant risk factor for ROP with an RR of 3.48 [95%CI 2.61-4.64], p=0.001. Multivariate logistic regression analysis revealed that extremely low birth weight, mechanical ventilation, oxygen duration >218 hours, and SpO2 >95% were significant risk factors.

Teoh et al. carried out a prospective, observational cohort study in Kuala Lumpur Maternity Hospital, Malaysia, between December 1, 1989 and December 31, 1992, to assess the association between the duration of oxygen therapy and exchange transfusion and ROP development in infants with a birth weight <1500 g.[5] The study included 113 newborns admitted to the neonatal intensive care unit (NICU) who survived for at least 6 months. These infants were treated with supplemental oxygen to maintain specific arterial oxygen tension levels and received endotracheal intubation and intermittent positive pressure ventilation for severe respiratory conditions. The infants were weaned off ventilatory support and supplemental oxygen As soon as their clinical condition and blood gases improved, they were weaned off ventilatory support and supplemental oxygen. Exchange blood transfusions were performed for indirect serum bilirubin levels exceeding 280 micromol/l or in cases of unresponsive overwhelming septicemia. have not responded to antibiotic treatment. Among the 113 participants, 36 infants (31.9%) developed ROP, with logistic regression analysis indicating that both prolonged supplemental oxygen therapy (OR=1.156, [95%CI 1.056-1.254], p=0.0005) and exchange transfusions (OR=5.754, [95%CI 1.002-32.997], p=0.049) significantly increased the risk of ROP.

Kanya Chutasmit et al. Carried out a retrospective, cross-sectional, comparative study at the Division of Neonatology, Department of Pediatrics, Faculty of Medicine at Siriraj Hospital to study incidence and risk factor of prematurity between January 2010 and December 2019.[6] The study include infants with a birth weight ≤1,500g or born at <33 weeks of gestation. The study include 1,247 infants, there were 174 (14%) had ROP at various stages and 26 (2.1%) had threshold ROP requiring treatment. The study compared risk factor between pre-threshold and threshold ROP group revealed that lower gestational age and positive-culture septicemia were found to be a statistically significant risk factor.

To date, no definitive conclusions have been established regarding the correlation between the parameters of oxygen therapy, including its concentration and duration, and the onset and severity of ROP. Therefore, this study aims to evaluate these relationships, aiming to contribute to the development of effective prevention and mitigation strategies for ROP. Additionally, it seeks to examine the incidence of ROP at Naresuan University Hospital.

MATERIALS AND METHODS

This retrospective observational cohort study collected data from infants admitted to the Neonatal Intensive Care Unit, Naresuan University Hospital, Phitsanulok, Thailand, from January 1, 2016 to December 31, 2022. The medical records of all included infants were reviewed following approval from the Institutional Review Board of Naresuan University (COA No. 082/2022).

Inclusion criteria for infants who underwent ophthalmologic screening for ROP were as follows:

1) Infants with a birth weight ≤1,500 grams.
2) Infants with a gestational age ≤30 weeks.
3) Infants with a birth weight between 1,500-2,000 grams or with a gestational age >30 weeks, who experienced medically unstable course, required cardiorespiratory support, or were identified as at-risk for developing ROP by pediatricians or ophthalmologists.

Exclusion criteria included infants with:

1) Cyanotic heart disease.
2) Congenital abnormalities affecting the brain or eyes, such as cataracts, glaucoma, ocular neoplasms, or holoprosencephaly.
3) Incomplete medical data.

All eligible infants underwent ophthalmologic screening and were diagnosed with ROP by an ophthalmologist, using the International Classification of ROP (ICROP3) standards.[7] ROP screening was initiated either after the infant reached 31 weeks' postmenstrual age or 4 weeks after birth, whichever came later, and it continued until the retina was fully vascularized to the ora serrata. However, if a pediatrician determined that an infant exhibited unstable clinical signs or vital signs to an extent that precluded the use of dilating eye drops for ophthalmologic examination, the ROP screening was deferred until the infant's condition stabilized sufficiently for evaluation.

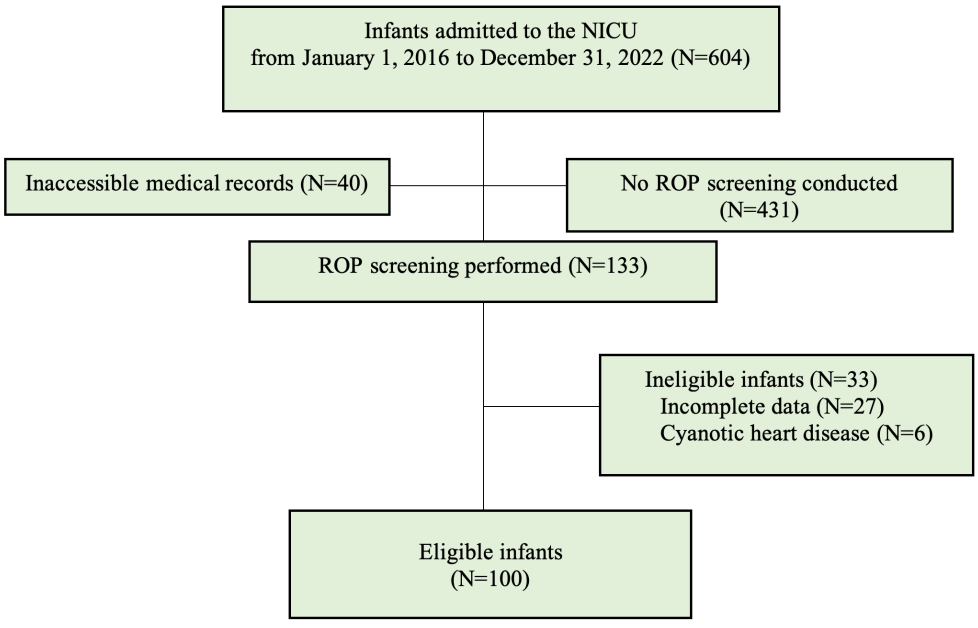

Fig 1. Flow diagram of study's screening and selection process.

Data containing both antenatal and postnatal periods were comprehensively collected. The scope of data included the duration of oxygen therapy, measured in hours from birth to the ophthalmologic assessment, and the concentration, expressed as the mean fraction of inspired oxygen (average FiO2) per infant. Records of ROP diagnoses were collected, along with the results of the most severe cases of ROP in each eye. In the absence of ROP detection during the initial assessment, follow-up examinations were conducted at intervals of two to three weeks until full retinal vascularization was confirmed.

Statistical analysis

Data analysis was conducted using STATA version 11.0. The statistical methods applied were as follows:

1) Descriptive statistics were utilized to analyze the data. Continuous variables conforming to a normal distribution were summarized using the mean and standard deviation, while those deviating from normality were described using the median and interquartile range. Categorical data were expressed as percentages and frequencies.
2) Comparative analysis between two independent numerical variable groups was conducted using an independent t-test for normally distributed data and the Mann-Whitney U test for data with a non-normal distribution. For categorical variables, the exact probability test was used, with findings reported as P-values.
3) Variables associated with ROP were selected based on insights from extant research, with the adjusted risk ratio (95% confidence interval; 95% CI) calculated using the multiple logistic regression analysis to ascertain factors linked with ROP onset.
4) The relationship between oxygen therapy duration and ROP severity was examined by calculating the mean difference in oxygen therapy duration (95% CI) through mean difference regression analysis.
5) A P-value < 0.05 was considered statistically significant.

RESULTS

A total of 100 eligible infants were screened for ROP. Their gestational ages ranged from 23 to 36 weeks (31.04 ± 3.16 weeks), birth weights ranged from 490 to 2,715 grams (1,475.20 ± 516.76 grams), the duration of oxygen therapy varied from 8 to 1,835 hours (560.62 ± 529.96 hours), and the oxygen concentration ranged from an FiO2 of 0.21 to 0.61 (0.27 ± 0.07). Ophthalmologic examinations identified ROP in 27 infants (27%), with a distribution of severity across different stages: of ROP, stage 1 in 17 infants (62.96%), stage 2 in 9 infants (33.33%), and stage 3 in 1 infant (3.70%). No cases of stage 4 or 5 ROP were detected.

Factors correlating with the development of ROP included gestational age, birth weight, APGAR score, IVH, sepsis, pneumonia, RDS, BPD, NEC, PDA, apnea, oxygen concentration, and duration of oxygen therapy. These factors demonstrated statistical significance when contrasting the ROP and non-ROP groups (P-value < 0.05), as detailed in Table 1.

TABLE 1. Baseline characteristics of infants.

Characteristics	ROP (n=27) n (%)	No ROP (n=73) n (%)	P-value
Gender			
Male	12 (44.4)	43 (58.9)	0.197[a]
Female	15 (55.6)	30 (41.1)	
Maternal age (year)			
Mean (±SD)	30.7 (±7.7)	29.3 (±7.9)	0.422[b]
Parity			
1	10 (37.0)	34 (46.6)	0.209[a]
2	10 (37.0)	23 (31.5)	
3	7 (25.9)	10 (13.7)	
4	0 (0)	6 (8.2)	
Multiple pregnancy	9 (33.3)	17 (23.3)	0.309[a]
Type of delivery			
Cesarean section	21 (77.8)	48 (65.8)	0.248[a]
Vaginal delivery	6 (22.2)	25 (34.3)	
Gestational age (week)			
Mean (±SD)	27.9 (±2.5)	32.2 (±2.5)	<0.001[b]
Postmenstrual age* (week)			
Mean (±SD)	34.9 (±1.9)	37.8 (±1.9)	<0.001[b]
Birth weight (gram)			
Mean (±SD)	974.4 (±318.4)	1660.4 (±449.2)	<0.001[b]
Birth weight classification			
Low birth weight (1,500-2,500 g.)	2 (7.4)	43 (58.9)	<0.001[a]
Very low birth weight (1,000-1,499 g.)	9 (33.3)	23 (31.5)	0.862[a]
Extremely low birth weight (<1,000 g.)	16 (59.3)	4 (5.5)	<0.001[a]
SGA	4 (14.8)	3 (4.1)	0.063[a]
APGAR score at 1 minute			
(Percentile 25, 50, 75)	(2, 4, 7)	(6, 7, 9)	<0.001[c]
APGAR score at 5 minutes			
(Percentile 25, 50, 75)	(6, 7, 9)	(8, 9, 10)	<0.001[c]
Comorbidity			
IVH	24 (88.9)	47 (64.4)	0.017[a]
IUGR	2 (7.4)	4 (5.5)	0.719[a]
Sepsis	25 (92.6)	53 (72.6)	0.032[a]
Pneumonia	19 (70.4)	26 (35.6)	0.002[a]
RDS	25 (92.6)	44 (60.3)	0.002[a]
BPD	20 (74.1)	10 (13.7)	<0.001[a]
NEC	16 (59.3)	27 (37.0)	0.046[a]
PDA	18 (66.7)	17 (23.3)	<0.001[a]
Apnea	18 (66.7)	32 (43.8)	0.043[a]

TABLE 1. Baseline characteristics of infants. (Continue)

Characteristics	ROP (n=27) n (%)	No ROP (n=73) n (%)	P-value
Intervention			
Perinatal steroid	27 (100.0)	54 (74.0)	0.003[a]
Blood transfusion	24 (88.9)	38 (52.1)	0.001[a]
Surfactant therapy	23 (85.2)	34 (46.6)	0.001[a]
Oxygen therapy**			
Average duration (day)			
(Percentile 25, 50, 75)	(25.9, 48.1, 56.8)	(3.5, 10.2, 21.5)	<0.001[c]
Average FiO_2 (hour)			
(Percentile 25, 50, 75)	(0.23, 0.24, 0.29)	(0.22, 0.24, 0.27)	0.003[c]

Abbreviations: SGA, Small for Gestational Age; IVH, Intraventricular Hemorrhage; IUGR, Intrauterine Growth Restriction; RDS, Respiratory Distress Syndrome; BPD, Bronchopulmonary Dysplasia; NEC, Necrotizing enterocolitis; PDA, Patent Ductus Arteriosus; FiO2, Fraction of Inspired Oxygen; SD, Standard deviation
[a] Results of the exact probability test
[b] Results of the independent t-test
[c] Results of the Mann-Whitney U test
*Postmenstrual age at the time of ophthalmologic examination
** oxygen therapy modalities comprised mechanical ventilation, nasal intermittent positive pressure ventilation, continuous positive airway pressure, duo positive airway pressure, heated humidified high flow nasal cannula, standard oxygen cannula, and oxygen box.

Furthermore, the incidence of ROP was higher among infants with lower birth weights: 16 out of 27 infants (59.3%) weighing less than 1,000 grams were diagnosed with ROP. In infants with a birth weight of 1,000 to 1,499 grams, ROP was diagnosed in 9 out of 27 (33.3%), and for those weighing between 1,500-2,499 grams, ROP was found in 2 out of 27 infants (7.4%).

The analysis conducted to determine the adjusted risk ratio revealed a significant correlation between oxygen concentration and the occurrence of ROP. Particularly, infants subjected to an average FiO2 of 0.3 or higher were observed to have a 1.64-fold increased risk of ROP [95%CI 1.03-2.62], with a P-value of 0.038, as shown in Table 2.

TABLE 2. Adjusted risk ratio analysis.

Potential Risk Factor	Adjusted risk ratio	95% CI (Lower – Upper)	P-value
FiO2 ≥ 0.3	1.64	1.03-2.62	0.038*
Gestational age (week)	0.97	0.86-1.09	1.09
Very low birth weight	0.23	0.01-3.81	0.304
SGA	1.24	0.70-2.19	0.467
IUGR	1.86	0.92-3.76	0.085
APGAR score at 1 minute	0.90	0.75-1.08	0.257
APGAR score at 5 minutes	1.03	0.91-1.17	0.645
Sepsis	1.02	0.54-1.92	0.962
Pneumonia	1.16	0.71-1.89	0.565
RDS	4.95	0.16-154.96	0.363
BPD	2.01	0.71-5.70	0.187
Apnea	0.84	0.57-1.24	0.375
Surfactant therapy	0.78	0.16-3.74	0.752

* P-value < 0.05

The data further revealed a significant relationship between the duration of oxygen therapy and the severity of ROP (Table 3). Mean difference regression analysis indicated a strong correlation between the length of oxygen therapy and ROP severity. Specifically, Stage 1 ROP was associated with an additional 23.3 days of therapy [95% CI 13.5-33.0], Stage 2 with an added 31.1 days [95% CI 18.3-43.9], and Stage 3 with an extra 52.7 days [95% CI 16.2-89.2], all compared to infants without ROP. These findings were statistically significant, with P-values of <0.001 for Stages 1 and 2, and 0.005 for Stage 3, as illustrated in Fig 2.

DISCUSSION

The current study, conducted at the Neonatal Intensive Care Unit of Naresuan University Hospital from January 1, 2016, to December 31, 2021, revealed a 27% incidence of ROP in admitted infants. This research notably identified a significant correlation between the concentration of oxygen administered and the onset of ROP, as well as a direct relationship between the duration of oxygen therapy and the severity of ROP. Specifically, infants exposed to high concentrations of oxygen (average FiO2 ≥ 0.3) demonstrated a statistically significant predisposition to ROP. These findings are consistent with those reported in several other studies.[4,5,8-10] However, the observed range of FiO2 in this study contradicts the findings by Das, et al.,[4] who reported an association of ROP with FiO2 ranging from 0.41 to 0.60. This discrepancy could stem from differences in the timing of outcome measurements. Das et al.[4] performed the outcome measurement at the third and final ophthalmologic examination, while the current study carried out the assessment at the initial ophthalmologic examination.

It is important to note that ROP stage 1 may spontaneously regress with controlled risk factors. Conversely, prolonged exposure to high concentrations of oxygen therapy can exacerbate the severity of ROP. The detrimental effects of high-concentration oxygen therapy on ROP development are attributable to the resultant relative hyperoxia. This condition disrupts the balance of oxygen-regulated angiogenic growth factors like erythropoietin and vascular endothelial growth factor (VEGF), marking the initial phase of ROP. The subsequent phase involves the hypoxic retina, which becomes metabolically active yet poorly vascularized,

TABLE 3. Stage of ROP and duration of oxygen therapy.

Stage of ROP	Average duration (day)	Total (n=100)
No ROP	16.08	73
1	39.34	17
2	47.20	9
3	68.80	1

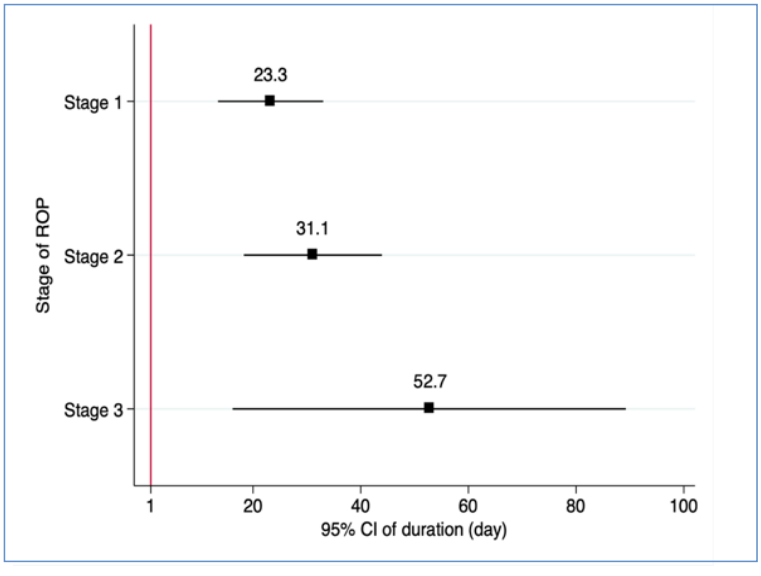

Fig 2. Regression analysis of mean differences in oxygen therapy duration across ROP stages (95% Confidence Interval).

leading to neovascularization. These neovessels, formed due to an overproduction of growth factors, inadequately perfuse the retina and are prone to leakage, resulting in fibrous scar formation and potential retinal detachment.[2]

Interestingly, this study not only highlighted the role of oxygen concentration, but also demonstrated that the duration of oxygen therapy in the ROP group was significantly longer compared to the non-ROP group, a finding consistent with previous studies.[4,5,11-13] Moreover, the relationship between oxygen therapy duration and ROP severity was substantiated by a mean difference regression analysis. The results revealed a statistically significant correlation between the duration of oxygen therapy and the severity of ROP. The mean differences in days for ROP stages 1, 2, and 3, compared to infants without ROP, were 23.3, 31.1, and 52.7, respectively.

In this study, data regarding the concentration and duration of oxygen therapy were comprehensively collected on an hourly basis and subsequently averaged for each infant, facilitating a more accurate statistical analysis. However, this study is limited by its single-center design, which inherently restricts the sample size. Future research conducted across multiple centers could accommodate a larger participant base, thereby enhancing the potential to identify a broader array of risk factors associated with the development of ROP.

CONCLUSION

Infants exposed to high oxygen concentrations, specifically from FiO2 0.3 or higher, exhibited a significantly increased risk – 1.64 times higher – of developing ROP, as evidenced by initial ophthalmologic screening examinations. Moreover, prolonged oxygen therapy was observed to exacerbate the risk of severe ROP. Therefore, it is recommended to limit oxygen provision to a maximum FiO2 of 0.3 and to administer it only when clinically essential. This approach could potentially mitigate the risk of ROP and its severe manifestations. The findings of this study are instrumental in enhancing the understanding and management of premature infants' care, contributing significantly to the body of knowledge in neonatal health.

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Author contribution statement

Krittaporn Phruksarudee: Conceptualization, Data curation, Software, Resources, formal analysis, Writing-Original draft, Visualization and Funding acquisition. **Kanrawee Sungprem:** Conceptualization, Investigation, Supervision, Project administration, Writing-Review & editing and Validation. **Mayuree Montriwet:** Methodology, Writing-Review & editing and validation.

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