Effect of the type of respiratory support and oxygenation indices on the development of different stages of retinopathy of prematurity

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Вплив видів респіраторної підтримки та показників оксигенації на розвиток різних стадій ретинопатії недоношених

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Abstract

Purpose. *To examine the effect size of the type of respiratory support and oxygenation indices on the development of different stages of retinopathy of prematurity (RoP).*

Material and methods*. We retrospectively reviewed the medical records of 290 preterm infants who were under supervision during 2015-2018. The preterm infants were divided into four groups: group 1 of 117 infants without RoP; group 2 of 86 infants with autoregressive RoP; group 3 of 57 infants that required treatment for RoP; and group 4 of 30 infants with aggressive RoP. All these infants underwent ROP screening in accordance with international standards in due time.*

Results. *There was a significant difference in gestation age (GA) among the four groups (ANOVA: F= 74.13; p < 0.0001), with a significant pairwise difference between most group pairs, but not between groups 3 and 4 (p = 0.9). Additionally, there was a significant difference in birth body weight (BBW) among the four groups (analysis of variance (ANOVA): F= 54.1; p < 0.0001), but the pairwise difference between groups 3 and 4 was not significant (p = 0.9). For FiO_2, Welch's ANOVA was applied when the homogeneity of dispersions was violated (Levene's test p = 0.03): F = 4.6; p = 0.005; the pairwise differences between groups 1 and 3, 2 and 3, and 3 and 4 were significant (p = 0.0006, p = 0.001, and p = 0.048, respectively). The frequency of mechanical ventilation (MV) use increased from group 1 to group 4 (90/117, 71/86, 55/57, and 30/30, respectively), with a significant difference among groups (Kruskal-Wallis test: H = 17.3; p = 0.006). No significant difference among groups was found for the frequency of use of nasal continuous positive airway pressure (NCPAP) (114/117, 85/86, 57/57, and 30/30, respectively; Kruskal-Wallis test: H = 2.4; p = 0.48). Transcutaneously measured oxygen saturation (SpO_2) was similar among groups (Welch ANOVA: F = 0.7; p = 0.5). The effect size as measured by partial η^2 was the largest for GA (0.437) and BBW (0.36) and less for MV (0.05) and FiO_2 (0.046).*

Conclusion. *GA and BBW had the largest effects (with a partial η^2 of 0.437 and 0.36, respectively) on the development of different stages of RoP. There was a significant difference among groups in FiO_2 or the frequency of MV use (indicating their effects on the development of different stages of RoP), but not in SpO_2 or the frequency of NCPAP use.*

Keywords: *retinopathy, preterm infants, lung ventilation, saturation, risk factors, laser photocoagulation, vasculogenesis, screening, retina.*

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Резюме

Мета. *Вивчити вплив видів респіраторної підтримки та показників оксигенації на розвиток різних стадій ретинопатії недоношених.*

Матеріал та методи. *Ретроспективно було проведено аналіз історій хвороб 290 недоношених дітей, що перебували під наглядом у період з 2015 по 2018 рік. Недоношених дітей розподілено на чотири групи: 1-ша – без РН (n=117); 2-га – саморегресуюча РН (n=86); 3-тя – РН, що потребувала лікування (n=57); 4-та – АРН (агресивна ретинопатія недоношених) – n=30. Діти в декретовані терміни пройшли скринінг РН, скринінг відповідав міжнародним стандартам.*

Результати*. Гестаційний вік статистично значуще відрізнявся між чотирма групами (ANOVA: F=74,13; p<0,0001); попарно значущі відмінності встановлено між більшістю груп, окрім 3-ї–4-ї (p=0,9). Маса тіла при народженні також відрізнялася між групами (ANOVA: F=54,1; p<0,0001); різниця між групами 3–4 була незначущою (p=0,9). Для FiO_2, за умов порушення гомогенності дисперсій (Levene p=0,03), застосовано Welch ANOVA: F=4,6; p=0,005; рівень значущості попарних відмінностей між групами: 1–3 (p=0,0006), 2–3 (p=0,001), 2–4 (p=0,048). Частота застосування ШВЛ зростала від групи 1 до 4 (90/117; 71/86; 55/57; 30/30) та відрізнялася між групами (Kruskal – Wallis: H=17,3; p=0,006). Для NCPAP відмінностей між групами не виявлено (114/117; 85/86; 57/57; 30/30; H=2,4; p=0,48). SpO_2 була подібною між групами (Welch ANOVA: F=0,7; p=0,5). Найбільша сила впливу за partial η² встановлена для гестаційного віку (0,437) та маси тіла (0,36); менша – для ШВЛ (0,05) і FiO2 (0,046).*

Висновки. *Гестаційний вік і маса тіла при народженні мали найбільший вплив на розвиток різних стадій ретинопатії недоношених (partial η²=0,437 та 0,36). FiO_2 і частота застосування ШВЛ статистично значуще відрізнялися між групами, що свідчить про їх вплив на розвиток різних стадій ретинопатії недоношених. SpO_2 та використання NCPAP статистично значущих міжгрупових відмінностей не мали.*

Ключові слова: *ретинопатія, недоношені діти, вентиляція легень, сатурація, фактори ризику, лазерна коагуляція, васкулогенез, скринінг, сітківка.*

Introduction

Immaturity of the organs of a premature infant at birth and failure to complete organogenesis in a favorable intrauterine environment not only pose a direct threat to its life, but also lay the groundwork for an increased risk of disability. One of the most serious visual complications of prematurity is retinopathy of prematurity (RoP). Despite advances in the diagnosis and treatment of RoP, the disease is still a leading cause of blindness in children worldwide. Investigation of the etiological factors of the disease remains relevant today [1].

The administration of additional oxygen became a standard practice of caring for extremely immature infants with respiratory disorders as early as 1940s. It is largely due to the unmonitored use of high levels of oxygen in incubators that the first RoP epidemic occurred in the 1940s and 1950s. The finding of an association between ROP and high oxygen concentrations by Campbell [2] was an important milestone in the development of modern neonatology.

The second RoP epidemic occurred in the 1970s and 1980s, when improved survival of extremely preterm infants triggered a second rise in RoP cases. At that time, the immaturity of a preterm baby was believed to be a major factor in the development of the disease, because infants were born with a younger gestational age (GA) and smaller birth weight (BW) than during the first RoP epidemic [3, 4].

The third epidemic of RoP began in the 1990s and continues today in low- and middle-income countries. Similar to the first epidemic of RoP, infants in the third epidemic have higher BW and GA than traditionally seen since the second epidemic. Mean GAs of infants from highly developed countries ranged from 25.3 to 25.6 weeks compared with 26.3 to 33.5 weeks in less developed countries [3]. Despite advances in understanding the pathogenesis, unified standards for safe oxygenation levels in preterm infants have not yet been defined. There are substantial differences in target oxygen saturation among neonatologic centers over the world, which may account for the variability in the incidence of RoP [3, 4].

Randomized clinical trials investigating the effect of oxygenation level on the course of ROP have been conducted. These included such multicenter trials as Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT, 2005–2009) and Oxygen Saturation Targeting II (BOOST II, 2013). Both trials were terminated early due to increased mortality among preterm infants, which indicates the complexity of establishing safe oxygen saturation ranges in this category of patients [5, 6, 7].

Because administering supplemental oxygen to preterm infants is a challenging clinical task, doctors must maintain a balance between the risk of insufficient oxygenation and the risk of oxygen toxicity. Failure to manage either of these risks may potentially result in damage to different organs and systems such as the eye, lungs and brain. Despite advances in neonatal intensive therapy, optimal target oxygen-saturation ranges for preterm infants are still under discussion. Given this, key factors in the development of RoP are the type of respiratory support [nasal continuous positive airway pressure (NCPAP) and/or

mechanical ventilation (MV)] and oxygenation parameters [transcutaneously measured oxygen saturation (SpO2) and oxygen partial pressure in the inspired gas mixture (FiO_2)].

The purpose of this study was to examine the effect size of the type of respiratory support and oxygenation indices on the development of different stages of RoP in the first month of life.

Material and Methods

This retrospective analysis included medical records of 290 preterm infants with a GA of 24 to 36 weeks and a BW of 670 to 2500 g who were followed up at the Odesa Regional Pediatric Clinical Hospital and Odesa Municipal Pediatric Clinical Hospital No. 2 between 2015 and 2018. The preterm infants were divided into four groups: group 1 of 117 infants with avascular retinal areas (without ROP); group 2 of 86 infants with autoregressive ROP (stage 1 ROP, stage 2 ROP or type 2 pre-threshold ROP); group 3 of 57 infants that required treatment for ROP (type 1 pre-threshold RoP); and group 4 of 30 infants with aggressive ROP. All these infants underwent ROP screening in accordance with international standards in due time. Infants with stage 4 ROP, stage 5 ROP or a fatal disease were excluded from the study.

Indirect ophthalmoscopy was conducted using a binocular ophthalmoscope, 30 D-lens, eyelid speculum and scleral depressor after topical anesthetic (oxybuprocaine hydrochloride 0.4%) was instilled. A combination of eye drops, 0.5% tropicamidum and 0.2% irifrin, was used to achieve mydriasis. Risk factors analyzed included GA, BW, types of respiratory support (NCPAP and/or MV) and oxygenation parameters (SpO_2 and FiO_2).

Statistical analyses were performed using SPSS Demo Version 26 (IBM Corporation, Armonk, NY). Quantitative data are presented as mean ± standard deviation (SD), whereas nominal data, as number and percentage. Kolmogorov-Smirnov test was used to test data for normality. The Leven's test was used to determine homogeneity of variance before parametric tests were performed. If all the data were distributed normally, a one-way analysis of variance (ANOVA) was used to compare the four independent groups for mean values. When appropriate, post-hoc pairwise between-group comparisons were also performed. Welch's test was used if the assumption of homogeneity of variance was violated. Chi square test was applied for the analysis of categorical data. For pairwise comparisons of proportions, Chi-square test was used. Kruskal-Wallis test was used if the data were not normal. Reported effect sizes followed partial eta-squared (η^2) criteria for ANOVAs (small = 0.01, medium = 0.06 and large = 0.14). Risk ratio (RR) and 95% confidence interval (CI) were calculated for FiO2 values in study groups.

Results

The effect of GA on the development of RoP stages was analyzed (Table 1). In group 1, GA was 4 weeks older than in group 4, and 3 weeks older than in group 3, and the difference was significant. Because Levene's test revealed that the assumption of homogeneity was met across groups ($p = 0.5$), ANOVA was used to compare the four independent groups for mean values. ANOVA confirmed statistically significant differences between groups ($F = 74.13$; $p < 0.0001$). This indicated a significant effect of the GA on the distribution of patients among the groups: the younger the GA, the greater was the likelihood of an infant having a severe RoP requiring preventive laser treatment.

All pairwise comparisons were statistically significant with the exception of the comparison between groups 3 and 4 ($p = 0.9$). That is, in the vast majority of cases with a severe RoP requiring preventive laser treatment (groups 3 and 4), GA ranged from 27.4 to 28.3 weeks (Table 1).

Post-hoc comparisons found significant differences between group 1 and other groups ($p = 0.00$ for 1–2, 1–3, and 1–4), groups 2 and 3 ($p = 0.01$) and groups 2 and 4 ($p = 0.05$), but not between groups 3 and 4 ($p = 0.9$). In groups 3 and 4, the mean BW was 1105 ± 259 g, which was 33 % less than in group 1 ($p < 0.001$) and 13 % less than in group 2 ($p < 0.001$).

This indicated that BW is a significant risk factor for ROP: the larger the BW, the smaller was the likelihood of an infant having a severe RoP requiring preventive laser treatment (Table 2).

FiO_2 was included in the analysis as a key postnatal factor associated with the respiratory support and oxygenation in preterm neonates (Table 3). Welch's test was used because the assumption of homogeneity of variance was violated (Levene's test $p=0.03$). It revealed significant differences among groups ($F=4.6$; $p=0.005$). Post-hoc comparisons found significant differences between group 1 and 3 ($p=0.0006$), 2 and 3 ($p=0.001$) and 2 and 4 ($p=0.048$). That is, FiO_2 was higher in the groups with a severe RoP requiring preventive laser treatment.

In order to assess the clinical significance of FiO_2, we additionally analyzed its distribution against a critical threshold of 0.30 (Table 4). This threshold was used as a cut-off for transforming a continuous variable into a categorical variable (< 0.30 and ≥ 0.30) for further frequency analysis. Chi-square test was used to assess between group comparisons. There were significant differences between groups 1 and 3 ($p=0.002$), 1 and 4 ($p=0.002$), 2 and 3 ($p=0.001$) and 2 and 4 ($p=0.004$), but not between groups 3 and 4 ($p=0.9$). Because there was no significant difference between groups 3 and 4, these two groups were combined for further analysis. In the combined group 3 and 4, a FiO_2 less than 0.30 was noted in 31 infants, and a FiO_2 greater or equal to 0.30, in 56 infants. In groups 1 and 2, the respective values were 140 and 63 infants. That is, in the groups with severe ROP, a FiO_2 greater or equal to 0.30 was 2.1 times more frequent ($\chi^2 = 26.6$ $p < 0.001$) compared to the group without ROP and the group with autoregressive ROP. The relative risk of more severe ROP for oxygen support with $FiO_2 \geq 0.30$ was estimated to be 2.08 times greater than for that with $FiO_2 < 0.30$ (RR=2.08; 95% CI: 1.61–2.68).

Table 1. Mean gestational age in the group without RoP and groups with different stages of RoP

Group	n	Gestational age (weeks) mean ± SD	P, significance of between group difference
Group 1, infants without RoP	117	31.75 ± 1.79	$P_{1-2} = 0.00$ $P_{1-3} = 0.00$ $P_{1-4} = 0.00$ $P_{2-3} = 0.00$ $P_{2-4} = 0.00$ $P_{3-4} = 0.9$
Group 2, infants with autoregressive RoP	86	29.70 ± 1.84	
Group 3, infants with RoP requiring treatment	57	27.91 ± 1.90	
Group 4, infants with aggressive RoP	30	27.67 ± 2.20	

Note: n, number of patients; RoP, retinopathy of prematurity; SD, standard deviation

Table 2. Mean birth weight in the group without RoP and groups with different stages of RoP

Group	n	Birth weight (g) mean ± SD	P, significance of between group difference
Group 1, infants without RoP	117	1654 ± 330	$P_{1-2} = 0.00$ $P_{1-3} = 0.00$ $P_{1-4} = 0.00$ $P_{2-3} = 0.01$ $P_{2-4} = 0.05$ $P_{3-4} = 0.9$
Group 2, infants with autoregressive RoP	86	1269 ± 317	
Group 3, infants with RoP requiring treatment	57	1107 ± 267	
Group 4, infants with aggressive RoP	30	1096 ± 246	

Note: n, number of patients; RoP, retinopathy of prematurity; SD, standard deviation

SpO_2 was included in the analysis as an integral characteristic of the efficacy of oxygenation during respiratory support in premature infants (Table 5). A between group comparison for this parameter was conducted because SpO_2 is used to survey current oxygen saturation targets in neonatology. Welch test did not found significant difference between study groups (F=0.7; p=0.5). Therefore, the SpO_2 was comparable among all study groups, suggesting that target oxygenation parameters were similar for the groups.

Frequency of MV was included in the analysis because MV is a key type of oxygen support in neonatal intensive care for infants born preterm immediately after birth (Table 6). Because prolonged or intensive support with MV may be accompanied by fluctuations of oxygenation and changes in systemic hemodynamics, groups were compared for the frequency of MV. The Kruskal-Wallis test was used for analysis of between group differences in the frequency of MV. We found the frequency of MV use had a significant effect on the distribution of patients among the groups ($H = 17.3$; $p = 0.006$). Pairwise comparisons showed significant differences between groups 1 and 3 ($p = 0.002$), 1 and 4 ($p = 0.008$), 2 and 3 ($p = 0.02$) and 2 and 4 ($p = 0.03$), indicating a significant increase in the frequency of MV use in groups with severe RoP requiring preventive treatment. In groups 3 and 4, the mean frequency of MV use was 97.7%, which was 20.8% higher than in group 1 ($\chi^2 = 16.6$, $p < 0.001$), and 15.1% higher than in group 2 ($\chi^2 = 9.5$, $p = 0.002$).

The frequency of NCPAP was included in the analysis because NCPAP is a common mode of non-invasive support in premature infants with respiratory disorders (Table 7). Since NCPAP is used to stabilize respiration and provide non-invasive oxygenation support, the assessment of the frequency of NCPAP in groups enables an indirect characterization of the approach to first-line/supportive respiratory therapy in various clinical categories. The Kruskal-Wallis test found no significant between group differences with respect to the frequency of MV ($H = 2.4$; $p = 0.48$). Therefore, the frequency of NCPAP was found to be comparable among all study groups, suggesting a unified approach to the administration of non-inva-

Table 3. Mean concentration of oxygen in the inspired gas mixture (*FiO_2*) in the group without RoP and groups with different stages of RoP

Group	n	FiO_2 mean ± SD	P, significance of between group difference
Group 1, infants without RoP	117	0.27± 0.12	P_{1-2} = 0.5 P_{1-3} = 0.0006 P_{1-4} = 0.1 P_{2-3} = 0.001 P_{2-4} = 0.048 P_{3-4} = 0.3
Group 2, infants with autoregressive RoP	86	0.27± 0.11	
Group 3, infants with RoP requiring treatment	57	0.35 ± 0.17	
Group 4, infants with aggressive RoP	30	0.32 ± 0.11	

Note: FiO_2, the oxygen partial pressure in the inspired gas mixture; n, number of patients; RoP, retinopathy of

Table 4. Numbers and proportions of patients with a mean concentration of oxygen in the inspired gas mixture (FiO_2) < 0.30 versus ≥ 0.30 in the group without RoP and groups with different stages of RoP

Group	FiO_2	FiO_2	P, significance of between group difference
	< 0.30	≥ 0.30	
Group 1, infants without RoP	78 (66.7%)	39 (43.3%)	P_{1-2} = 0.5; $\chi2$ = 0.4 P_{1-3} = 0.002; $\chi2$ = 13.9 P_{1-4} = 0.002; $\chi2$ = 9.7 P_{2-3} = 0.001; $\chi2$ = 16.7 P_{2-4} = 0.004; $\chi2$ = 12.6 P_{3-4} = 0.9
Group 2, infants with autoregressive RoP	62 (72.0%)	24 (28.0%)	
Group 3, infants with RoP requiring treatment	21 (36.8%)	36(63.2%)	
Group 4, infants with aggressive RoP	10 (33.3%)	20 (66.7%)	

Note: FiO_2, the oxygen partial pressure in the inspired gas mixture; n, number of patients; RoP, retinopathy of prematurity

sive respiratory support regardless of the group to which the patient belonged.

The effect size was measured by partial η^2 to complement the analysis of statistical significance and quantify the importance of differences identified. The use of partial η^2 allows us to determine the proportion of variance in the dependent variable (like the risk of developing severe RoP) that is explained by a specific independent variable. We found that the GA accounted for the largest proportion of variance in the risk of developing severe RoP requiring preventive treatment (partial $\eta^2 = 0.437$) followed by the BW (partial $\eta^2 = 0.36$). This indicates that it is these two characteristics that explain the greatest proportion of differences between groups and have the greatest association with the development of severe RoP. Parameters of oxygenation and types of oxygen support accounted for smaller effect sizes, with partial $\eta^2 = 0.05$ for the frequency of MV use and partial $\eta^2 = 0.046$ for FiO_2. The values obtained indicate that, although the frequency of MV use and FiO_2 accounted for a smaller proportion of variance in the risk of severe RoP than the GA and BW in the cohort examined, they may remain clinically significant in the multifactorial context.

Discussion

In this study, we deemed it appropriate and relevant to analyze possible risk factors for RoP based on the data from southern Ukraine. We have previously studied the effect of different risk factors on the development of RoP, and found that the four factors (the GA, BW, surfactant therapy, and cardiovascular disease) were closely associated with RoP, while other four factors (elevated intracranial pressure, blood transfusion, MV and hemodynamic abnormalities) were associated with severe RoP requiring treatment. Other risk factors for RoP include intraventricular hemorrhages, in vitro fertilization, history of medical abortion, maternal infections, premature rupture of membranes and pregnancy bleeding [8, 9, 10].

In the present study, we examined the effect of the type of respiratory support and oxygenation indices on the development of different stages of retinopathy of prematurity.

Table 5. Mean oxygen saturation as assessed by pulse oximetry (SpO_2) in the group without RoP and groups with different stages of RoP

Groups	n	SpO_2, mean ± SD
Group 1, infants without RoP	117	97.0 ± 1.9
Group 2, infants with autoregressive RoP	86	97.2 ± 2.4
Group 3, infants with RoP requiring treatment	57	97.2 ± 2.7
Group 4, infants with aggressive RoP	30	96.4 ± 2.4

Note: n, number of patients; RoP, retinopathy of prematurity; SpO_2, *t*ranscutaneously measured oxygen saturation

Table 6. Frequency of mechanical ventilation use in the group without RoP and groups with different stages of RoP

Group	n	Mechanical ventilation		P, significance of between group difference
		Yes	No	
Group 1, infants without RoP	117	90 (76.9%)	27 (23.1%)	P_{1-3} = 0.002; $\chi2$ = 9.2 P_{1-4} = 0.008; $\chi2$ = 7.0 P_{2-3} = 0.02; $\chi2$ = 5.1 P_{2-4} = 0.03; $\chi2$ = 4.6
Group 2, infants with autoregressive RoP	86	71 (82.6%)	15 (17.4%)	
Group 3, infants with RoP requiring treatment	57	55 (96.5%)	2 (3.5%)	
Group 4, infants with aggressive RoP	30	30 (100%)	0 (0%)	

Note: n, number of patients; RoP, retinopathy of prematurity

Oxygen has a significant effect on retinal vessels. The retinal vessels begin forming around 14-15 weeks of gestation, starting from the optic nerve and growing out to the periphery of the retina. Mesenchymal progenitor cells form capillaries from the first weeks to 21 weeks of gestation. Subsequently, vascularization occurs through angiogenesis, the development of new blood vessels from existing vasculature. Astrocytes respond to hypoxia by secreting VEGF, which plays a key role in retinal neovascularization in response to hypoxia. Hyperoxia inhibits VEGF synthesis, which results in cell proliferation through apoptosis [11, 12, 13, 14, 15, 16].

Randomized clinical trials have been conducted to examine the effect of oxygenation on preterm infants. The two largest-scale trials have proved to be quite telling, but have not fully answered the question of what is the target oxygen saturation range for the respiratory support of preterm infants.

In 2005–2009, the SUPPORT trial randomized 1316 infants of 24 0/7 weeks to 27 6/7 weeks GA to oxygen saturation target ranges of 85–89% or 91–95%. Among survivors to discharge, the lower target group had a reduced risk of severe ROP, however, the lower target group had an unexpected increase in mortality [6, 7].

The Benefits of Oxygen Saturation Targeting II (BOOST II) trial recruited 973 infants and 1123 infants born at less than 28 weeks' gestation in the United Kingdom and Australia, respectively, and was terminated early for similar mortality findings (the lower SpO2 group was associated with more deaths and cases of severe necrotizing enterocolitis). The rate of death was significantly higher in the lower target group (85-89%) than in the higher target group (91-95%) for oxygen saturation. The trial reported higher risk of necrotizing enterocolitis for infants kept at lower oxygen saturation, and the risk of RoP was reduced while on lower oxygen [5].

Chow and colleagues found a reduction in incidence of stages 3 and 4 RoP with an implementation of a strict oxygen management policy with saturation limits of 85% to 93% for infants younger than 32 weeks gestation [17, 18].

The Neonatal Oxygenation Prospective Meta-analysis (NeOProM) collaboration consisted of an international

Table 7. Frequency of NCPAP use in the group without RoP and groups with different stages of RoP

Group	n	NCPAP	
		Yes	No
Group 1, infants without RoP	117	114 (97.4%)	3 (2.6%)
Group 2, infants with autoregressive RoP	86	85 (98.8 %)	1 (1.2%)
Group 3, infants with RoP requiring treatment	57	57 (100%)	0 (0%)
Group 4, infants with aggressive RoP	30	30 (100%)	0 (0%)

Table 8. Effect sizes for risk factors examined in the group without RoP and groups with different stages of RoP

Group	Factor	Partial η^2	Percent of variance explained by factors
Group 1, infants without RoP	GA (weeks)	0.437 (a large effect on RoP)	44%
Group 2, infants with autoregressive RoP	BW (g)	0.36 (a large effect on RoP)	36%
Group 3, infants with RoP requiring treatment	MV	0.05 (a small effect on RoP)	5%
Group 4, infants with aggressive RoP	FiO_2	0.046 (a small effect on RoP)	4.6%

Note: Note: BW, birth weight; FiO_2, the oxygen fraction of inhaled gas; GA, gestational age; MV, mechanical ventilation; n, number of patients; RoP, retinopathy of prematurity

group of neonatologists aimed at determining the optimal SpO_2 level in premature infants. Study authors sought to compare SpO_2 targets of 85% to 89% in infants born at less than 28 weeks' gestation with the primary outcome of death or major disability at 18 to 24 months of age. Analysis of the data revealed that insufficient oxygen levels increase the risk of death, and maintaining a SpO2 target of 90% to 94% is recommended [19, 20].

In the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) study, 649 premature infants were enrolled at 30 centers over 5 years. 325 infants received conventional oxygen supplementation (89% to 94% O_2 saturation by pulse oximetry) and 324 received “high” supplemental oxygen (96% to 99% O_2 saturation by pulse oximetry). The use of supplemental oxygen did not cause additional progression of moderate-to-severe ROP but also did not significantly reduce the number of infants requiring peripheral retinal ablative surgery. A post hoc subgroup analysis of plus disease (dilated and tortuous vessels in at least 2 quadrants of the posterior pole) suggested that infants without plus disease may be more responsive to supplemental therapy than infants with plus disease [21].

Given the above, the first important step to be taken while managing extremely preterm infants, especially those with a low or extremely low BW, is providing adequate respiratory support and oxygenation. Of note that mean GAs of infants from highly developed countries ranged from 25.3 to 25.6 weeks compared with 26.3 to 33.5 weeks in less developed countries [3, 4].

In the current study, in each group, the mean SpO_2 was 96-97%. Therefore, based on the data obtained, the mean SpO_2 was comparable among study groups, suggesting that target oxygenation parameters were similar for the groups. This is the reason for the absence of significant difference in the effect of SpO_2 on the development of different stages of RoP.

FiO_2 is an important index of the severity of the respiratory status of a preterm infant and has a direct effect on the overall condition of the infant. The selection of FiO_2 threshold has a key value because it determines a balance between the benefit of early oxygen therapy onset and the risk of excessive oxygen exposure. Higher FiO_2 values are associated with more severe respiratory failure which may require invasive ventilation, but if optimized, FiO_2 will contribute to stabilizing the respiratory function and

reducing the rate of complications. Therefore, FiO_2 represents not only a respiratory support parameter, but also an important prognostic marker of the overall condition of a preterm infant. Compared with a higher FiO_2 threshold (0.30), a lower FiO_2 threshold (0.25) enables earlier oxygen support, but increases the risk of excessive oxygen therapy. A higher FiO_2 threshold, however, corresponds to a more conservative strategy with a potential delay in treatment, but may be accompanied by longer hypoxia and deterioration in the overall condition of the patient [22].

Pathologic retinal angiogenesis and ROP create the conditions for a change in the partial pressure of oxygen and carbon dioxide in blood. During prolonged oxygen therapy, a FiO_2 level higher than 0.30 causes vasoconstriction, vasoobliteration and destruction of the capillaries of an immature retina, not infrequently leading to RoP. Avoiding diurnal FiO_2 fluctuations and minimizing titration of FiO_2 is critically important [17]. A 2023 study by Lin and colleagues [23] concluded that the development of severe RoP might not only be influenced by oxygen exposure but also by its fluctuation.

We found FiO_2 (along with GA and BW) to be a key postnatal factor associated with severe RoP (Table 3). Additionally, the relative risk of more severe ROP for oxygen support with $FiO_2 \geq 0.30$ was estimated to be 2.08 times greater than for that with FiO2 < 0.30 (RR = 2.08; 95% CI: 1.61–2.68).

We also examined the effect of the type of oxygen support on the development of RoP. Current practice guidelines recommend administration of surfactant at or soon after birth in preterm infants with respiratory distress syndrome (RDS) [24]. According to the 2019 European Consensus Guidelines on the Management of Respiratory Distress Syndrome [16], CPAP or (s) nasal intermittent positive pressure ventilation (NIPPV) should be started from birth in all babies at risk of RDS, such as those <30 weeks of gestation who do not need intubation for stabilization. A 2020 study [25], however, concluded that, compared with NCPAP, HFNC shortened oxygen consumption time and was effective in preventing extubation failure in mechanically ventilated preterm extremely low-birthweight infants (ELBWI). Using CPAP as a remedy for the treatment failure of HFNC could not avoid intubation. For premature infants with the gestational age <28 weeks, HFNC as primary respiratory support still needs to be further elucidated [26].

The current study also found that MV as a type of respiratory support is a significant factor that has an effect on the development of different stages of RoP. This is likely associated with the fact that younger infants have more severe respiratory disorders requiring MV.

We can conclude that the findings of this study indicate that the risk factors specified (i.e., GA, BW, the frequency of MV use and $FiO_2 > 0.30$) within the framework of this model explain the effect on severe RoP requiring preventive treatment.

Therefore, it was found that younger GA is associated with an increased risk of severe RoP. In the study sample, severe ROP was more frequently seen in neonates with a GA of 27.4–28.3 weeks. There was a significant difference in GA among the four groups (ANOVA: F= 74.13; $p < 0.0001$), with a significant pairwise difference between most group pairs, but not between groups 3 and 4 ($p = 0.9$). A smaller BW was associated with an increased risk of severe RoP, requiring preventive treatment. There was a significant difference in the BW among the four groups (F= 54.1; $p < 0.0001$). In groups with severe RoP, the mean BW was 33 % less than in the group without RoP ($p < 0.001$) and 13 % less than in the group with autoregressive RoP ($p < 0.001$). With an increase in the FiO_2, there was an increase in the effect on the development of severe RoP, requiring preventive treatment. There was a significant difference in the FiO_2 among the four groups (Welch ANOVA: $F = 4.6$; $p = 0.005$). In the groups with severe ROP, a FiO_2 greater or equal to 0.30 was 2.1 times more frequent compared to the group without ROP and the group with autoregressive ROP ($p < 0.05$). MV was found to have an effect of the development of severe RoP, requiring preventive treatment. The frequency of MV use increased from group 1 to group 4, with a significant difference among groups (Kruskal-Wallis test: $H = 17.3$; $p = 0.006$). In groups with severe RoP, the mean frequency of MV use was 20.8% higher than in the group without RoP ($\chi^2 = 16.6$, $p < 0.001$), and 15.1% higher than in the group with autoregressive RoP ($\chi^2 = 9.5$, $p = 0.002$). No significant difference among groups was found for the frequency of use of NCPAP ($H = 2.4$; $p = 0.48$). SpO_2 was similar among groups ($F = 0.7$; $p = 0.5$). The size of the effect on development of severe RoP as measured by partial η^2 was the largest for GA (0.437), followed by BW (0.36), MV (0.05) and FiO_2 (0.046).

Author Contributions

BOS, concept development, design; data collection and research; data analysis and interpretation; manuscript writing, editing and review; KSV, concept development, design; data analysis and interpretation; manuscript writing, editing and review; TNV, manuscript writing, editing and review; ZKS, data collection and research; manuscript writing, editing and review. All authors read and approved the final version of the manuscript.

Disclaimers

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Ethical Declaration

This study involved human subjects, was approved by the local bioethics committee, and followed ethical standards as outlined in the Declaration of Helsinki. Informed consent was not obtained due to the retrospective nature of the study. This study did not include animal experiments..

Conflict of Interest

The authors state that they have no conflict of interest that could influence their view on the subject matter or materials described and discussed in this manuscript.

Data Availability Declaration

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations

ARP, aggressive retinopathy of prematurity; BW, body weight; FiO2, oxygen partial pressure in the inspired gas mixture; GA, gestational age; HFNC therapy, high-flow nasal cannula therapy; MV, mechanical ventilation; NCPAP technique, nasal continuous positive airway pressure technique; ROP, retinopathy of prematurity; SpO2, transcutaneously measured oxygen saturation.

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