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Study Of Oxygen Toxicity Induced Retinopathy In Premature Infants

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Abstract
Background*: Oxygen is essential for sustaining aerobic life, facilitating cellular respiration and energy production. In neonatal care, oxygen supplementation is often necessary to address respiratory distress syndrome or hypoxemia, which can be life-threatening if not promptly treated. But excessive oxygen exposure can lead to complications like retinopathy of prematurity or lung damage due to oxidative stress. Monitoring oxygen levels and adjusting supplementation accordingly are crucial to minimize the potential for harm while ensuring adequate oxygenation for vital functions.*
Aims & Objectives: *To determine the relationship between Oxygen therapy and ROP.*
Materials and methods*: This retrospective study was conducted on 123 preterm infants (≤36 weeks gestational age and ≤2.5kg gm birth weight) screened for ROP from December 2022 to May 2024, in the department of Ophthalmology and Paediatrics.*
Results*: The incidence of ROP in any stage was 27.6% (34). Mean Gestational age among ROP positive neonates was 31.76 weeks. Most of the infants had stage 2 (7) followed by stage 1(9), stage 3 and AP ROP in 4 each. Mean oxygen supply was 3.66 +1.79 lts and mean duration was 14.18 + 12.29 days. There is significant correlation ROP with the duration of oxygen supply.*
Conclusion*: Incidence of ROP is more due to lack of awareness among parents for retinopathy of prematurity and its risk factors. Most of the infants who developed ROP were exposed to oxygen at an early age and duration. Strategies to keep oxygen saturation (SpO2) within targets, for those on supplemental oxygen might help in decreasing the incidence.*
Key words*: Preterm, Retinopathy of prematurity, Oxygen, Neovascularization.*

INTRODUCTION:
Premature infants are at high risk of developing retinopathy of prematurity (ROP), a sight-threatening disease arising from aberrant retinal vascular development. Under normal conditions, retinal angiogenesis begins around 16 weeks of gestation and completes near term (40 weeks), particularly in the peripheral retina. However, premature birth disrupts this timeline, leaving portions of the retina avascular. [1]
Shortly after birth, preterm neonates transition from a hypoxic intrauterine environment to higher ambient oxygen levels. Supplemental oxygen, while lifesaving, often results in hyperoxia, leading to suppression of hypoxia-inducible factors (e.g., HIF-1α), VEGF, and IGF-1, causing vaso-obliteration in phase I of ROP. [2]
Subsequent reduction of oxygen support reveals the avascular retina to hypoxia, triggering uncontrolled pathological neovascularization in phase II, characterized by fragile vessels that can hemorrhage, form fibrous tissue, and detach the retina. [3]
A critical mechanism underpinning oxygen toxicity involves overproduction of reactive oxygen and nitrogen species (ROS/RNS) in the immature retina, which lacks adequate antioxidant defenses. These free radicals induce lipid peroxidation, microvascular injury, and further dysregulation of angiogenic signaling pathways. [4]
Moreover, fluctuations in arterial oxygen saturation appear to exacerbate oxidative damage compared to constant high levels* and are linked with increased ROP severity. [5]
Modern neonatal intensive care units mitigate these risks by targeting narrow oxygen saturation ranges (typically 85–95 % SpO_2) and closely monitoring PaO_2 to avoid both hyperoxia and hypoxia. While this strategy has reduced—but not eliminated—the incidence of ROP, emerging evidence suggests that optimizing antioxidant support, stabilizing oxygen exposure patterns, and modulating growth factors like IGF-1 may further improve outcomes. [6]
Aims & Objectives: To determine the relationship between Oxygen therapy and ROP.

Materials and methods: This retrospective study was conducted on 123 preterm infants (≤36 weeks gestational age and ≤2.5kg gm birth weight) screened for ROP from December 2022 to May 2024, in the department of Ophthalmology and Paediatrics. Patients with Gestational age < 34 weeks and if > 34 weeks suggested by pediatrician, Preterm having birth weight < 2500g, ROP of any stage in either eye and ROP detected at 1st / 2nd examination were included. After obtaining approval from the Institutional Ethics Committee the medical records of retinopathy of prematurity babies and neonatal intensive care unit babies screened from April 2021 to June 2023 was reviewed and analysed. Data were collected including amount and duration of oxygen supply, birth weight, gestational age, gender, details of ROP screening.

Results:

Clinical characteristics		Number	Percentage
Gender	Male	62	50.4
	Female	61	49.6
Birth weight (gm)	< 1250	23	19
	1251–1500	29	23.9
	1501–1750	35	28.9
	> 1750	34	28

Table 1. Clinical Characteristics of study participants

A total of 123 premature infants were enrolled. The cohort showed an almost equal gender distribution, with males accounting for 50.4% (n = 62) and females for 49.6% (n = 61). Birth weight distribution demonstrated that the majority of infants (56.9%) weighed more than 1500 g at birth, while 19.0% (n = 23) had very low birth weight (<1250 g). Infants weighing 1251–1500 g constituted 23.9% (n = 29) of the study population. [Table 1]

	ROP		No ROP		P value
Gestational age	Mean	SD	Mean	SD	**0.001**
	30.9	2.177	32.76	1.902	

Table 2. Comparison between Gestational age and ROP

The mean gestational age of infants who developed ROP was significantly lower (30.9 ± 2.18 weeks) compared to those who did not develop ROP (32.76 ± 1.90 weeks). This difference was statistically significant (p = 0.001), indicating that lower gestational age was strongly associated with the development of ROP. [Table 2]

Parameters		Retinopathy of prematurity		Total	P Value
		No	Yes		
Birth weight	< 1250	13	10	23	0.022
	1251–1500	19	10	29	
	1501–1750	25	10	35	
	> 1750	31	3	34	
Oxygen supply	< 4 litres	65	12	77	0.000
	> 4 litres	23	21	44	
Duration of O2 supply	< 10 days	65	12	77	0.000
	> 10 days	23	21	44	
Oxygen saturation	<91	2	1	3	0.048
	91-95	61	21	82	
	>95	25	11	36	

Table 3. Association between ROP and other parameters

Birth weight showed a significant association with the development of retinopathy of prematurity (ROP) (p = 0.022), with a higher proportion of ROP observed among infants with lower birth weights. Infants weighing less

than 1250 g had the highest proportion of ROP (10/23), whereas those weighing more than 1750 g had the lowest incidence (3/34).

Oxygen exposure was significantly associated with ROP. Infants receiving oxygen at flow rates greater than 4 litres had a significantly higher incidence of ROP (21/44) compared to those receiving less than 4 litres (12/77) ($p < 0.001$). Similarly, prolonged duration of oxygen therapy (>10 days) was strongly associated with ROP development, with 21 of 44 infants affected, compared to 12 of 77 infants who received oxygen for less than 10 days ($p < 0.001$).

Oxygen saturation levels were also significantly related to ROP occurrence ($p = 0.048$). A greater proportion of ROP was observed in infants maintained at higher oxygen saturation ranges, particularly between 91–95%, compared to those with lower saturation levels.

DISCUSSION:

The clinical characteristics of cohort of premature infants are generally consistent with distributions observed in other large ROP studies. Our cohort demonstrated a nearly equal gender distribution (50.4% male and 49.6% female), which aligns with population-based reports where sex is not a strong independent predictor of ROP incidence in most screened cohorts. For example, a large retrospective cohort from Palestine observed a nearly balanced male (49.6%) and female (50.4%) distribution with no significant gender effect on ROP risk ($p = 0.98$), indicating that sex alone does not substantially alter ROP occurrence in similarly broad premature populations.[7] However, systematic analyses have suggested that male sex may confer slightly increased susceptibility for severe, treatment-warranted ROP, potentially due to sex-specific differences in vulnerability to prematurity complications.[8] In terms of birth weight, 19.0% of infants in our cohort were <1250 g, while the remainder spanned higher weight categories up to >1750 g. This distribution reflects the broad inclusion criteria often used in modern ROP screening programs and is comparable to other tertiary-centre studies where a substantial proportion of screened infants weigh ≤1500 g at birth, the group at highest documented risk for ROP.

Consistent with the established literature, lower birth weight is a key determinant of ROP risk: numerous studies have demonstrated that infants with birth weights <1250 g or extremely low birth weights have significantly higher rates of ROP compared with heavier infants, reinforcing the role of low birth weight as a major risk factor in retinopathy pathogenesis.[9]

The findings align with well-established risk profiles for retinopathy of prematurity (ROP) reported in the literature. Consistent with previous studies, lower birth weight was significantly associated with increased ROP incidence in our cohort ($p = 0.022$), supporting evidence that very low birth weight remains a strong predictor of ROP development. Low birth weight and gestational age are the most consistently identified risk factors for ROP due to the immaturity of retinal vascularization in these infants.[10]

Also observed a significant relationship between supplemental oxygen exposure and ROP, with both higher flow rates (>4 L) and prolonged oxygen duration (>10 days) associated with greater ROP occurrence ($p < 0.001$). Previous research has similarly shown that duration of oxygen therapy and greater fraction of inspired oxygen are important contributors to ROP risk, likely due to hyperoxic injury to the developing retinal vasculature thus advocating for judicious oxygen use in NICUs.[11,12]

Oxygen saturation levels were also significantly related to ROP ($p = 0.048$), echoing findings that both hyperoxia and fluctuations in oxygen saturation influence ROP progression. The infants maintained at oxygen saturations >95% had significantly higher ROP incidence. Sanghi et al. reported similar trends, advocating for narrow target SpO2 ranges (90–95%) to mitigate ROP development. [13] Meta-analytic evidence supports an association between high or low oxygen saturation targets and severe ROP, suggesting that oxygen management plays a critical and complex role in disease pathogenesis.[14]

Overall, the results confirm that immaturity (low birth weight and gestational age) and aspects of oxygen therapy (flow, duration, and saturation targets) are key determinants of ROP, comparable to patterns observed in large clinical studies and reviews of risk factors for ROP.[15] Early screening, awareness among caregivers, and NICU-level monitoring protocols are essential in lowering the incidence of this preventable blindness.

CONCLUSION:

Incidence of ROP is more due to lack of awareness among parents for retinopathy of prematurity and its risk factors. Most of the infants who developed ROP were exposed to oxygen at an early age and duration. Strategies to keep oxygen saturation (SpO2) within targets, for those on supplemental oxygen might help in decreasing the incidence.

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