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SINGLE ARTERIAL OXYGEN TENSION ELEVATION INCREASES THE RISK OF STAGE OF ACUTE DISEASE RETINOPATHY OF PREMATURITY

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Abstract

Introduction: Numerous studies have shown inconclusive results regarding ideal parameter for oxygen supplementation to balance the risk of mortality and retinopathy of prematurity (ROP) development. The purpose of this study is to compare mean partial oxygen tension (PO_2) level in ROP.

Methods: This retrospective study was performed on premature infants (PI) undergoing ROP screening at our neonatal intensive care unit during 2021. All infants born at our hospital at ≤ 30 weeks, birth weight (BW) ≤ 1500 grams, or high-risk infants with prolonged ventilation were included. ROP screening was performed at chronological age four to six weeks, were followed and managed according to the severity. ROP severity was categorized by International Classification of ROP 3rd edition (ICROP3). We reviewed the characteristics of each group and compared mean PO_2 values in day 1, day 5, and day 10 between incomplete vascularization (IV) group, stage of acute disease (SAD) group, and Aggressive ROP (A-ROP) group.

Result: We investigated 124 eyes from 62 eligible PI. The incidence of IV, stage 1, stage 2, stage 3, and A-ROP were 58.9%, 2.4%, 7.3%, 23.4%, and 8.1%, respectively. Mean PO_2 value in day 5 was higher in SAD group compared to IV group (p=0.002). For each value increase in PO_2, there was 1.042 times higher odds of developing SAD (p=0.004). Multivariable logistic regression analysis showed consistent results, simultaneously, each week increase in GA was associated with lower risk of SAD development (p=0.018) and each level increase in PO_2 was associated with higher risk for SAD development (p=0.005).

Conclusion: A single elevation in PO2 during early life of PI increases the risk of developing stage of acute disease ROP, particularly in younger infants. Careful monitoring for PO_2 is mandatory to prevent development of ROP.

Keywords: Retinopathy of prematurity, Neonatal care, Partial oxygen tension

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INTRODUCTION

Retinopathy of Prematurity (ROP) has been the lead cause of visual impairment and blindness in premature infants.[1, 2] In Indonesia, ROP developed in 18-30% premature infants born before 32 weeks of gestational age.[3] This number is similar to ROP incidence in USA in 2018, which was 32 % for all ROP and 4.6 - 6 % for severe ROP.[4, 5] Blindness from ROP is a result of abnormal retinal vascular growth with the ability to progress to fibrovascular contraction and detachment.[6] ROP blindness can be prevented by doing ROP screening and managing ROP accordingly in timely manner.

Supplemental oxygen is a standard of care for neonatal resuscitation and respiratory problems in the neonatal intensive care unit (NICU). Low oxygen exposure may increase risk of mortality, cerebral palsy, intraventricular hemorrhage (IVH), necrotizing enterocolitis, patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), pulmonary vascular resistance, and apnea.[7-9] On the contrary, high oxygen exposure also put them at risk of developing ROP, disrupt normal intestine physiological function, induce neuronal apoptosis and inflammation, and chronic lung disease.[8, 10]

ROP is believed to develop through two phases. The first phase is hyperoxia-induced vaso-obliteration and delayed physiologic retinal growth, then followed by second phase of hypoxia induced vaso-proliferation.[11, 12] The first phase starts since birth and terminates when oxygen supplementation ends. Premature infants are exposed to higher oxygen tension than in utero, which then suppress the angiogenic factors release[7]. Addition of oxygen supplementation results in more profound suppression, thus creates a vaso-obliteration.[13] The second phase initiates after supplemental oxygen cessation. At this point, the premature infants have become mature, and their retina are metabolically active but hypoxic. Subsequently, angiogenic factors such as VEGF, and IGF-1, are upregulated and promote irregular retinal growth inside and outside the retinal plane to form intravitreal neovascularization.[11, 13-15]

Blood gas analysis (BGA) is routine blood work done for preterm infants in the NICU. However, neither normal range nor safe values for preterm infants are yet established. BGA yields partial pressure of oxygen (PO_2) which can be a useful tool to determine oxygen tension in blood. Hauspurg et al reported that infants exposed with high PO_2 were at increased risk of developing severe ROP[16] On the contrary, York et al found that PO_2 value was inversely related to ROP stage. Furthermore, this study emphasized that it was the PO_2 fluctuation which was responsible for developing threshold ROP.[17]

Numerous studies have been done to investigate ideal parameter for oxygen supplementation to balance the risk of mortality and ROP development with an inconclusive result. Previous studies have shown contradictory results regarding PO_2 value in ROP. The purpose of this study is to compare PO_2 mean in each stage of ROP to aid our understanding about ROP and to improve clinical management for ROP.

METHODS

This retrospective study included all premature infants born at Cipto Mangunkusumo Tertiary Hospital and underwent ROP screening during admission to NICU between January 2021 to December 2021. All premature infants who were born at 30 weeks or earlier, weighed 1500 gram or less, or older infants with high risk profile such as receiving oxygen supplementation for long period, severe and unstable respiratory disease, or hypotension requiring inotropes, were referred for

ROP screening. ROP screening was carried out at chronological age four to six weeks in most cases and was followed by subsequent examinations according to the severity of the disease until complete vascularization of the retinas was achieved. When the neonatologist considered the infant was unfit for ROP screening, some allowance was made, and the examination was deferred by a week. ROP screening was performed on fully dilated eyes with an indirect ophthalmoscope and was documented with RetCam. The stages of ROP were recorded according to International Classification of ROP 3rd edition (ICROP3) with the highest active stage of ROP during screening was used for analysis. Infants with no ROP lesion was included in incomplete vascularization (IV) group. Stage of acute disease is defined by the appearance of a structure at the vascular-avascular juncture as stage 1 (demarcation line), stage 2 (ridge), and stage 3 (extraretinal neovascular proliferation or flat neovascularization).[18] Infants with such retinal lesion were grouped accordingly. Aggressive ROP (A-ROP) is rapid development of pathologic neovascularization and severe plus disease without progression being observed through the typical stages of ROP.

We excluded data from incomplete medical records including nonrecorded PO_2 values from blood gas analysis at each time frame sampling. During 2021, ROP screening was scheduled in 250 premature infants at NICU. Twenty-nine infants were excluded due to being born outside our hospital, 159 infants were excluded due to incomplete data. One-hundred-twenty-four eyes from 62 infants were included in the analysis. The study was conducted with institutional ethical board approval.

Demographic factors and other associated clinical variables including birth weight (BW), gestational age (GA), gender, BPD defined as requirement of oxygen supplementation for more than 28 days, duration of oxygen supplementation, IVH, sepsis proven with blood culture, symptomatic PDA and other congenital heart anomaly, APGAR score, single or multiple pregnancy, packed red cell transfusion were assessed. Results of all capillary blood gases (CBG) obtained during period of care in NICU were extracted from the medical records. We recorded CBG result on three specific periods, first 24 hour (d1), fifth day of life (d5), and tenth day of life (d10) or within 24-hour range if samples were not taken on those days. All samples were taken with capillary approach. Aseptic procedures were done in the infant's heel. The heel was then punctured, and blood gas samples were collected by a capillary tub. The samples then were analyzed immediately with a blood gas analyzer, pHOx plus C from Nova Biomedical, located in the NICU.

For the descriptive analysis, the infants were divided into five categories according to ICROP3 (incomplete vascularization, stage 1, stage 2, stage 3, and A-ROP)[18] to analyze demographic and clinical characteristic variables. Data are presented in mean and number. The chi-square test conducted comparisons of mean values of the categorical variables. To assess the Partial Oxygen (PO_2) mean in each group, infants were categorized into three groups according to ICROP3: IV, SAD, and A-ROP. Mean PO_2 differences in each group were tested using one-way analysis of variance. We also calculated PO_2 mean in three-day samples in each infant as well as coefficient of variation (CoV) to assess the fluctuation of PO_2. Logistic regression was used to find independent risk factors of ROP. All the risk factors with p value less than 0.025 found in univariate logistic regression analysis were included for further multivariate analysis. Data analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS) Version 26.0 (SPSS Inc., Chicago, IL, USA).

Table 1. Clinical Characteristic of the study population.

	IV Group	*Stage 1 Group*	*Stage 2 Group*	*Stage 3 Group*	*A-ROP Group*	*P Value*
Male (%)	43.8	33	33	51.7	20	0.693[a)]
GA (Week)	30.53	29.00	28.44	29.52	30.20	0.037[b)]
BW (Gram)	1376.66	1196.67	1282.22	1168.97	1234.20	0.178[b)]
Sepsis (%)	89.04	100	66.67	68.9	60	0.034[a)]
PRC Transfusion (%)	94.5	100	100	93.1	100	0.835[a)]
Singleton (%)	82.1	0	88.8	96.5	60	0.000[a)]
VD (%)	30.1	0	11	24.1	20	0.559[a)]
IVH (%)	30.1	66,67	44.44	55.17	40	0.291[a)]
PDA	21.9	0	22.2	27.51	40	0.522 [a)]
All CHD	24.6	0	22.2	34.48	40	0.255 [a)]
BPD (%)	33.33	100	33.33	10.34	40	0.015 [a)]

GA (gestational age), BW (birth weight), PRC (packed Red Cell), VD (Vaginal Delivery), IVH (intraventricular hemorrhage), PDA (Patent Ductus Arteriosus), CHD (Congenital Heart Disease), BPD (Bronchopulmonary Dysplasia), IV (incomplete vascularization), A-ROP (Aggressive Retinopathy of Prematurity).

a) Intergroup differences were analyzed using the chi-square test
b) Intergroup differences were assessed using one-way analysis of variance. Boldface indicates a statistically significant difference with P<0.05.

RESULT

We investigated 124 eyes from 62 infants and included their highest ROP staging during serial of ROP screenings for the analysis. There were 58.9% premature infants in IV group, 2.4% in stage 1 group, 7.3% in stage 2 group, 23.4% in stage 3 group, and the rest 8.1% in A-ROP group. Stage 4 and stage 5 ROP were not found during screening. These infants had a mean BW of 1, 305.32 ± 398.65 gr and a mean of GA of 30.02 ± 2.2 weeks. Table 1 summarizes clinical variables according to the degree of ROP severity.

There was a trend of younger GA in stage 1,2, and 3 compared to IV group. However, we further analyzed this difference using T-test for each group and found that the statistically different GA were between IV group and stage 2 group as well as IV group and stage 3 group. Mean GA in stage 2 group was 2.09 weeks younger than IV group (P = 0,010). Mean GA in stage 3 group was 1.017 weeks younger than IV group (P = 0,052).

There was a significant association between sepsis and ROP stage 3 (X^2 = 6.023, P = 0.014). The odds of having a stage 3 ROP are 3.656 times higher in premature infants with sepsis (CI = 1.246 to 10.726). We also found a significant association between sepsis and A-ROP (X^2 = 5.998, P = 0.014). The odds of experiencing A-ROP were 5.417 times for premature infants with sepsis (CI = 1.254 to 23.390).

BPD status was also another significant variable for ROP development in this study. Upon further analysis, we investigated that BPD was strongly associated with ROP stage 3 only (X^2 = 5.578, P = 0.018). The odd ratio for developing ROP stage 3 was 4.333 times higher in premature infants with BPD (CI=1.191-15.768).

There was a significant difference between the singleton and multiple pregnancy in this study. Further analysis was done and found the statistically significant variable was for IV group and stage 1 group. Singleton pregnancy was at increased risk for developing stage 1 ROP, however this finding was insignificant (CI = 0.973-1.557), suggesting that singleton pregnancy was a weak factor contributing for stage 1 development.

We investigated the mean of partial oxygen pressure in day 1, 5 and 10, the mean partial oxygen pressure in each infant and the CoV as well. There was a tendency of higher PO_2 value in infants from SAD group and A-ROP group, however this finding is not statistically significant. We conducted T-test analysis to compare the mean PO_2 between IV group and SAD group and found a significant difference in the mean PO_2 in day 5 in which SAD group had a 15.17 mmHg higher than IV group (P = 0.001). There were no statistically significant differences between IV group and A-ROP group and SAD group and A-ROP group regarding mean PO_2.

PO_2 spiked on day 5 in SAD group. A paired T-test analysis was conducted on preterm infants in SAD group to determine if there was any difference in mean PO_2 level at each day sampling. Results showed that the mean was statistically significantly different between the PO_2^{D1} and PO_2^{D5} (P = 0.002) as well as PO_2^{D5} and PO_2^{D10} (P = 0.031).

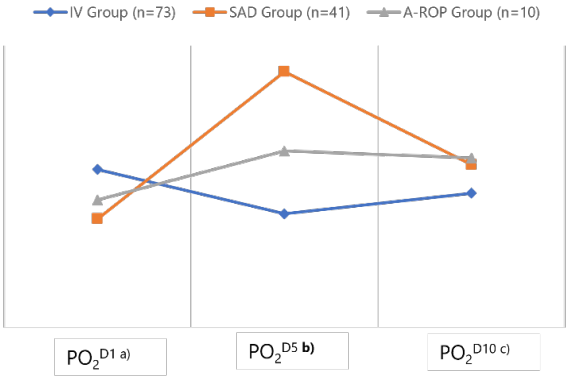

Figure 1. Mean partial arterial oxygen pressure and ROP development.

PO_2 (Partial Oxygen Tension), D1 (day 1), D5 (day 5), D10 (day 10), IV (incomplete vascularization), SAD (Stage of Acute Disease), A-ROP (Aggressive Retinopathy of Prematurity). Intergroup differences were assessed using one-way analysis of variance. [a)] p=0,286, [b)] p=0,002, [c)] p=0,541.

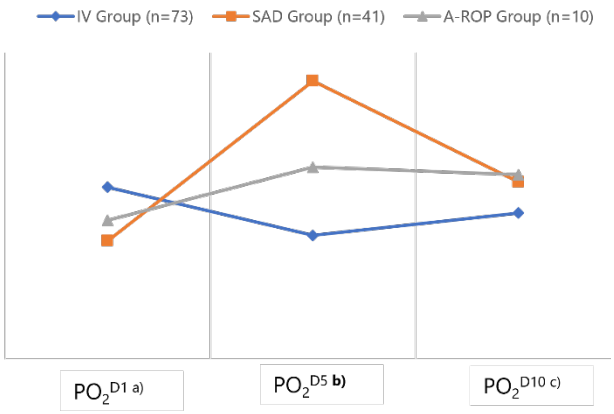

Figure 2. Mean partial arterial oxygen pressure and Plus disease development.

PO_2 (Partial Arterial Oxygen), D1 (day 1), D5 (day 5), D10 (day 10). Intergroup differences were assessed using independent T-test. [a)] p=0,157 [b)] p=0,946, [c)] p=0,965.

Table 2. Mean Partial Oxygen Pressure relatives to ROP and Plus disease development.

	IV Group (n=73)	SAD Group (n=41)	A-ROP Group (n=10)	P value	Plus Disease (n=13)	No Plus Disease (n=111)	P value
Mean PO_2 (mmHg)	44.95	46.21	51.88	0.250[a)]	47.62	45.73	0.694[b)]
CoV (%)	24.87	28.15	24.98	0.475[a)]	25.65	26.01	0.933[b)]

PO_2 (Partial oxygen tension), IV (incomplete vascularization), SAD (Stage of Acute Disease), A-ROP (Aggressive Retinopathy of Prematurity).
[a)] Intergroup differences were assessed using one-way analysis of variance. [b)] Intergroup differences were assessed using independent T-test.

Table 2 displays the mean PO_2 and CoV for premature infants in each stage of ROP as well as with and without plus disease. There was no difference found between each group.

Logistic regression was performed to determine statistically significant variables which affect SAD development. Five statistically significant variables were GA, PO_2^{D5}, BW, sepsis, and duration of oxygen supplementation. Each additional week increase in GA was associated with a 23% reduction of SAD development (*P* = 0.007, CI = 0.638-0.930). For each mmHg increase in PO_2^{D5} , there was 1.041 odd risk for premature infant to develop SAD (*P* = 0.004, CI = 1.013-1.069). Each additional 100-gram increase in BW was associated with 1% reduction of SAD development (*P* = 0,029, CI 0.998-1.000). The odd risk for SAD development was 1.032 in each additional day increase in duration of oxygen supplementation (*P* = 0,035, 95% CI = 1.002-1.063). The odds of premature infants without sepsis to develop SAD was 3.362 of the odds of premature infants with sepsis (*P* = 0.014, CI = 1,242-9.102). However, this result became non-statistically significant on multivariable analysis.

Table 3 shows multivariate logistic regression for SAD development. Variables with p value less than 0,025 were included in multivariate analysis. Simultaneously, each week increase in GA was associated with lower risk of SAD development and each unit increase in PO_2^{D5} was associated with higher risk for SAD development.

Table 3. Risk factors for SAD development.

Variables	SAD development		
	OR	95 % CI	P value
Sepsis	1.433	0.443-4.635	0.548
GA	0.787	0.646-0.959	0.018
PO_2^{D5}	1.042	1.013-1.072	0.005

D5 (day 5), GA (gestational age), PO_2 (Partial Arterial Oxygen), SAD (Stage of Acute Disease). OR (odds ratio), CI (confidence interval). OR and 95% CI were calculated using multivariate logistic regression. Boldface indicates a statistically significant difference with P<0.05.

DISCUSSION

Numerous studies are conducted to investigate risk factors for ROP. Definite risk factors for ROP are low gestational age and low birth weight.[1, 19, 20] Caberry et al found the risk of ROP was 30.7% among infants born at GA ≤ 30 weeks with BW ≤ 1500 gram.[1] In our study, we found that GA was a significant factor for ROP and but not BW which was comparable for each stage. This could be explained by an independency for both variables to develop ROP.[1][1] Thereby, ROP screening is mandatory for infants with GA ≤ 30 weeks or BW ≤ 1500 gram to ensure all infants at risk are included.

Retinal vascularization develops before the 16th weeks of pregnancy by two-sequence mechanism: vasculogenesis and angiogenesis.[21] Vasculogenesis starts with formation of endothelial cells cords and subsequently evolves to an immature retinal vascular tree in the inner plexus layer around optic disc up to central one-third of posterior retina. Angiogenesis takes turn around 25-26 weeks by increasing the vascular density and then this developing retinal vessels sprout from optic disc nasally and temporally with a growth rate of 0.1 mm per day for the rest two-third part of retina.[15, 21, 22] By the 32nd week, retinal vessels reach nasal ora serrata. Temporal growth is usually achieved until term or rarely before 37th week.[23, 24] This mechanism explains how younger premature infants more likely to develop severe form of ROP.[15, 25] Caberry et al found that for each week decrease in GA, there was 1.2-1.9 fold higher odds of developing ROP, which is similar to our study.[1] We found the risk of developing SAD was 1.298 in each week decrease of GA (P=0.007, CI = 1.075-1.568). The relative long period of retinal development results in an increased of susceptibility of growing retina to environmental insults that may cause retinal pathology.[23, 26, 27]

Oxygen supplementation is lifesaving; however, it is toxic in excess. Measurement of PO_2 may detect how oxygen works in the body because oxygen-dependent physiological systems, such as oxygen sensing, respond to changes in PO_2.[28] In most situation, oxygen saturation and tension move in the same direction as in oxygen-hemoglobin dissociation curve. However, exposure from continuous oxygen supplementation, may rise PO_2 even when oxygen saturation has already reach 100%.[28, 29] Thus, PO_2 value may assist to monitor when the supplementation is in excess.

Bordkorb et al reported the average value of capillary PO_2 preterm infants were 30.2-45.8 mmHg.[33] In our study, higher mean PO_2 was found in SAD group and A-ROP group. Although it was not statistically significant probably due to relatively low number of A-ROP group, this finding is supported by previous study that infants with higher oxygen was at an increased risk of ROP.[9, 16] Hauspurg et al reported that infants in the highest quartile of PO_2 was at risk for developing severe ROP.[16] Choo et al did not find any difference in ROP in infants exposed to lower oxygen exposure (88-92%) and higher oxygen exposure (90-95%). However, serial ROP screenings showed cases that worsened was doubled in higher oxygen exposure.[9]

We found that sepsis and BPD were significant variables to stage 3 ROP. In accordance with our findings, previous studies reported that premature infants with sepsis and BPD were found more frequently in higher degree of ROP.[9, 17] Possible explanations how sepsis may induce ROP are related to the pathological microorganism and the toxins they produced which cause sepsis-related vascular damage, aggravated oxidative stress, and inflammatory mediators release in response to sepsis.[34] However, multivariable analysis showed that sepsis was not a significant risk factor for SAD development. Previous studies report that sepsis increased the risk of severe ROP, however, SAD group included mostly milder ROP in this study.[35, 36] BPD and ROP both share dysregulation of pro- and anti-angiogenic factors involved in vascular development of the lung and retina. Whether BPD

induces ROP or BPD applies as another concomitant finding as ROP in premature infants, is still inconclusive. [37]

Premature infants are exposed to lower oxygen tension in utero compare to after birth.[7] This relative hypoxia induces production of VEGF, IGF-1, and EPO by astrocytes, Muller cells, pericytes, and RPE, in a balance composition to promote normal retinal vascular development.[13, 15] Exposure to higher oxygen tension after birth and addition of supplemental oxygen increase oxygen tension in premature infants. Following this high oxygen tension, the choroidal vasculature floods the retina with oxygen. At this point, the retina is still partially developed and hyperoxia promotes a down-regulation of the forementioned growth factors, thereby, delaying normal vascular maturation.[14, 15] On the contrary, retinal neuronal elements growth is not impaired due to its independency of oxygen tension. As a result, premature infants will have varying degrees of non-vascularized retina yet very metabolically active retina.[26] This imbalance is read as a hypoxic signal, and consequently up-regulates $VEGF_{165}$ promotes neovascularization in the retina.[11, 14, 15, 30]

To avoid the development of neovascularization, Colaizy et al recommend the use of targeted supplemental oxygen therapy protocol.[31] Under this adjustment, oxygen saturation was kept ≥ 97% and resulted in significant decrease in stage 2 to stage 3 progression without damaging the lungs any further. Meta-analysis report by Chen et al concluded that early low and late high oxygen saturation associated with a reduced risk of ROP. A target of 70-96% oxygen saturation in first few weeks of life and continue with higher oxygen saturation within the range of 94-99% at ≥ 32 weeks reduced the risk of ROP by 52% and 46% consecutively.[32] Transition from high oxygen levels to room air dilates the vessels, however, restoring to the normal vessel caliber can be done by increasing oxygenation.[30]

There was a trend of fluctuations in mean PO_2 in each day of CBG samplings. However, this fluctuation was not statistically significant. On the contrary, previous studies found that VLWBs and extremely preterm infants experiencing fluctuations of oxygen are at a higher risk of developing severe form of ROP.[17, 25] Furthermore, infants with longer, more variable, and less predictable episodes of intermittent hypoxia were associated with severe ROP.[38] Preterm infants experience minute-to-minute fluctuations. [12, 14, 38] We observed a statistically significant higher PO_2 value in day 5 for SAD group as shown in figure 1. It is very likely that such elevation not only occurred on day 5, however, data recorded in our study was limited to day 1, 5, and 10.

Our study confirmed that even a single elevation of recorded PO_2 value during supplementation oxygen period was enough to increase the risk of premature infants to develop SAD. It is important to note that every stage of ROP may progress to higher stage with the higher blinding potential.[9] Thus, preterm infants should be monitored closely to stay in lower degree of oxygen supplementation. Our finding might answer question from previous ROP studies, whether any amount of high oxygen is sufficient to increase the risk of ROP.[20, 30]

To our knowledge, this is the first study to report PO_2 as a surrogate of oxygen role on ROP development using the newest ICROP3 classification. Under the new classification, this study adds that even milder, observation-only stage of ROP has an exposure of high PO_2 value to the same level of severe ROP that requires immediate treatment.

The most important limitation of this study was its retrospective nature. Data was taken from non-electronic medical records with numerous incomplete CBG data for each sampling day. We only analyzed those with complete CBG results. Thereby, unavailability of information on confounders which leads to bias was avoided. Another limitation was the blood gas sampling was taken from capillary

approach on infants' heel which was not directly represent the oxygen tension in the retina. This study opens the possibility of future studies to investigate blood oxygenation estimates in the retina.

CONCLUSION

In conclusion, our data showed that any single elevation in PO_2 during early life of premature infants increase the risk of developing stage of acute disease of ROP, particularly in younger infants. Careful monitoring for PO_2 is mandatory to prevent development of ROP. Further prospective studies are warranted to establish the estimate of PO_2 level in the retina to improve our understanding on high oxygen exposure and ROP development and to provide specific range of oxygen safety net that is acceptable for systemic organs and the retina.

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