



The relation between oxygen saturation level and retinopathy of prematurity

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ABSTRACT

Introduction: Oxygen therapy used for preterm infant disease might be associated with oxygen toxicity or oxidative stress. The exact oxygen concentration to control and maintain the arterial oxygen saturation balance is not certainly clear. We aimed to compare the efficacy of higher or lower oxygen saturations on the development of severe retinopathy of prematurity which is a major cause of blindness in preterm neonates.

Methods: PubMed was searched for obtaining the relevant articles. A total of seven articles were included after studying the titles, abstracts, and the full text of retrieved articles at initial search. Inclusion criteria were all the English language human clinical randomized controlled trials with no time limitation, which studied the efficacy of low versus high oxygen saturation measured by pulse oximetry in preterm infants.

Result: It can be suggested that lower limits of oxygen saturations have higher efficacy at postmenstrual age of ≤ 28 weeks in preterm neonates. This relation has been demonstrated in five large clinical trials including three Boost trials, COT, and Support. **Discussion:** Applying higher concentrations of oxygen supplementations at menstrual age ≥ 32 weeks reduced the development of retinopathy of prematurity. Lower concentrations of oxygen saturation decreased the incidence and the development of retinopathy of prematurity in preterm neonates while applied soon after the birth.

Conclusions: Targeting levels of oxygen saturation in the low or high range should be performed cautiously with attention to the postmenstrual age in preterm infants at the time of starting the procedures.

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Introduction

Retinopathy of prematurity (ROP) or (retrolental fibroplasia (RLF) mostly occurs in premature infants as a result of abnormal vessel development in the retina of the eye, subsequent detachment from the back of the eye, and leading to blindness (1).

ROP, a major developmental disorder, threatens the quality of life in premature infants.

ROP has been reported as the second major cause of blindness in premature infants in USA.

Based on pathological evidence, this condition

has been made of two distinct phases including hyperoxia and cessation of normal retinal blood vessel growth (phase 1), and hypoxia and pathological neovascularization (2).

The presence of ROP could be estimated through routine ophthalmic examinations at two-week intervals after the oxygen therapy until the resolution of retinopathy and the assessment of the grading based on the International Classification of Retinopathy of Prematurity (3).

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This vasoproliferative disease was firstly discovered by Terry in 1942 and it has been proposed as a common cause of blindness in premature infants until now.

Application of oxygen administration during neonatal treatment procedures is a complex and critical field of perinatal medicine with various discrepancies (4,5). Although oxygen administration might be vital during therapeutic strategies in preterm neonates, some adverse effects might be associated with these procedures such as ROP, adverse neurodevelopmental outcomes such as hearing loss, bronchopulmonary dysplasia, and necrotizing enterocolitis (6).

Administration of excessive oxygen in premature infants has been proposed as a major risk factor contributing with the progression of ROP for more than 50 years ago (7,8). The appropriate oxygen-saturation level in preterm infants is an important issue which is still under investigation. Several studies have been performed to address the association between reduced oxygen-saturation at early weeks after birth and reduction of severe ROP in preterm neonates (9-11). These studies showed that a simple change in oxygen saturation limits could reduce the occurrence of prethreshold ROP in preterm infants. They also proposed that the exposure of preterm neonates to hyperoxia could negatively affect the retinal vascular endothelial growth factor (VEGF) and damage normal retinal vascular migration which leads to vaso-oblivation. Thus, it is proposed that exposure to SpO₂ (arterial oxygen saturation) values between 83% and 93%, avoids the vaso-oblivative phase and the following expansion of severe ROP (11,12). In contrast, based on different protocols, application of higher oxygen saturation at later postmenstrual ages is proposed to be effective in reducing the progression and occurrence of ROP (13,14).

In this systematic review, we aim to compare the efficacy of higher or lower oxygen saturations on the development of severe retinopathy of prematurity which is a major cause of blindness in preterm neonates.

Methods

Relevant articles were retrieved through a comprehensive literature search in PubMed. All English language articles were identified with no time limitation based on the following search terms: "retinopathy of prematurity and oxygen therapy". All the human randomized controlled clinical trials (RCTs) published in English studied the efficacy of supplemental low and high SpO₂ in premature infants, measured by pulse oximetry were eligible to be included. The incidence of ROP at different stag-

es was also regarded as the outcome in all the included studies. Exclusion criteria were all the case reports, reviews, and the studies with no certain oxygen saturation level.

Study selection

Abstract and title of the articles obtained at primary search were studied. The results of those that discussed the effect of oxygen on the incidence of ROP were extracted. Reference lists of the retrieved articles were also studied to prevent the possibility of missing any relevant article.

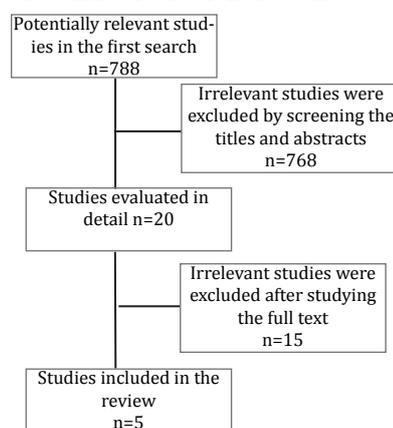
Data extraction

Based on the retrieved studies, the effect of low oxygen saturation (70% - 96%) versus high oxygen saturation (85% - 100%), at any time before the hospital discharge of extremely premature infants born at a gestational age of ≤ 30 weeks was estimated. Quality assessment of the included studies is detailed in Table 1.

Result

At the initial search, 788 articles were obtained from which 768 articles were excluded based on the exclusion criteria by screening the title and abstracts. Therefore, 20 articles were selected for further evaluation of the full text. Overall, five articles that were the most relevant studies were included. Included studies were published between 1999 and 2013.

Figure 1. Flowchart of selection of studies



A total of 5918 infants were evaluated in included studies, 2959 infants were in groups treated with low oxygen supplementation and the same number in groups with high oxygen saturation. The mean gestational age was almost 26 weeks. Two RCTs compared the efficacy of lower oxygen (<96-89%) and higher oxygen (<99%-94%) levels at postmenstrual ages of ≥ 32 weeks with a total number of 1007 infants, while in other studies, low oxygen saturation (96%-70%) versus high oxygen saturation (89%-85%) were studied (15,16).

Table 1. Quality assessment of the included articles

Study Reference	Randomization method	Binding	Intention to treat	Lost to follow up	Similarity of the groups at initial	The classification of ROP was objective
Support group (17)	Permuted-block	NA ¹	Yes	NO	Yes	Yes
Askie (15)	Dynamic balancing method	NA	Yes	NA	Yes	Yes
Boost UK (18)	Computer	NO	Yes	1/973	Yes	Yes
BOOST AU (18)	Computer	NO	Yes	1/973	Yes	Yes
BOOST NZ (18)	Computer	All the care givers	Yes	5/340	Yes	Yes
COT (19)	Computer	NA	Yes	108/1147	Yes	Yes

¹NA: Not available**Table 2.** Characteristics of the included clinical trials

Study group Year Reference	Number cases of	Recruitment Period	Gestational age	Oxygen Timing	Target Oxygen Saturation (%)	Severe ROP ¹ , %	Risk reduction (95% Confidence interval)
STOP-ROP Multicenter Study Group 1999 (16)	Total:649 Low:325 High:324	1994-1999	25.4 ± 1.5 (mean)	35.4 ₂ (mean PMA ²)	High (96-99) versus low (89-94)	Prethreshold to threshold ROP (41 versus 48)	0.84 (0.71-1.01)
Askie 2003 (15)	358 (178 with low oxygen and 180 with high)	1996-2000	<30	32 +1 to -10 (PMA)	High (95-98) versus low (91-94)	Stage 3 or 4: 12 versus 16	0.78 (0.46-1.31)
SUPPORT Study Group³ 2010 (17)	Total: 1316 654 (low) / 662 (high)	2005-2009	26±1	Soon after birth	High (91 to 95) versus low (85 to 89)	17.9 vs. 8.6	0.52 (0.37-0.73)
BOOST UK⁴ 2013 (18)	Total:973 Low:486 High: 487	2006-2010	Low 26.0 (1.3) vs. high 26.0 (1.3)	From <24 hours of age	High (91 to 95) versus low (85 to 89)	13.5-10.6	0.79 (0.63-1.00)
Boost AU⁵ 2013 (18)	Total:1135 Low:568 High: 567	2006-2010	26.0 (1.2) vs. 26.0 (1.2) weeks	From <24 hours of age	High (91 to 95) versus low (85 to 89)	13.5-10.6	0.79 (0.63-1.00)
BOOST NZ⁶ 2013 (18)	Total:340 Low:170 High:170	2006-2010	26.1 (1.2) vs. 26.1 (1.2)	From <24 hours of age	High (91 to 95) versus low (85 to 89)	13.5-10.6	0.79 (0.63-1.00)
COT⁷ 2013 (19)	Total:1147 Low:578 High:569	2006-2010	23 w-27 w	Within 24 hours after birth	High (91 to 95) versus low (85 to 89)	High: 66/503 (13.1) Low: 64/500 (12.8)	0.98 (0.71-1.34)

¹ROP: Retinopathy of prematurity; ²PMA: postmenstrual age; ³SUPPORT study group: Surfactant, positive pressure, and pulse oximetry randomized trial (SUPPORT) study group of the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development; ⁴BOOST group: The benefits of oxygen saturation targeting II (BOOST II) trials of United Kingdom (UK), ⁵Australia (AU), and ⁶New Zealand (NZ) collaborative groups; ⁷COT: The Canadian oxygen trial

Discussion

In this review, we aimed to study the incidence rate and progression of severe ROP in premature infants under the oxygen-saturation procedure measured by pulse oximetry.

The advantages of low and high oxygen saturation on severe ROP depend on the pathological phases of the disease. It has been proposed that the first phase of the ROP consists of hyperoxia and following by vaso-obliterative phase during 30 to 32 weeks of postmenstrual age; supplemental oxygen could arrest VEGF, interrupt normal vessel growth, and deteriorate the existing vessels. During the second phase of the disease (after the 32 weeks of gestation), the presence of hypoxia increases VEGF expression and the subsequent pathologic neovascularization. Therefore, administration of appropriate level of therapeutic oxygen-saturation at each phase of the disease could adjust VEGF expression and pathologic neovascularization due to the ROP. In this regard, there is a positive relation between postmenstrual age and the development of ROP.

Previous laboratory and experimental examinations have proven the contribution of elevated VEGF in pathological retinal vasculature of animal models, transgenic mouse models, and nonhuman primates (20-22).

Although the appropriate level of oxygen saturation is not clearly revealed, pulse oximetry is nowadays routinely used for the monitoring of oxygen-fluctuation in preterm infants.

In accordance with the mentioned subjects, it could be suggested that lower limits of oxygen saturations have higher efficacy at postmenstrual age of ≤ 28 weeks in preterm neonates. This relation has been demonstrated in 5 large clinical trials including three Boost trials, COT, and Support study groups (17-19).

Based on the study of Askie et al., in 2003, applying a higher oxygen-saturation range after the postmenstrual of 32 weeks in a subgroup of extremely preterm infants, requirement for ophthalmic intervention might decrease the due to severe eye disease (15).

Nevertheless, this trial did not have appropriate statistical strength to reveal the significant differences in secondary eye-related outcomes by applying higher levels of oxygen saturation, and further large trials are suggested to confirm the efficacy of different oxygen saturation ranges on the incidence rate of ROP. Similar result was also reported in another study performed in 2000, which suggested a no significant decreased risk of ROP progression following higher oxygen-saturation levels applied at almost 2.5 ± 35.4 weeks of postmenstrual age (16).

Some limitations were associated with the study of STOP-ROP multicenter group, including the application of high saturation oxygen at a mean of 2.5 ± 35.4 weeks of age. Because of the possibility of the enrolled infants to be at phase 1 or 2 of the ROP (postmenstrual age ranged from 30 to 48 weeks), the protective effect of oxygen-saturation therapy could not be determined exactly. According to the STOP-ROP study, high-oxygen administration might be started too early in patients at phase 1 of the ROP and too late in patients at phase 2 of the disease (16).

Although the optimum oxygen level for the treatment of ROP in preterm infants remained uncertain, the high level of oxygen-saturation chosen in the STOP-ROP trial and the one performed by Askie et al., might be another contributing factor that reduced the strength of the treatment efficacy on neonates; 96% to 99% of oxygen level, versus $\geq 98\%$ in other surveys (14,16).

Therefore, it seems that higher oxygen levels ($\geq 98\%$) could result in more protective effect regarding the regression of prethreshold ROP.

In contrast with the two mentioned studies, results obtained through three large clinical randomized trials (COT, three BOOST studies, and Support) showed that application of high oxygen saturation compared with low concentration, within the initial time after the birth could increase the mortality rate and also develop severe ROP (17-19).

In all these five trials, supplemental oxygen saturation was applied soon after birth, and they confirmed that lower target ranges of oxygenation reduced the incidence of severe retinopathy.

Strategies of targeting levels of oxygen saturation in low or high range should be performed cautiously and careful attention should be devoted to the postmenstrual age at the time of starting the procedures in preterm infants.

Conclusion

Based on included articles, it can be suggested that both the concentration of the applied oxygen and the timing of the oxygen application are important factors in severe ROP risk reduction. According to the results, higher oxygen saturation levels ($\geq 94\%$ - 99%) reveal higher advantages in ROP risk reduction, at ≥ 36 weeks of postmenstrual age.

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Conflict of Interest

The authors declare no conflict of interest.

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