Review Article

Meta-Analysis on the Effects of Supplemental Oxygen on Retinopathy of Prematurity

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Background: Despite an improved survival rate due to advances in modern medical technology, exposure to high concentration of oxygen has been reported to predispose infants to the risk of retinopathy of prematurity (ROP). This study aims at investigating the impact of oxygen saturation (SaO_2) on the development of ROP through literature review.

Methods: Literature search, data abstraction, assessment of study quality, and data analysis were performed. Inclusion criteria included studies recruiting preterm infants with gestation less than 30 weeks and body weight less than 1,500 gm, intervention of lower concentration of supplemental therapeutic oxygen, comparison with higher concentration of supplemental therapeutic oxygen, and the outcome parameter of percentage of ROP. Studies involved a mixture of preterm and term infants, these did not provide a comparison group using oxygen concentration other than that in the experimental group and they did not show data for calculation effects that were excluded. Five databases were searched, the latest being January 8, 2015. The databases searched were: the Chinese Electronic Periodical Services (CEPS), CINAHL, Cochrane library, PubMed, and Medline. Additional literature was also acquired through hand searching. Appraisal of the literature was performed using the 2011 Oxford Centre for Evidence-Based Medicine levels of evidence.

Results: A total of 736 studies were retrieved. After excluding duplications and studies that did not fit the inclusion criteria, five studies from 2000 to 2013 remained that consisted of four randomized clinical trials and one non-randomized study. The total patient number was 5,514 with a mean gestational age, body weight, range of SaO_2, and incidence of ROP being 25 – 27 weeks, 808 – 888 gm, 89%, and 92%, respectively. The Oxford level of evidence was two in four studies and four in one study. The present meta-analysis demonstrated that lower SaO_2 (i.e., 85 – 89%) was significantly associated with a lower incidence of ROP compared to that in the higher SaO_2 group (i.e., 91 – 95%) (95% CI: 0.296 – 1.436) ($p = 0.003$).

Conclusion: Despite a relatively small number of studies included, lower SaO_2 was found to be associated with a significantly reduced incidence of ROP compared to that in the higher SaO_2 group. Judicious use of supplemental oxygen, therefore, may reduce the risk of ROP in premature infants.

Key words: retinopathy, prematurity, neonate, oxygen saturation

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Received: May 5, 2017 Accepted: February 13, 2018

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Introduction

Too much oxygen administration could be toxic to premature newborn infants. In early 1950s, blindness from retrolental fibroplasia (RLF) was an epidemic, occurring in over 10,000 premature babies.[1] Retinopathy of prematurity (ROP), which is characterized by neo-vasulazontion in preterm infants, is a slowly progressive disease associated with the exposure to high concentration of oxygen. It mostly happens in premature infants born with gestational age between 24 – 32 weeks and body weight less than 1500 gm requiring treatment with high concentration of oxygen during hospitalization. ROP is a pathologic process that occurs only in immature retinal tissue and can progress to tractional retinal detachment, which can result in functional or complete blindness.[4]

Clinically, ROP is scaled from I to IV with increasing severity. Despite the four specified stages of ROP, there is a more severe form of ROP called "Plus" disease characterized by a marked shunting between arterial and venous blood of retina that reflects rapid progression of ROP.

There was a multicenter randomized control trial sponsored by the National Institute of Health to compare "routine oxygen" and "curtailed oxygen" in babies weighing less than 1,500 grams.[1] The outcome demonstrated that blindness from RLF was reduced significantly with curtailed oxygen delivery, but the inability to monitor blood oxygen saturation resulted in increased infant morbidity and mortality.[1]

This study aims at investigating the impact of oxygen saturation (SaO_2) on the development of ROP through literature review and it will be analyzed by using meta-analysis.

Methods

Literature search and selection strategy

Literature search, data abstraction, assessment of study quality, and data analysis were performed. Inclusion criteria included studies recruiting preterm Infants with gestation less than 30 weeks and body weight less than 1,500 gm, intervention of lower concentration of supplemental therapeutic oxygen, comparison with higher concentration of supplemental therapeutic oxygen, and the outcome parameter of percentage of ROP. Studies involved a mixture of preterm and term infants, these did not provide a comparison group using oxygen concentration other than that in the experimental group, and they did not show data for calculation effects that were excluded. The mortality is also one of the concerns for preterm infants as reduced oxygen supplement might cause hypoxia and lead to death.

As the mortality rate has already been defined with all infant deaths and that happens at any age before discharge home in Neonatal Intensive Care Unit (NICU), therefore; the infants with cardiovascular or congenital problems with reduced oxygen supplement is inappropriate on the protocol.[1] Because preterm infants are very fragile and most of them require oxygen treatment, therefore the selection strategy needs to be careful. Five databases were searched, the latest being January 8, 2015. The databases searched were: the Chinese Electronic Periodical Services (CEPS), CINAHL, Cochrane library, PubMed, and Medline. Additional literature was also acquired through hand searching. Appraisal of the literature was performed using the 2011 Oxford Centre for Evidence-Based Medicine levels of evidence.

Definitions

Plus disease is defined as abnormal dilation and tortuosity of the posterior retinal blood vessels in two or more quadrants of the retina meeting or exceeding the degree of

abnormality.

Statistical analysis

Categorical data were expressed as relative risk and risk difference with 95% confidence interval and number needed to treat or harm as appropriate. Continuous data were analyzed using weighted mean difference with 95% confidence intervals. A fixed effects model was to be used for meta-analysis. In order to assess the effect of missing data on the primary outcome, progression to threshold ROP, analyses of best case/worst case scenarios were undertaken.[3]

Results

A total of 736 studies were retrieved. After excluding duplications and studies that did not fit the inclusion criteria, five studies from 2000 to 2013 remained that consisted of four randomized clinical trials and one non-randomized study (Table 1). The total patient number was 5,514 with a mean gestational age, body weight, range of SaO_2, and incidence of ROP being 25 – 27 weeks, 808 – 888 gm, 89%, and 92%, respectively (Table 1). The Oxford level of evidence was two in four studies and four in one study. Meta-analysis demonstrated that lower SaO_2 (i.e., 85 – 89%) was significantly associated with a lower incidence of ROP compared to that in the higher SaO_2 group (i.e., 91 – 95%) (95% CI: 0.296 – 1.436) ($p = 0.003$) (Table 2).

There are only two journals included in this article because three of the studies were not consistent with the lower concentration of O_2 Saturation. Due to the lack of information provided by Lloyd, we will only analyze the remaining two journals. The results showed that premature newborn infants with severe ROP might require cryo-therapy treatment. In addition, peripheral ablation may be preferred to conservative treatment for patients with plus disease involving Zone I or II. Treatment should be initiated for the following retinal findings: Zone I ROP: any stage with plus disease or stage 3 without plus disease; Zone II: stage 2 or 3 with plus disease.

The majority of reviews draw the

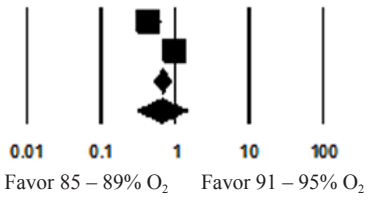
Table 1. Characteristics of studies

Study	STOP-ROP (2000)[8]	Wright (2006)[1]	SUPPORT Study Group (2010)[7]	BOOST II Collaborative Group (2013)[3]	Schmidt (2013)[2]
N (E/C)	597/600 (2 weeks: 298/299) (3 months: 299/301)	350 (92/88;54/41; 45/30)	1316	2448	1147
Nation	US	US, SG	US	UK, AU, AZ	CA, US, AS, Fl, DE, IL
Units	30	3	144		25
Random	Yes	No	Yes	Yes	Yes
Blind	Yes	No	Yes		Yes
Group equality	Yes	Yes	Yes		Yes
Gestational age (week)	25 ± 1.5		26 ± 1	< 28 (11.5 – 22.5)	25.6 ± 1.2 (23 – 27)
Birth weight (gm)	726 ± 160	500 – 1500	830		835

N: Number; E: Experiment group; C: Control group; US: United States; SG: Singapore; UK: United Kingdom; AU: Australia; NZ: New Zealand; CA: Canada; AS: Argentina; FL: Finland; DE: Germany; IL: Israel

Table 2. The comparison of retinopathy of prematurity (ROP) between lower and higher oxygen saturation

Model	Study name	Statistics for each study					Odds ratio and 95% CI
		Odds ratio	Lower limit	Upper limit	Z-value	*p*-value	
	Carlo (2010)[7]	0.434	0.293	0.642	-4.170	0.000	
	Schmidt (2013)[2]	0.972	0.672	1.405	-0.151	0.880	
Fixed		0.666	0.509	0.871	-2.966	0.003	
Random		0.651	0.296	1.435	-1.063	0.288	



N(n)	WES (95 % CI)	*p*	Heterogeneity		
			Q	*p*	I-squared
2(1,987)	0.651 (0.296 – 1.436)	0.288	2.288	0.003	88.399

WES: Wound evaluation scale

attention to how high concentration oxygen might have affected premature infants who are born less than 30 weeks gestation and caused ROP occurrence. The readings of oxygen saturation levels often exceed the target levels whether the infants are breathing room air or receiving oxygen supplements. There are a number of complications that may occur whilst the premature infants receive insufficient oxygen supplement and especially on cardio-respiratory support, such as swinging saturation readings and respiratory distress syndrome (RDS). Therefore continuous monitoring the potential complications and ROP are crucial.

Discussion

According to the reviews, use of oxygen in neonatal units began in the early 1940s and by the mid-1950s; oxygen was implicated as a cause of blindness from RLF.[1] In Taiwan, there are a number of premature infants have developed ROP in some Neonatal units; some are curable and some might require surgery treatments, therefore preventing and regularly screening the disease on the certain gestation age for premature infants has become crucial. The majority of premature infants require oxygen administration due to immature lungs, and according to the review, too much oxygen could lead to ROP development and resulted in blindness. According to one of the reviews, the lower target range of oxygen saturation increased the risk of in-hospital death, whereas it reduced the risk of severe retinopathy among survivors,[3] therefore the incidence of morbidity and mortality has drawn the attention from the researchers. The outcomes from all the reviews have demonstrated different results. Different range of target of oxygen administration has different outcome according to the research. How to set up the ideal saturation limits is difficult because optimal oxygen saturations for low birth weight premature infants are still not well established.[1] In the western countries such as United States (US), United Kingdom (UK), oxidation guidelines were established to guide oxygen therapy, however the evidence used was not clearly addressed (Table 3).

Moreover, neonatal staff nurses should be aware of the alarm limits setting of oximeter to ensure the safety of premature infants. Proper saturation limits setting could influence the infant from receiving too much oxygen. Lower saturation thresholds that would trigger an alarm were not prescribed in the UK protocol. However alarm settings greatly influence how caregivers adjust the concentration of oxygen.[2] Blindness from RLF was reduced significantly with curtailed oxygen delivery, but the inability

Table 3. Oxidation guidelines were established to guide oxygen therapy in some United Kingdom (UK) and United States (US) hospitals, however, evidence used were not clearly addressed.

	Infants	Alarm limits
Initial saturation limits	Preterm: < 34 weeks at birth very low birth weight	84 – 96%
	Low birth weight	89 – 96%
	Term/post term	94% (lower limit)
Changes at 28 days and/or > 36 weeks	Very low birth weight (> 28 days old)	89 – 96%
	With chronic lung disease and 36 weeks corrected	94% (lower limit)
	Heart congenital malformations	As prescribed by doctor

A different range from the above for an individual baby should be prescribed and signed by a doctor .
Guideline of Trevor Mann Baby Unit, Brighton and Royal Sussex County Hospital,UK.

to monitor blood oxygen saturation resulted in increased infant morbidity and mortality.[1]

The primary outcome may progress to threshold ROP or require retinal ablation operation, and even cause blindness or severe visual problems. Apart from the primary outcome, the secondary outcomes have minor affects that include visual function in short or long term, and even affect the longer hospital stays with oxygen supplement requirement, moreover, it also has affected the mortality before discharge home, chronic lung diseases, other respiratory problems and short/long term weight gain.[3]

In Taiwan, most hospital neonatal units have not generally established the guidelines or protocols for oxidation yet; therefore in order to monitoring the occurrence of ROP, regular screening for preterm infants who are born less than 32 weeks gestation on ROP has become an important procedure for premature infants.

Saturation monitoring is very important for the NICU infants, especially ROP has become one of the complications of premature infants and ROP might cause blindness and hypoxia, therefore establishing saturations protocols for the NICU infants will be beneficial for them. In the UK and US, every cot in the NICU has the protocol attached by the cot side; the purpose is to ensure that premature infants do not receive excess oxygen and to maintain the saturation at the ideal levels.

Since ROP has become the problem of premature infants' visual impairment, and the decrease is gradual, not abrupt,[5] also it is preventable if the medical staff are aware of the harm may be caused by the high oxygen supplement. Although curtailed oxygen might cause mortality and morbidity, however, it is becoming common practice to use lower target ranges of oxygen saturation with the goal of reducing the risk of ROP.

In order to reduce the incidence rate of ROP, establishing protocols might be helpful for the premature infants with the appropriate saturation limits according to the infant's gestation. Too much oxygen supplement could cause toxicity, and oxygen toxicity may also increase the risk of death,[6] thus, apart from monitoring the ROP occurrence, also the comorbidity must be monitoring very closely at the same time.

As the topic has been reported in a number of studies, and the results demonstrated that lower oxygen saturation limits are favorable for the premature infants. Oxygen used must be very careful for the preterm infants as they are very vulnerable and immature, however, for the safety and risk factors, more considerations must be taken into account.

Conclusion

Even though the current studies do not provide strong and consistent evidence to

suggest a best O_2 saturation level for preventing ROP and mortality, there is still a number of premature newborn infants who have developed ROP through receiving too much oxygen which should not have occurred if the appropriate saturation limits were correctly set.

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