Original Article

Can High Average Oxygen Saturation be a Risk Factor for Necrotizing Enterocolitis in VLBW Infants?

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Abstract

Background: Avoiding hyperoxia with oxygen saturation monitoring is important in the follow-up of very low birth weight (VLBW) infants. Role of oxygen-derived free radicals in the pathogenesis of necrotizing enterocolitis (NEC) has been well defined. However, a great majority of the evidence supporting the role of hyperoxia in NEC development are data from experimental studies and there are very few clinical studies. In this study, the association between NEC and average oxygen saturation (SpO_2) levels in VLBW infants was researched. **Methods:** Average SpO_2 values of VLBW infants in the last 24 h were recorded prospectively with pulse oximeter. Average SpO_2 records were continued at least for 10 days starting from the first day after birth. In the follow-up, the average SpO_2 values of the patients who developed NEC and those who did not were compared. **Results:** A total of 127 VLBW infants were followed up. Thirteen patients developed NEC (Bell's classification ≥ stage II). No differences were found between the average SpO_2 levels (94.9 and 94.8%) of the patients who developed NEC and those who did not. It was found that average SpO_2 value higher than 93 or 95 was not a risk for NEC development ($P = 0.693$ and $P = 0.771$). **Conclusions:** In this study, no association was found between average SpO_2 values recorded in the first weeks of VLBW infants and NEC.

Keywords: *Enterocolitis, hyperoxia, infant, necrotizing, premature*

Introduction

Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency disease in the newborn intensive care units.[1] Role of oxygen-derived free radicals in the pathogenesis of NEC has been well defined.[2,3] Free radical production is the final point of the various biochemical phenomena cascade such as hypoxia, hyperoxia, and inflammation. Oxidative stress starts with the imbalance between free radical production and antioxidant systems, and as gestational age decreases, so does the capacity of antioxidant systems.[4]

Avoiding persistent and variable hyperoxia with oxygen saturation monitoring is very important for very low birth weight (VLBW) newborns.[5] *In vivo*, hyperoxia creates intestinal serosal and submucosal vasodilatation, vascularization, and growth retardation in neonatal rats.[6] Because the intestinal villi and mucosa continue to grow and differentiate after birth, the long-term effects of postnatal hyperoxia exposure may be more different in the human infant.[7]

Free oxygen radicals have been shown to have a role in the pathogenesis of many diseases in preterm infants. However, most of the evidence supporting this are data from experimental studies and there are few clinical studies.[8,9] Clinical studies have frequently assessed the effect of different target partial oxygen saturation (SpO_2) ranges on neonatal mortality and morbidity.[9] However, in these studies, the actual median levels of oxygen saturation were above the intended targets in both low and high oxygen saturation periods or study groups were assessed in different time periods.[8] In this study, we recorded average SpO_2 levels of VLBW infants for at least 10 days starting from the first day after birth.

The primary outcome of the study was to compare the average SpO_2 values of the patients who developed NEC and who did not during the follow-up, while the secondary outcome was to determine different threshold SpO_2 values (93 and 95) and to examine the frequency of NEC in patients who had saturation values lower and higher than this value.

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Methods

A prospective study was designed and conducted in our hospital between September 2010 and February 2012. Patients born under 1500 g and less than 32 weeks were included in the study. Patients who had major congenital or gastrointestinal system anomaly, those who had cyanotic congenital heart disease, or those who had severe metabolic acidosis (pH <7.0 or base excess <−12) in blood gas analysis within the postnatal first hour were not included in the study. The study was approved (30/2010) by the Local Ethics Committee of our hospital. The patients included in the study were followed for SpO_2 with Masimo Radical-7® (Masimo Corporation, Irvine, CA, USA) pulse oximeter starting from postnatal day 1. This device can give the highest, lowest, and average SpO_2 values up to last 72 h. SpO_2 trends (minimum, maximum, and average SpO_2 values) of the last 24 h were recorded everyday between 14:30 and 16:30. The records were made for at least 10 days starting from the postnatal first day, and the arithmetic mean of all records of the related patient was taken. The patients who were not recorded for 2 or more consecutive days or those who did not have at least 10 days of record starting from the first day were excluded from the follow-up. The patients' demographic and clinical features, type of feeding, the day when 70% of the total calorie need was taken enterally, and presence of NEC (modified Bell's classification ≥stage II) were recorded.[10]

In our unit, upper and lower pulse oximeter alarm limits are adjusted as 89 and 95%, respectively, for premature infants of less than 32 weeks. During the study, only average SpO_2 values of the patients were recorded irrespective of whether patients received free-flow oxygen support, noninvasive respiratory support, or mechanical ventilation support.

Statistical analysis

Demographic data were summarized as means with standard deviation and median with ranges. Differences between the patient who developed NEC and those who did not were found by two-tailed bivariate analyses using χ^2 test for categorical data. Student's *t*-test was used for continuous data. The frequency of NEC was compared in patients who had saturation values lower and higher than determined average SpO_2 value using χ^2 test.

Results

A total of 208 infants with a birth weight of <1500 g and gestational age of <32 weeks were started SpO_2 follow-up with Masimo Radical-7® pulse oximeter between September 2010 and February 2012. Twenty-eight patients were excluded from the study since they died in the first 10 days, 51 patients were excluded since their consecutive follow-ups were not performed, 1 patient was excluded since spontaneous intestinal perforation developed, and 1 patient was excluded since midgut volvulus developed. Regular SpO_2 records of 10 days and longer were completed for a total of 127 patients. The average gestational weeks of these patients were 28.2 ± 2 weeks, the average birth weight was 1052 ± 243 g, and 48.8% were male. In the follow-up, 13 patients developed modified Bell's classification ≥stage II NEC. In these patients, NEC developed between days 8 and 46, with a median on day 20. SpO_2 follow-up duration had a median of 16 days (min–max, 10–46 days) in NEC group, while it was 20 days (min-max, 11–35 days) in the group which did not develop NEC. A total of 2594 patient days were recorded. No statistically significant difference was found between the clinical and demographic findings of patients who developed NEC and those who did not [Table 1]. As expected, the average hospital stay day was longer (median

Table 1: Demographic and clinical characteristics of study infants with and without NEC (*n*=127)

	Not developing NEC, *n*=114	Developing NEC*, *n*=13	*P*
Gestational age, week (mean±SD)	28.3±2.0	27.8±2.1	0.50
Birth weight, g (mean±SD)	1065±246	939±192	0.09
Male gender, *n* (%)	54 (47.3%)	8 (61.5%)	0.335
Apgar score at 5 min, median (min-max)	7 (2-8)	6 (1-8)	0.34
Small for gestational age, *n* (%)	22 (19.3%)	2 (15.4%)	0.734
Maternal preeclampsia, *n* (%)	21 (18.4%)	4 (30.8%)	0.29
Antenatal steroids, *n* (%)	80 (70.2%)	8 (61.5%)	0.52
Umbilical venous catheter, *n* (%)	89 (78.1%)	13 (100%)	0.061
PDA requiring medical treatment, n (%)	36 (31.6%)	4 (30.8%)	0.953
The day when 70% of the total calorie need was taken enterally, day (mean±SD)	9.5±3.9	11.3±6.5	0.48
Infants only breastfeeding, *n* (%)	81 (71.1%)	8 (61.5%)	0.84
SpO_2 follow-up time, day median (min-max)	20 (11-35)	16 (10-46)	0.081
Average level of SpO_2	94.8±1.6	94.9±1.3	0.80
Day of discharge, day, median (min-max)	59 (11-144)	74 (57-145)	0.009

*Necrotizing enterocolitis diagnosed modified Bell's classification stage ≥2. NEC=Necrotizing enterocolitis; SD=Standard deviation; PDA=Patent ductus arteriosus

74 vs 59 days, $P = 0.009$) in patients who developed NEC in the follow-up [Table 1].

The average SpO_2 value was 94.9 ± 1.3% in the patient group that developed NEC and 94.8 ± 1.6% in the patient group that did not develop NEC. No statistically significant difference was found between the average SpO_2 levels of both groups [Table 1]. When SpO_2 threshold value was taken as 93%, the average SpO_2 level of 21 patients was under 93% and NEC developed in one of these patients. The average SpO_2 level of 106 patients was ≥93% and NEC developed in 12 of these. It was found that the average SpO_2 level of higher than 93% was not an additional risk for NEC development ($P = 0.693$). Similarly, when SpO_2 threshold value was taken as 95%, the average SpO_2 level of 60 patients was under 95% and NEC developed in 7 of these patients. The average SpO_2 level of 67 patients was ≥95% and NEC developed in 6 of these. It was found that the average SpO_2 level of ≥95 was not an additional risk for NEC development ($P = 0.771$). Birth weeks and birth weights of patients with an average SpO_2 level of ≥95 were found to be higher; in addition, these patients were discharged earlier [Table 2].

Discussion

We did not find a significant difference between the average SpO_2 levels of patients who developed NEC and those who did not. In addition, when we determined two different threshold SpO_2 values (93% and 95%), we did not find a difference between patients below and over average SpO_2 level in terms of NEC development.

Antioxidant defenses of preterm infants are weak and they are sensitive to oxidant injury.[11] Studies have associated neonatal hyperoxia with injury to the developing brain, lung, and retina.[12-14] However, there is minimal research regarding the role of postnatal hyperoxia in intestinal development.

A great number of studies on oxidant injury and intestinal effects have been based on cell cultures and inspired or medium oxygen concentration. Hyperoxia increases the level of reactive oxygen species in intestinal epithelium cells.[15] In addition, it has been shown that in newborn rats, hyperoxia disrupts barrier function and makes intestinal epithelium cells susceptible to bacterial invasion and this can be associated with NEC.[16] Despite these negative effects of hyperoxia on intestinal epithelium cells, Sukhotnik *et al*. showed that 100% oxygen following ischemia-reperfusion damage reduces small bowel injury, accelerates enterocyte turnover, and improves intestinal rehabilitation.[17] These studies conducted on animal models and cell cultures give us some ideas about the effects of hyperoxia on intestinal epithelium cells. However, these studies cannot clearly establish what kind of intestinal system reflections hyperoxia will have on sick preterm infants.

Almost all the clinical studies researching the association between NEC and oxygen saturation are in the form of comparison of NEC frequency in periods when different target SpO_2 ranges are determined. In Stenson's study which included VLBW infants, it was found that when compared with high target SpO_2 range (91%–95%), the rate of NEC which required surgery in low target SpO_2 range (85%–89%) increased.[18] In our study, none of the patients who developed NEC and those who did not had an average SpO_2 level lower than 90%. In another study which compared different target SpO_2 levels in VLBW infants, it was found that the frequency of premature of retinopathy (ROP) and chronic lung disease decreased in target SpO_2 period avoiding hyperoxia (85%–93%).[8] In the same study, no increase was found in NEC frequency

Table 2: Demographic and clinical characteristics of patients with an average SpO_2 value of ≥95% and <95%

	Infants with average SpO_2 <95%, *n*=60	Infant with average SpO_2 ≥95%, *n*=67	*P*
Gestational age, week, (mean±SD)	27.6±2.1	28.8±1.7	0.001
Birth weight, g (mean±SD)	996±242	1108±247	0.01
Male gender, *n* (%)	26 (43.3%)	36 (53.7%)	0.24
Apgar score at 5 min, median (min-max)	7 (1-8)	7 (2-8)	0.98
Small for gestational age, *n* (%)	9 (15%)	15 (22.3%)	0.28
Maternal preeclampsia, *n* (%)	13 (21.6%)	12 (18%)	0.59
Antenatal steroids, *n* (%)	43 (71.6%)	45 (67.1%)	0.58
Umbilical venous catheter, *n* (%)	54 (90%)	48 (71.6%)	0.009
PDA requiring medical treatment, *n* (%)	24 (40%)	16 (23.8%)	0.05
Number of patients with NEC, *n* (%)	7 (11.6%)	6 (8.9%)	0.77
The day when 70% of the total calorie need was taken enterally, day (mean±SD)	9.3±3.6	10.0±4.8	0.31
Infants only breastfeeding, *n* (%)	38 (63.3%)	51 (76.1%)	0.20
SpO_2 follow-up time, day, median (min-max)	22 (11-46)	18 (10-41)	0.002
Average level of SpO_2	93.4±1.2	96.1±0.57	0.001
Day of discharge, day, median (min-max)	72 (42-145)	56 (11-134)	0.001

SD=Standard deviation; PDA=Patent ductus arteriosus; NEC=Necrotizing enterocolitis

when target SpO_2 level was adjusted high (92%–100%). Similarly, in SUPPORT study, no significant difference was found in stage ≥2 NEC frequency (10.8% and 11.9%, respectively) in low and high target range of oxygen saturation periods in preterm newborns.[9]

Our study shows this result more clearly with its different design. We designed a simple and result-oriented study. We recorded the average SpO_2 levels of VLBW infants starting from the first day. We compared the average SpO_2 values of patients who developed NEC and those who did not during follow-up and we did not find a significant difference ($P = 0.80$). In addition, we found that when 93% and 95% were taken as threshold SpO_2 value, the average SpO_2 values higher than the threshold values did not increase the risk of NEC.

In our study, we found that the average SpO_2 levels of the patients (94.9% in NEC group and 94.8% in non-NEC group) were within the upper limit of target SpO_2 ranges (89%–95%) in our unit. Similarly, it was reported in SUPPORT study that the actual median levels of oxygen saturation were above the intended targets in both low and high oxygen saturation periods.[9] This situation can be associated with the fact that the average SpO_2 value of most of the patients who did not receive oxygen support was above 94%.

In the assessment of oxygenation, the measurement of partial arterial oxygen pressure (PaO_2) is accepted as the golden standard. However, artery catheter should be placed for the continuous monitorization of oxygenation with this method. Today, pulse oximeter is a part of standard care in newborn intensive care units.[19] Pulse oximeter provides continuous information on oxygenation noninvasively. Most studies showed a relatively tight relationship between SpO_2 and PaO_2, suggesting that if babies were kept with SpO_2 between 85% and 95%, with PaO_2 values between 40 and 80 mmHg. Using SpO_2 >95% as cut-off, for detecting hyperoxia (PaO_2 >80 mmHg), the pulse oximeter had a sensitivity of 72.7% and a specificity of 96%.[20]

Due to the difficulty of long-term consecutive follow-up (when the monitor is off for some reason, average values of previous hours are deleted), we considered that at least 10 days of consecutive follow-up was sufficient starting from birth. We could not find any studies investigating the association between average SpO_2 level in the first days of life and NEC. However, Chen *et al*. reported that the decrease in ROP frequency in low target SpO_2 periods was associated with the decrease in target SpO_2 value in the first week of life.[21]

The weak side of the study was the fact that it was conducted with limited number of patients from one center. In addition, two patients with similar average SpO_2 value can have been exposed to different numbers of hypoxic or hyperoxic periods. Thus, their reoxygenization exposures may also be different. Studies conducted with more sophisticated devices that can record the periods in hypoxic and hyperoxic end points are needed to assess this.

We found that the average SpO_2 values recorded from the first day were similar for infants who developed NEC and those who did not in the follow-up and that an average SpO_2 value of ≥95% in the first weeks of life did not increase NEC risk. Our results are in parallel with a wide range of studies designed by taking the target saturation range as basis and this result is clearly shown with its different design.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Lee JS, Polin RA. Treatment and prevention of necrotizing enterocolitis. Semin Neonatol 2003;8:449-59.
2. Neu J. Necrotizing enterocolitis: The search for a unifying pathogenic theory leading to prevention. Pediatr Clin North Am 1996;43:409-32.
3. Czyrko C, Steigman C, Turley DL, Drott HR, Ziegler MM. The role of reperfusion injury in occlusive intestinal ischemia of the neonate: Malonaldehyde-derived fluorescent products and correlation of histology. J Surg Res 1991;v51:1-4.
4. Perrone S, Tataranno ML, Negro S, Longini M, Marzocchi B, Proietti F, *et al*. Early identification of the risk for free radical-related diseases in preterm newborns. Early Hum Dev 2010;86:241-4.
5. Tin W. Optimal oxygen saturation for preterm babies. Do we really know? Biol Neonate 2004;85:319-25.
6. Torbati D, Tan GH, Smith S, Frazier KS, Gelvez J, Fakioglu H, *et al*. Multiple-organ effect of normobaric hyperoxia in neonatal rats. J Crit Care 2006;21:85-93; discussion 93-94.
7. Giannone PJ, Bauer JA, Schanbacher BL, Reber KM. Effects of hyperoxia on postnatal intestinal development. Biotech Histochem 2007;82:17-22.
8. Deulofeut R, Critz A, Adams-Chapman I, Sola A. Avoiding hyperoxia in infants < or = 1250 g is associated with improved short- and long-term outcomes. J Perinatol 2006;26:700-5.
9. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, *et al*. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 2010;362:1959-69.
10. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, *et al*. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1-7.
11. Thibeault DW. The precarious antioxidant defenses of the preterm infant. Am J Perinatol 2000;17:167-81.

12. Haynes RL, Baud O, Li J, Kinney HC, Volpe JJ, Folkerth DR. Oxidative and nitrative injury in periventricular leukomalacia: A review. Brain Pathol 2005;15:225-33.
13. Chow LC, Wright KW, Sola A; CSMC Oxygen Administration Study Group. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics 2003;111:339-45.
14. Saugstad OD. Bronchopulmonary dysplasia-oxidative stress and antioxidants. Semin Neonatol 2003;8:39-49.
15. Zhao M, Tang S, Xin J, Wei Y, Liu D. Reactive oxygen species induce injury of the intestinal epithelium during hyperoxia. Int J Mol Med 2018;41:322-30.
16. Chen CM, Chou HC. Hyperoxia disrupts the intestinal barrier in newborn rats. Exp Mol Pathol 2016;101:44-9.
17. Sukhotnik I, Brod V, Lurie M, Rahat MA, Shnizer S, Lahat N, *et al*. The effect of 100% oxygen on intestinal preservation and recovery following ischemia-reperfusion injury in rats. Crit Care Med 2009;37:1054-61.
18. Stenson BJ. Oxygen saturation targets for extremely preterm infants after the NeOProM trials. Neonatology 2016;109:352-8.
19. Bancalari E, Claure N. Control of oxygenation during mechanical ventilation in the premature infant. Clin Perinatol 2012;39:563-72.
20. Castillo A, Sola A, Baquero H, Neira F, Alvis R, Deulofeut R. *et al*. Pulse oxygen saturation levels and arterial oxygen tension values in newborns receiving oxygen therapy in the neonatal intensive care unit: Is 85% to 93% an acceptable range? Pediatrics 2008;121:882-9.
21. Chen ML, Guo L, Smith LE, Dammann CE, Dammann O. High or low oxygen saturation and severe retinopathy of prematurity: A meta-analysis. Pediatrics 2010;125:e1483-92.