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Publication Date

2019-06-01

DOI

10.1016/j.jpeds.2019.01.048

Peer reviewed



Published in final edited form as:

J Pediatr. 2019 June ; 209: 17–22.e2. doi:10.1016/j.jpeds.2019.01.048.

Association between Policy Changes for Oxygen Saturation Alarm Settings and Neonatal Morbidity and Mortality in Very Preterm Infants

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Portions of this study were presented as an abstract at the Pediatric Academic Societies annual meeting, May 6-9, 2017, San Francisco, California.

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Abstract

Objective: To determine the impact of policy changes for oxygen saturation (SpO₂) alarm limits on neonatal mortality and morbidity among very preterm infants.

Study design: Retrospective cohort study of very preterm infants in the NICHD Neonatal Research Network. Infants were classified based on treatment at a hospital with an SpO₂ alarm policy change and study epoch (before vs after policy change). We used a generalized linear mixed model to determine the effect of hospital group and epoch on the primary outcomes of mortality and severe retinopathy of prematurity (ROP) and secondary outcomes of necrotizing enterocolitis, bronchopulmonary dysplasia, and any ROP.

Results: There were 3,809 infants in 10 hospitals with an SpO₂ alarm policy change and 3,685 infants in 9 hospitals without a policy change. The nature of most policy changes was to narrow the SpO₂ alarm settings. Mortality was lower in hospitals without a policy change (adjusted Odds Ratio [aOR] 0.63; 95% Confidence Interval 0.50, 0.80) but did not differ between epochs in policy change hospitals. The odds of bronchopulmonary dysplasia were higher for hospitals with a policy change (aOR 1.65; 95% Confidence Interval 1.36, 2.00) but did not differ for hospitals without a policy change. Severe ROP and necrotizing enterocolitis did not differ between epochs for either group. The adjusted odds of any ROP were lower in recent years in both hospital groups.

Conclusion: Changing SpO₂ alarm policies was not associated with reduced mortality or increased severe ROP among very preterm infants.

Keywords

Preterm; oxygen saturation; mortality; retinopathy of prematurity

Oxygen is commonly used in the treatment of extremely preterm infants. Like many interventions, oxygen has a therapeutic window. Clinicians must titrate supplemental oxygen to provide adequate oxygen delivery to tissues while avoiding oxygen-related injury to developing organs. The optimal target pulse oximetry saturation (SpO₂) range to achieve this balance remains undefined.

Five large international randomized trials were undertaken to determine the impact of lower (85-89%) vs. higher (91-95%) SpO₂ target ranges on mortality and morbidity in extremely preterm infants.(1-3) None of these individual trials demonstrated superiority for either SpO₂ target with respect to the composite primary outcome of death or neurodevelopmental disability. However, the individual trials and pooled analysis of these trials suggest that there

is a tradeoff in secondary outcomes for either SpO₂ target.(4,5) Assignment to the higher SpO₂ target reduced the incidence of death and necrotizing enterocolitis, and assignment to the lower SpO₂ target reduced the incidence of severe retinopathy of prematurity (ROP).

These findings have led to continued debate regarding optimal SpO₂ targets in extremely preterm infants, (6) with many NICUs implementing changes to their SpO₂ targets.(7) Previous authors have reported higher rates of ROP following an increase in SpO₂ targets, (8) but this finding is not consistent.(9) Further, secular trends in infant demographics and clinical practice may influence clinical outcomes in a before/after study design, particularly in a single-site setting.

We designed the current multi-site study within the National Institute of Child Health and Human Development Neonatal Research Network (NRN) to investigate the interaction between changes in SpO₂ alarm limit policies in NRN hospitals and time (before/after policy changes). Our objective was to identify the association between changes in SpO₂ alarm limit policies on neonatal mortality and morbidity and supplemental oxygen exposure among very preterm infants.

Methods

This was a retrospective cohort study using prospectively collected data in the NRN Generic Database (GDB). We included infants in the GDB who were born between 1/1/2006-12/31/2014 with birth weight 401-1000 grams or gestational age <29 weeks and who were treated at a hospital that participated in the NRN continuously from 2006-2014. We excluded infants who were born during the study washout period (see Study Epoch Definition, below), infants who died within the first 12 hours of life (as they were not included in the GDB), infants with major congenital anomalies, infants who were born at referring hospitals and transferred to an NRN hospital (as these infants were not consistently enrolled in the GDB throughout the study period), and infants who had been identified as likely to be eligible for enrollment in SUPPORT(1) (Surfactant Positive Pressure and Pulse Oximetry Randomized Trial).

Each enrolled infant was classified on the basis of 2 exposures: treatment at a hospital with an SpO₂ alarm policy change during the study period, and the study epoch in which they were born (before or after policy change).

Policy Change Definition

We administered a questionnaire to NRN site principal investigators in October 2016 to identify hospitals that changed their SpO₂ alarm setting policy between 2006 and 2014. SpO₂ policies, including alarm settings, had to be clearly documented (such as within a practice standard). Because SpO₂ alarm settings may match or slightly exceed the extremes of the desired SpO₂ targets,(6) we characterized policies based on the presence of change in the SpO₂ alarm settings, not the specified SpO₂ targets. Hospitals with an SpO₂ alarm setting policy change during the study period were designated “policy change.” Hospitals without a policy change during the study period were classified “no policy change.”

Study Epoch Definition

For hospitals with a policy change, we defined the study epochs based on the date of the policy change for each individual hospital. We designated a 6-month period before and after the policy change as the “washout” period. For each of these hospitals, Epoch 1 was defined as 1/1/06 until 6 months prior to that hospital’s policy change, and Epoch 2 was defined as the interval starting 6 months after the hospital’s policy change until 12/31/14. Infants born during the 1-year washout period were not included in this analysis.

For hospitals without a policy change, we designated the calendar year 2010 (the year SUPPORT results became available) as the transition between Epoch 1 and 2. For those hospitals, we defined Epoch 1 as 1/1/06-12/31/09, and Epoch 2 as 1/1/11-12/31/14. Infants born during the 1-year washout period 1/1/10-12/31/10 were not included in this analysis.

Clinical Outcomes

The primary outcomes were mortality before hospital discharge, transfer, or 120 days of life for infants with longer hospitalization; severe ROP, defined as ROP treatment or retinal detachment in either eye. These were selected because of the observed tradeoff in the risks of these outcomes in the oxygen targeting randomized trials. Infants who were diagnosed with severe ROP prior to death were considered to have both primary outcomes. Each primary outcome was reported separately. Secondary outcomes included necrotizing enterocolitis stage 2 (10), any ROP, moderate/severe bronchopulmonary dysplasia (BPD) (NIH consensus definition (11)), supplemental oxygen use after discharge, and cumulative days on supplemental oxygen during the hospitalization among infants who survived to discharge.

Information on the highest FiO_2 level at pre-specified time points is recorded in the GDB. We examined the highest FiO_2 recorded on the following days: 24 hours, 3 days, 7 days, 14 days, and 28 days. We also assessed the highest FiO_2 across these time points; this analysis was restricted to infants who survived to 28 days to reduce bias introduced by early death.

Statistical Analyses

Our first objective was to assess the relationship between changes in SpO_2 alarm setting policies and changes in the primary and secondary outcomes between the study epochs. We used a generalized linear mixed model to explore the effect of instituting a change in hospital policy on the proportion of infants with each outcome between Epoch 1 and 2. Models included the hospital-level effect of policy change (yes/no), epoch, and the interaction between policy change and epoch. A significant interaction term would indicate that the difference in outcomes between Epoch 1 and 2 varied based on the hospital group (policy change or no policy change). We adjusted this analysis for the following infant-level characteristics: gestational age, birth weight, multiple gestation, antenatal steroid exposure, sex, race, ethnicity, intubation for resuscitation, small for gestational age status(12), and admission temperature(13). Although different infants were present during the two epochs, a random effect for hospital was included in the models to account for the fact that infants treated at the same hospital may have more similar outcomes.

Our second objective was to examine the relationship between instituting a change in SpO₂ alarm settings, epoch, and supplemental oxygen exposure in extremely preterm infants. Because the highest FiO₂ variable was highly skewed, with a large number of infants whose highest FiO₂ was 0.21, we modeled a dichotomous variable, highest FiO₂>0.21, based on hospital groupings and epochs. This analysis used a similar generalized linear mixed model and adjusted for the same covariates. *P* values < .05 were considered statistically significant, and hospital policy change (yes/no) and epoch interaction terms with *p*-values <0.05 were considered evidence of an epoch effect that differed between the two hospital groupings. No adjustment was made for multiple comparisons. Only non-missing data were included in analysis; statistical modeling methods assumed missing data were missing at random. All analyses were performed using SAS 9.4.

Results

There were 19 NRN hospitals with continuous participation in the GDB between 2006-2014. Of these, 10 changed the policy for SpO₂ alarm settings, and 9 did not change the policy during the study period. Among hospitals with a SpO₂ policy change, the median SpO₂ alarm limits transitioned from 85% (lower) and 96% (upper) to revised median limits of 89% (lower) and 95% (upper) (Figure 1). Among hospitals without a SpO₂ alarm policy change, the median SpO₂ alarm limits were 88% (lower) and 95% (upper).

Of 7,494 infants included in this study (Figure 2; available at www.jpeds.com), there were 3,809 infants in hospitals with a SpO₂ alarm policy change and 3,685 infants in hospitals without a policy change. Differences in demographic characteristics between epochs for each group of hospitals are shown in Table I. Mortality did not significantly differ between epochs for infants in hospitals with a SpO₂ alarm policy change, and mortality was significantly lower in Epoch 2 for infants in hospitals without a SpO₂ alarm policy change (Table 2). Severe ROP did not significantly differ between epochs for either group.

For infants in hospitals with a SpO₂ alarm policy change, the adjusted odds of BPD were significantly higher in Epoch 2. There was no difference in BPD between epochs among infants in hospitals without a SpO₂ alarm policy change. Necrotizing enterocolitis did not differ between epochs for either group. There was a reduction in the adjusted odds of any ROP in Epoch 2 for both groups of hospitals. The interaction term between epoch and hospital group was not significant for this outcome, indicating that the reduction in ROP between study epochs did not vary based on hospital group.

There was no significant interaction between hospital group and epoch for the outcomes of cumulative oxygen exposure or supplemental oxygen use after discharge. Averaged across both groups of hospitals, infants born in Epoch 2 who survived to discharge had longer exposure to supplemental oxygen (mean difference 2.79 days; 95% Confidence Interval [CI] 1.30, 4.28; *p*-value <0.001) and were more likely to be discharged home on supplemental oxygen (adjusted Odds Ratio 1.28; 95% CI 1.05, 1.57; *p*-value=0.015).

For both groups of hospitals, the adjusted odds of highest FiO₂ >0.21 at 14 and 28 days of life were higher in Epoch 2. There was no significant interaction between epoch and hospital

group for those individual time points. However, there was a significant interaction between hospital and epoch for the combined variable of highest $\text{FiO}_2 > 0.21$ across the first 28 days of life (Table 3).

Discussion

The target SpO_2 values to optimize outcomes for preterm infants remains a topic of active debate, with some authors uniformly advocating a higher SpO_2 target range.(14) Given the wide variation in SpO_2 targets employed across neonatal intensive care units,(15) reflexively implementing these higher targets would imply a change in oxygen targeting policies for many hospitals. We sought to determine the impact of changing SpO_2 alarm settings for preterm infants on neonatal mortality and morbidity. In the post SUPPORT era, half of NRN hospitals revised their policy for SpO_2 alarm settings and the other half made no changes. Among NRN hospitals that revised their oxygen saturation policy, the nature of most of these changes was to narrow the range of SpO_2 alarm settings, consistent with other reports. (7) We found no evidence that modifying the SpO_2 alarm setting policy reduced mortality or increased severe ROP. Supplemental oxygen exposure was higher in Epoch 2 in both groups of hospitals, but this finding was not significantly associated with a policy change in SpO_2 alarm settings.

Manley et al reported their single-center experience of 346 preterm infants after increasing SpO_2 targets from 88-92% to 91-95%. ROP was significantly more frequent among infants born after the SpO_2 target change, and mortality rates did not significantly differ.(8) Other authors have not observed significant differences in neonatal morbidity following changes to SpO_2 target policies.(9) The impact of changing SpO_2 alarm limits on clinical outcomes in a given setting likely depends on many factors, such as local baseline outcome rates.

Secular trends in infant demographics and clinical practice make it difficult to isolate the impact of a given change in practice on clinical outcomes in a single site before/after study. Due to our multisite study design, we were able to assess the interaction between epochs and hospital grouping in order to better account for concurrent secular trends. Previous authors have described decreasing mortality over time among extremely preterm infants.(16–18) Similarly, we observed a reduction in mortality in Epoch 2 among hospitals without a hospital policy change - where a wider range of acceptable SpO_2 alarm limits was retained. Conversely, the adjusted odds of BPD were significantly higher in Epoch 2 for hospitals where SpO_2 alarm settings were revised. The interaction between instituting a policy change and epoch was significant for both of these outcomes. We speculate that additional unmeasured differences in infant demographics and hospital practice may have contributed to these study findings. Nonetheless, our results do not suggest that changing SpO_2 alarm settings alone led to a significant benefit in neonatal outcomes.

Use of supplemental oxygen was assessed in multiple ways. More infants were exposed to $\text{FiO}_2 > 0.21$ at 14 and 28 days of life in Epoch 2 in both hospital groups. In addition, the cumulative duration of oxygen exposure and use of supplemental oxygen after discharge were both increased in Epoch 2 for both groups of hospitals. Although we adjusted for changes in important baseline characteristics, other unmeasured differences in patient

demographics may have contributed to increased oxygen use in Epoch 2. In addition, we speculate that the lower mortality rate in Epoch 2 within hospitals without an SpO₂ alarm policy change may have led to increased supplemental oxygen use among survivors. Despite the fact that supplemental oxygen use increased, we did not find any evidence of increased rates of severe ROP in Epoch 2 for infants born in either group of hospitals, and rates of any ROP were lower in Epoch 2 for both groups.

This analysis was restricted to SpO₂ policies in the neonatal intensive care unit setting. We did not account for changes in delivery room oxygen management following changes to neonatal resuscitation treatment recommendations in 2010.(19) Reassuringly, a meta-analysis of randomized trials comparing high versus low initial FiO₂ for delivery room resuscitation of infants <28 weeks gestation found no significant differences in clinical outcomes of death, ROP, or BPD.(20)

Study limitations include the observational study design. Although we accounted for important baseline demographic characteristics and interventions that changed between epochs, it is possible that other secular trends in practice at participating hospitals influenced the study results. In addition, we recognize that hospitals may vary in terms of how strictly the alarm policies were followed (15) or how tightly infants' SpO₂ levels were maintained within set alarm limits.(21) Finally, we classified hospitals based on a change to the SpO₂ alarm settings and not the absolute values of the alarm limits. Our objective was not to determine the impact of specific SpO₂ targets on patient outcomes. This question, addressed in the pooled analysis of 5 RCTs in the NeOProm collaboration, is unlikely to be answered in an observational study.

In conclusion, we did not find evidence that narrowing SpO₂ alarm limits had a significant impact on neonatal mortality or severe ROP among more than 7,000 extremely preterm infants in the NICHD NRN. These results suggest that changing policies for oxygen saturation alarm settings alone may not confer a significant benefit on preterm infants' outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr Abhik Das (DCC Principal Investigator), Dr Marie Gantz (DCC Statistician) and Mr Benjamin Carper (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

Supported by the National Institutes of Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (K23HD084727 to EEF). In addition, the National Institutes of Health, the NICHD, the National Center for Research Resources, and the National Center for Advancing Translational Sciences provided grant support for the Neonatal Research Network's Generic Database Study through cooperative agreements (U10 HD27904, U10 HD21364, M01 RR80, U10 HD27853, M01 RR8084, U10 HD40492, UL1

TR1117, M01 RR30, UL1 TR1111, U10 HD27851, M01 RR39, U10 HD27856, M01 RR750, U10 HD21373, U10 HD36790, U10 HD27880, M01 RR70, U10 HD34216, M01 RR32, U10 HD53109, M01 RR59, U10 HD53089, M01 RR997, U10 HD40689, M01 RR633, U10 HD21385). Although the NICHD staff did have input into the study design, conduct, analysis, and manuscript drafting, the content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors declare no conflicts of interest.

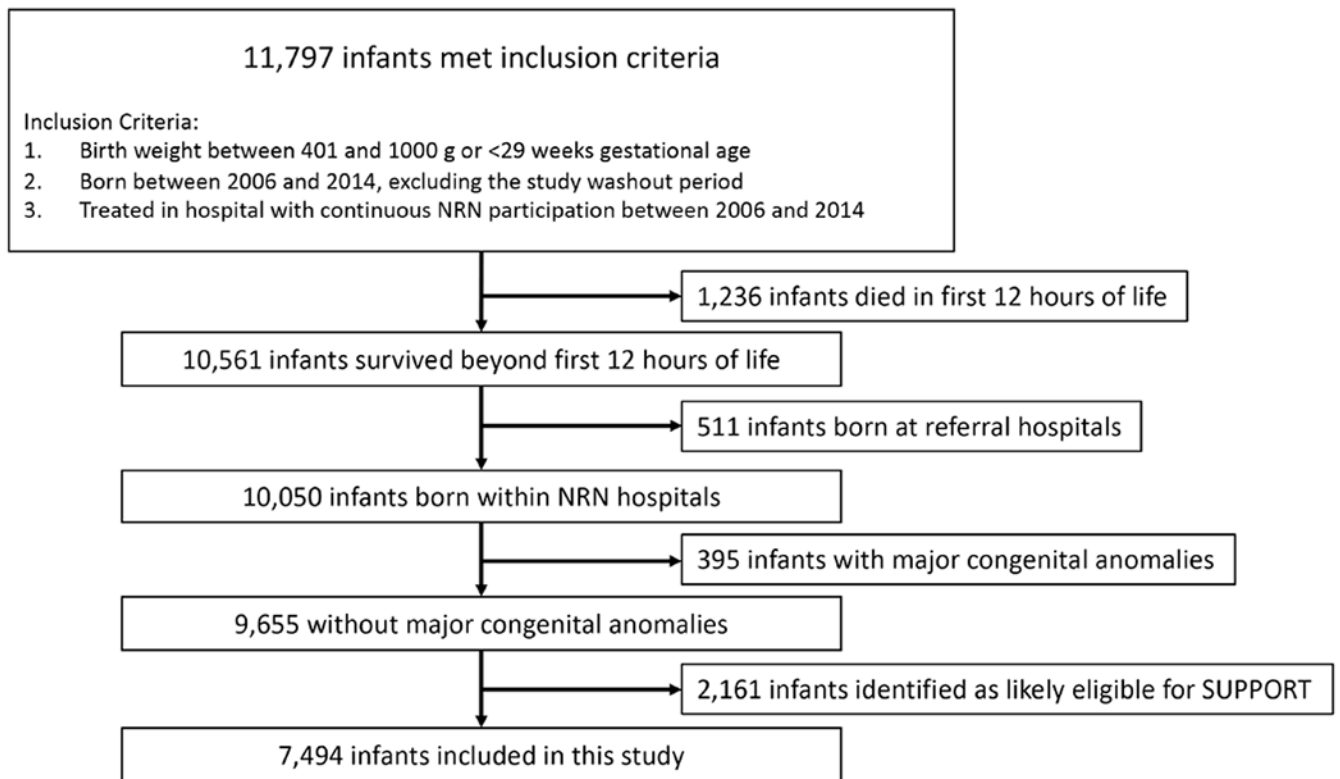
Abbreviations:

BPD:	bronchopulmonary dysplasia
CI:	confidence interval
FiO₂:	fraction of inspired oxygen
GDB:	Generic Database
NRN:	Neonatal Research Network
ROP:	retinopathy of prematurity
SpO₂:	pulse oximetry oxygen saturation

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**Figure 2.**

Study Flow Diagram.

NRN: Neonatal research network; SUPPORT: Surfactant Positive Pressure and Pulse Oximetry Randomized Trial

Table 1:

Baseline maternal and infant characteristics

Characteristic	Infants in hospitals with SpO ₂ alarm policy change (n=3809)			Infants in hospitals with no SpO ₂ alarm policy change (n=3685)		
	Epoch 1 n=1981	Epoch 2 n=1828	P value	Epoch 1 n=1620	Epoch 2 n=2065	P-value
Antenatal Steroids	1599/1977 (80.9%)	1676/1826 (91.8%)	<0.001	1387/1605 (86.4%)	1892/2063 (91.7%)	<0.001
Race			0.002			0.13
Black	816/1949 (41.9%)	816/1756 (46.5%)		724/1598 (45.3%)	867/2053 (42.2%)	
White	1046/1949 (53.7%)	830/1756 (47.3%)		746/1598 (46.7%)	1043/2053 (50.8%)	
Other	87/1949 (4.5%)	110/1756 (6.3%)		128/1598 (8.0%)	143/2053 (7.0%)	
Hispanic	424/1959 (21.6%)	276/1823 (15.1%)	<0.001	195/1464 (13.3%)	266/2035 (13.1%)	0.83
Multiple gestation	451/1981 (22.8%)	442/1828 (24.2%)	0.30	445/1620 (27.5%)	576/2065 (27.9%)	0.78
Gestational age, weeks; mean (SD)	26.7 (2.1)	26.2 (2.0)	<0.001	26.8 (2.0)	26.3 (1.9)	<0.001
Birth weight, grams; mean (SD)	891 (245)	840 (237)	<0.001	906 (240)	870 (233)	<0.001
Male sex	995/1981 (50.2%)	944/1828 (51.6%)	0.38	811/1620 (50.1%)	1064/2065 (51.5%)	0.38
SGA	337/1981 (17.0%)	294/1828 (16.1%)	0.44	246/1620 (15.2%)	282/2065 (13.7%)	0.19
Delivery room intubation	1158/1981 (58.5%)	1040/1827 (56.9%)	0.34	997/1620 (61.5%)	1286/2065 (62.3%)	0.65
Admission temperature, °F; mean (SD)	97.5 (1.6)	97.7 (1.3)	<0.001	96.9 (1.9)	97.6 (1.6)	<0.001

Abbreviations: F: Fahrenheit; SD: standard deviation; SGA: small for gestational age; SpO₂: oxygen saturation

Table 2:

Changes in outcomes between epochs for infants in hospitals with and without a SpO₂ alarm policy change.

Outcome	Infants in hospitals with SpO ₂ alarm policy change (n=3809)			Infants in hospitals with no SpO ₂ alarm policy change (n=3685)			Adjusted Interaction P-value
	Epoch 1 n=1981	Epoch 2 n=1828	aOR or Mean Difference (95% CI) [*]	Epoch 1 n=1620	Epoch 2 n=2065	aOR or Mean Difference (95% CI) [*]	
Mortality	297/1979 (15.0%)	324/1828 (17.7%)	0.94 (0.75, 1.18)	269/1615 (16.7%)	280/2061 (13.6%)	0.63 (0.50, 0.80)	0.01
Severe ROP	127/1703 (7.5%)	126/1535 (8.2%)	1.09 (0.78, 1.52)	88/1300 (6.8%)	127/1746 (7.3%)	0.91 (0.64, 1.29)	0.46
Necrotizing enterocolitis	245/1980 (12.4%)	250/1827 (13.7%)	0.96 (0.78, 1.20)	210/1620 (13.0%)	250/2065 (12.1%)	0.83 (0.67, 1.04)	0.35
BPD	592/1722 (34.4%)	700/1541 (45.4%)	1.65 (1.36, 2.00)	443/1343 (33.0%)	794/1797 (44.2%)	1.21 (0.99, 1.48)	0.03
Any ROP	829/1703 (48.7%)	655/1535 (42.7%)	0.71 (0.59, 0.86)	706/1300 (54.3%)	935/1746 (53.6%)	0.57 (0.47, 0.69)	0.11
Cumulative days on supplemental O ₂ (days), mean (SD) ^{**}	43.5 (39.8)	53.2 (42.5)	3.87 (1.80, 5.94)	39.5 (37.2)	49.8 (40.3)	1.70 (-0.038, 3.79)	0.14
Discharged home on O ₂ ^{**}	161/1395 (11.5%)	201/1113 (18.1%)	1.47 (1.09, 1.99)	223/1183 (18.9%)	331/1357 (24.4%)	1.12 (0.86, 1.45)	0.17

Abbreviations: aOR: adjusted Odds Ratio; BPD: bronchopulmonary dysplasia; CI: confidence interval; ROP: retinopathy of prematurity; SD: standard deviation; SpO₂: oxygen saturation

* Analyses adjusted for gestational age, birth weight, multiple gestation, antenatal steroids, sex, race, ethnicity, delivery room intubation, small for gestational age status, and admission temperature

** Among infants who survived to discharge

Table 3:

Change in supplemental oxygen exposure at specified time points between epochs for infants in hospitals with and without an oxygen saturation alarm policy change.

FiO ₂ >0.21 at time point	Infants in hospitals with SpO ₂ alarm policy change (n=3809)			Infants in hospitals with no SpO ₂ alarm policy change (n=3685)			Adjusted Interaction P-value
	Epoch 1 n=1981	Epoch 2 n=1828	aOR (95% CI) *	Epoch 1 n=1620	Epoch 2 n=2065	aOR (95% CI) *	
24 hours	1193/1952 (61.1%)	1199/1802 (66.5%)	1.00 (0.85, 1.17)	845/1582 (53.4%)	1133/2031 (55.8%)	1.08 (0.92, 1.27)	0.475
Day 3	1381/1923 (71.8%)	1403/1788 (78.5%)	1.15 (0.96, 1.39)	1010/1553 (65.0%)	1410/2020 (69.8%)	1.17 (0.99, 1.40)	0.881
Day 7	1010/1835 (55.0%)	1103/1718 (64.2%)	1.16 (0.96, 1.40)	694/1454 (47.7%)	1061/1956 (54.2%)	0.98 (0.81, 1.18)	0.215
Day 14	1005/1681 (59.8%)	1131/1647 (68.7%)	1.25 (1.01, 1.54)	697/1313 (53.1%)	1282/1889 (67.9%)	1.60 (1.30, 1.96)	0.096
Day 28	878/1570 (55.9%)	1042/1577 (66.1%)	1.28 (1.04, 1.59)	556/1165 (47.7%)	1163/1819 (63.9%)	1.68 (1.35, 2.09)	0.083
Across the first 28 days **	1408/1767 (79.7%)	1380/1593 (86.6%)	1.29 (1.02, 1.63)	1051/1416 (74.2%)	1584/1850 (85.6%)	1.79 (1.44, 2.23)	0.045

Abbreviation: aOR: adjusted odds ratio; CI: confidence interval; FiO₂: fraction of inspired oxygen; SpO₂: oxygen saturation

* Analyses adjusted for gestational age, birth weight, multiple gestation, antenatal steroids, sex, race, ethnicity, delivery room intubation, small for gestational age status, and admission temperature

** among infants who survived to 28 days of life