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Effects of Targeting Higher vs Lower Arterial Oxygen Saturations on Death or Disability in Extremely Preterm Infants

A Randomized Clinical Trial

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Importance The goal of oxygen therapy is to deliver sufficient oxygen to the tissues while minimizing oxygen toxicity and oxidative stress. It remains uncertain what values of arterial oxygen saturations achieve this balance in preterm infants.

Objective To compare the effects of targeting lower or higher arterial oxygen saturations on the rate of death or disability in extremely preterm infants.

Design, Setting, and Participants Randomized, double-blind trial in 25 hospitals in Canada, the United States, Argentina, Finland, Germany, and Israel in which 1201 infants with gestational ages of 23 weeks 0 days through 27 weeks 6 days were enrolled within 24 hours after birth between December 2006 and August 2010. Follow-up assessments began in October 2008 and ended in August 2012.

Interventions Study participants were monitored until postmenstrual ages of 36 to 40 weeks with pulse oximeters that displayed saturations of either 3% above or below the true values. Caregivers adjusted the concentration of oxygen to achieve saturations between 88% and 92%, which produced 2 treatment groups with true target saturations of 85% to 89% (n=602) or 91% to 95% (n=599). Alarms were triggered when displayed saturations decreased to 86% or increased to 94%.

Main Outcomes and Measures The primary outcome was a composite of death, gross motor disability, cognitive or language delay, severe hearing loss, or bilateral blindness at a corrected age of 18 months. Secondary outcomes included retinopathy of prematurity and brain injury.

Results Of the 578 infants with adequate data for the primary outcome who were assigned to the lower target range, 298 (51.6%) died or survived with disability compared with 283 of the 569 infants (49.7%) assigned to the higher target range (odds ratio adjusted for center, 1.08; 95% CI, 0.85 to 1.37; $P=.52$). The rates of death were 16.6% for those in the 85% to 89% group and 15.3% for those in the 91% to 95% group (adjusted odds ratio, 1.11; 95% CI, 0.80 to 1.54; $P=.54$). Targeting lower saturations reduced the postmenstrual age at last use of oxygen therapy (adjusted mean difference, −0.8 weeks; 95% CI, −1.5 to −0.1; $P=.03$) but did not alter any other outcomes.

Conclusion and Relevance In extremely preterm infants, targeting oxygen saturations of 85% to 89% compared with 91% to 95% had no significant effect on the rate of death or disability at 18 months. These results may help determine the optimal target oxygen saturation.

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EXTREMELY PRETERM INFANTS are monitored with pulse oximeters for several weeks after birth because they may require supplemental oxygen intermittently or continuously. The goal of oxygen therapy is to deliver sufficient oxygen to the tissues while minimizing oxygen toxicity and oxidative stress. It remains uncertain what values of arterial oxygen saturations achieve this balance in immature infants, who are especially vulnerable to the harmful effects of oxygen.[1-7]

Oxygen therapy for preterm infants was introduced in the 1940s. In the 1950s, after approximately 10 000 preterm children had been blinded, randomized trials confirmed that liberal oxygen therapy may cause retinopathy of prematurity.[8] In the 1960s, oxygen therapy was restricted and many nurseries adopted arbitrary upper limits for

For editorial comment see p 2161.

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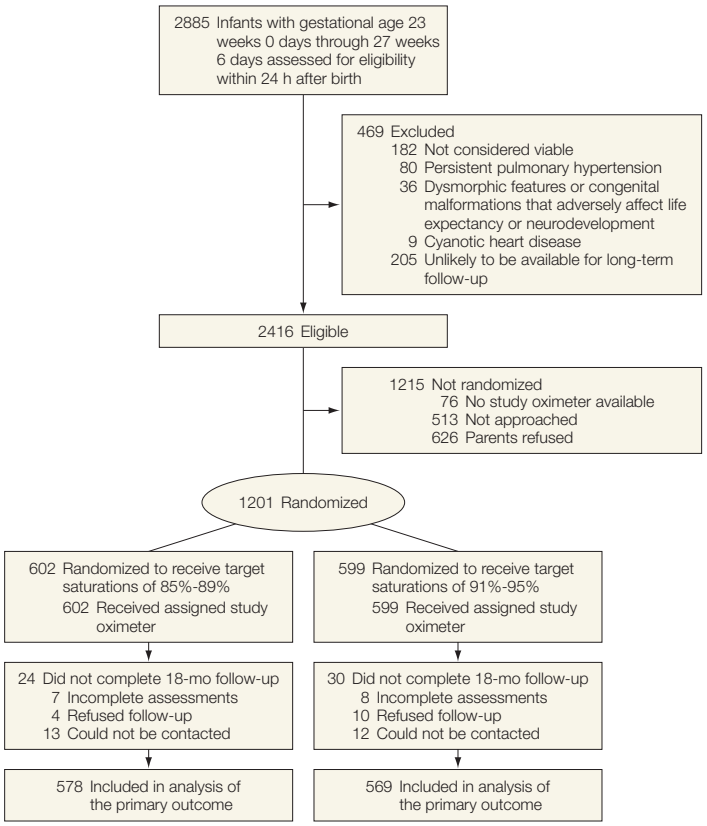
Figure 1. Canadian Oxygen Trial Study Flow Diagram



Infants could be excluded for more than 1 reason. Eligible infants had to be randomized within the first 24 hours of life. "Not approached" included situations in which, within this time limit, families could not be convened to discuss consent or were judged to be too stressed to be approached for consent, or no skilled research staff were available to elicit informed consent.

the concentration of inspired oxygen.[2,8] Since then, periods of liberal oxygen use have alternated with periods of restricted use as clinicians searched for the right balance between the competing risks of oxygen excess and oxygen deprivation.[1-3,8-10] More recently, investigators in England compared outcomes of extremely preterm infants in 4 neonatal units with different target ranges for oxygen saturations. The rates of retinopathy, chronic lung disease, and poor weight gain were lowest in the unit with the most restricted oxygen policy, whereas mortality was not increased.[11]

Between 2005 and 2007, 5 randomized trials were initiated to resolve the long-standing uncertainty of how to titrate oxygen therapy in extremely preterm infants. All trials examined the efficacy and safety of decreasing the concentration of supplemental oxygen to target arterial oxygen saturations of 85% to 89% compared with 91% to 95%.[12] In the US Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT), severe retinopathy was reduced but mortality increased in the lower saturation target group.[13] There was no difference between the 2 groups in the composite outcome of death or neurodevelopmental impairment at 18 months.[14] Recruitment in the Australian and UK trials was terminated early after an interim subgroup analysis showed that infants who were monitored with oximeters that contained revised software had an increased survival with the higher saturation target range.[15]

We report the results of the Canadian Oxygen Trial (COT), in which we compared the effects of targeting lower or higher oxygen saturations in extremely preterm infants on the rate of death or disability at 18 months.

METHODS

This randomized and parallel double-blind trial was conducted in 25 hospitals in Canada, the United States, Argentina, Finland, Germany, and Israel. Enrollment began on December 24, 2006, and ended on August 25, 2010. Follow-up assessments were performed between October 17, 2008, and August 15, 2012. The research ethics boards of all clinical centers approved the protocol and written informed consent was obtained from a parent or guardian of every study infant.

An independent data and safety monitoring board reviewed the study data annually during the enrollment phase. Interim analyses of efficacy were not planned because it was anticipated that recruitment would be completed before the primary outcome at 18 months had been assessed in sufficient numbers of patients. After the early termination of recruitment in the Australian and UK trials in December 2010,[15] our data and safety monitoring board requested mortality data by treatment group (A vs B) and oximeter software (original vs revised). The board concluded on January 27, 2011, that it had found "nothing in the COT mortality data that raises any safety concerns." Therefore, the steering committee decided to complete the ascertainment of the primary outcome before analyzing any trial data.

Participants

Infants with gestational ages of 23 weeks 0 days through 27 weeks 6 days were eligible for enrollment during the first 24 hours after birth. The reasons for exclusion are listed in FIGURE 1. Race or ethnic group was self-reported, with predetermined options to characterize the population.

Randomization

A computer-generated randomization scheme was produced by an indepen-

dent statistician at the coordinating center to assign the infants to treatment groups in a 1:1 ratio. Randomization was stratified by study center and balanced within randomly sized blocks of 2 or 4 patients. Siblings of multiple births were randomized individually. Study oximeters were labeled with sequential participant numbers according to the randomization scheme. The allocation remained unknown to the members of the clinical and research teams and all staff at the coordinating center.

Interventions

Pulse oximeters were leased from Masimo Corporation. The oximeters were modified to display and store oxygen saturations that were either 3% higher or lower than the true values. True values were displayed if the measured values decreased below 84% or increased above 96%.[13] Caregivers were instructed to adjust the concentration of oxygen to maintain saturation values between 88% and 92%, which produced 2 treatment groups with true target saturations of 85% to 89% or 91% to 95%. Alarms were triggered when the displayed saturations decreased to 86% or increased to 94%. During times without oxygen therapy, the upper alarm was disabled. The averaging time was set to 16 seconds.[16,17] Between February 12 and June 26, 2009, a technician from the coordinating center installed revised software on site in all study oximeters.[18]

To maintain masking, a 5-minute period without pulse oximetry was observed when infants were transferred from unmodified to study oximeters and vice versa. Study oximetry was continued until 36 weeks of postmenstrual age even if an infant was not receiving supplemental oxygen. Infants who were receiving any respiratory support including oxygen therapy at 35 weeks of postmenstrual age were monitored with their assigned study oximeter until a postmenstrual age of 40 weeks. Study oximetry was stopped earlier if infants were discharged home. All other aspects of respiratory management, such as ventilatory rate and airway pressures, were determined by the clinicians caring for the infants. The oxygen saturation data were stored every 10 seconds. Designated research staff in the clinical centers downloaded and submitted these data to the coordinating center after the first 3 study days and every 3 to 4 weeks thereafter until study oximetry was discontinued. During the first 3 days, caregivers recorded every change in the concentration of oxygen, which enabled the coordinating center to remove all saturations from the downloaded data that were obtained while the concentration of inspired oxygen was 21% and to provide monthly feedback to the clinical centers on their ability to maintain the displayed saturations within the study alarm limits during times of oxygen therapy. After the first 3 days, we recorded daily whether the infant received more than 12 hours of oxygen therapy.[19] Downloaded data on those days may include up to 12 hours per day of saturations obtained during times without supplemental oxygen.

Primary Outcome

The primary outcome was death before a corrected age of 18 months or survival with one or more of the following: gross motor disability, cognitive or language delay, severe hearing loss, and bilateral blindness. Motor disability was defined as a level of 2 or higher according to the Gross Motor Function Classification System.[20] A normal level is assigned if the child walks 10 steps independently at 18 months. Levels between 2 and 5 indicate increasingly serious limitations of gross motor function. Cognitive or language delay was defined as a composite cognitive or language score of less than 85 (1 SD below the mean of 100) on the Bayley Scales of Infant and Toddler Development, Third Edition.[21] The protocol was amended in February 2010 to change the definition of delay from 2 to 1 SD below the mean because the third edition of this test was found to significantly underestimate developmental delay.[22] The cognitive score was assumed to be less than 85 if the child could not be tested because of severe developmental delay or autism. Severe hearing loss was defined as the prescription of hearing aids or cochlear implants and bilateral blindness was a corrected visual acuity less than 20/200 in the better eye. Follow-up was targeted for a corrected age of 18 months, with a window of 18 to 21 months. Efforts to conduct assessments continued beyond this window when necessary.

Because a single missing component of the follow-up assessment may lead to the exclusion of an infant from the analysis of the composite primary outcome, we developed a priori criteria to determine what constituted "adequate evidence" for the presence or absence of each component. These criteria included the successful completion of the cognitive and language subtests. For infants with tracheostomies (n=3), only the receptive language score was used. When the language subtest was missing because of unavailability of an objective interpreter (n=2) or failure to administer this subtest (n=2), we used only the cognitive composite score in the analysis of the primary outcome.

Secondary Outcomes

Secondary prespecified neonatal outcomes included retinopathy of prematurity, brain injury, patent ductus arteriosus, necrotizing enterocolitis, bronchopulmonary dysplasia, and the duration of use of positive airway pressure and supplemental oxygen. Screening of all study infants for retinopathy was expected to be performed according to current guidelines.[23] Severe retinopathy was defined as unilateral or bilateral disease of stages 4 or 5. Infants were also classified as having severe retinopathy if they received cryotherapy or laser therapy in at least 1 eye or if they received retinal injection with bevacizumab or another anti–vascular endothelial growth factor agent. For infants who were discharged before the complete progression and subsequent regression of retinopathy, the worst disease stage and any retinal therapy received were documented during the follow-up visit. Cranial ultrasonography

was recommended during the first week of life, between the 14th and 28th days of life, and between 34 and 36 weeks' postmenstrual age. The following lesions were analyzed as a group because they are all indicative of brain injury: intraparenchymal echodense lesions (grade 4 hemorrhage), cystic periventricular leukomalacia, porencephalic cysts, and ventriculomegaly with or without intraventricular hemorrhage. We recorded drug and surgical therapies for a patent ductus arteriosus. Necrotizing enterocolitis was diagnosed during surgery, at autopsy, or by a finding of pneumatosis intestinalis, hepatobiliary gas, or free intraperitoneal air on radiography. Severe bronchopulmonary dysplasia was defined as the use of positive airway pressure or at least 30% supplemental oxygen at a postmenstrual age of 36 weeks after at least 28 days of oxygen therapy for more than 12 hours per day.[19]

Prespecified secondary outcomes at 18 months included a history of hospital readmissions for respiratory disease and of chronic use of respiratory medications, growth, and mean composite cognitive, language, and motor scores.[21] Individual percentiles for height, weight, and head circumference were computed in the coordinating center according to the corrected age at the measurements.[24]

Statistical Analysis

We estimated an event rate for the primary outcome in the higher saturation target group of no less than 30% and no more than 50%, and we wanted to be able to detect a relative risk reduction of at least 25%. For an event rate of 50%, we needed 600 infants in each group to detect a 19% relative reduction in the risk of death or disability with a statistical power of 90%. The analyses of all dichotomous outcomes were adjusted with a logistic regression model that included terms for treatment and center. Results from small centers with fewer than 20 infants with known outcome were combined. The regression coefficient associated with treatment in the fitted model yielded a point estimate and 95% CI for the treatment effect expressed as an odds ratio (OR). In a prespecified subgroup analysis, we compared the size of the treatment effect between the original and revised oximeter software by adding an indicator variable for the software version and the product of treatment and software version (interaction term) to the logistic model. Cumulative mortality curves were estimated with the Kaplan-Meier method, with survival censored on the date of last contact for infants who did not return at 18 months. The mean differences between the treatment groups for quantitative outcomes were adjusted for center with the use of multiple linear regressions. Two post hoc analyses of the primary outcome were conducted. The consistency of treatment effects over centers was examined by adding treatment × center interaction terms to the logistic model, which included treatment and center effects. The change in log likelihood provides a global test of homogeneity of treatment effect over centers. We used SAS GENMOD with birth siblings included as repeated observations to formally allow for any intercorrelation between siblings via the generalized estimating equations approach.

We used the downloaded saturation data to characterize every infant's oxygen saturation values. After converting displayed to true saturation by reversing the offset algorithm, the median saturation and percentages of time spent above and below various saturation values were calculated for every infant during exact times of oxygen therapy on study days 1 through 3 and for all days with more than 12 hours of supplemental oxygen. All *P* values were 2-sided and considered significant if $P < .05$. SAS version 9.2 was used for all statistical analyses. All outcome analyses followed the principle of intention-to-treat. We did not impute missing outcomes. We chose a composite primary outcome to protect against the problems of multiple testing. Additional adjustments for multiple comparisons were not made.

RESULTS

Participants

Of the 1201 infants enrolled, 1147 (95.5%) had adequate data for the analysis of the composite primary outcome at 18 months (Figure 1). The characteristics of these 1147 children and their families are shown in TABLE 1. Apart from the frequencies of surfactant administration and oxygen therapy before randomization, the characteristics were similar in both groups.

Study Oximetry

Study oximetry was continued until a median postmenstrual age of 36.6 weeks (interquartile range, 35.9-40.0 weeks) and 37.1 weeks (interquartile range, 35.9-40.0 weeks) for infants assigned to the lower and higher saturation target ranges, respectively. eTable 1 (available at www.jama.com) shows the duration of study oximetry in subgroups of infants according to the reasons for removal of the study oximeter. The median of the individual study participants' oxygen saturations on days with more than 12 hours of oxygen therapy was 90.9% in the lower target group (interquartile range, 89.6%-92.5%) and 93.4% in the higher target group (interquartile range, 92.7%-94.2%) (eTable 2; $P < .001$). The percentage of time individual infants spent with very low and very high oxygen saturations also differed significantly between the 2 groups (eTable 2). The replacement of the original with the revised oximeter software was not associated with improved targeting of the oxygen saturation values (eTable 2). On days 1 through 3, when the comparison of the oxygen saturations between the 2 groups could be limited to exact times spent receiving supplemental oxygen, the separation between the treatment groups was greater than on days with more than 12 hours of oxygen therapy (FIGURE 2). The latter analysis included saturation data from times when the inspired concentration of oxygen was 21% and therefore not modifiable.

Primary Outcome

The results for the primary composite outcome and for its components

are shown in TABLE 2. Targeting lower compared with higher oxygen saturations had no significant effect on the rate of death or disability at 18 months. Of the 578 infants with data for this outcome who were assigned to the lower target range, 298 (51.6%) died or survived with disability compared with 283 of the 569 infants (49.7%) assigned to the higher target range (OR adjusted for center, 1.08; 95% CI, 0.85 to 1.37;

Table 1. Characteristics of the Children and Their Families

Characteristics	Analysis Cohort, No. (%)[a]			Randomized Cohort, No. (%)	
	Target Saturation 85%-89% (n = 578)	Target Saturation 91%-95% (n = 569)	*P* Value	Target Saturation 85%-89% (n = 602)	Target Saturation 91%-95% (n = 599)
Mothers at birth					
Age, mean (SD), y	30.9 (6.3)	30.7 (6.2)	.63	30.9 (6.3)	30.7 (6.2)
Race or ethnic group[b]					
White	389 (67.3)	389 (68.4)	.85	400 (66.4)	402 (67.1)
Black	94 (16.3)	95 (16.7)		99 (16.4)	103 (17.2)
Asian	62 (10.7)	52 (9.1)		63 (10.5)	56 (9.3)
Other or unknown	33 (5.7)	33 (5.8)		40 (6.6)	38 (6.3)
Antenatal corticosteroids[c]	509 (88.2)	511 (90.0)	.35	531 (88.4)	537 (89.8)
Cesarean delivery	362 (62.6)	338 (59.4)	.28	377 (62.6)	355 (59.3)
Infants at birth					
Birth weight, mean (SD), g	827 (190)	844 (199)	.15	829 (188)	845 (197)
Gestational age, mean (SD), wk	25.6 (1.2)	25.6 (1.2)	.93	25.6 (1.2)	25.6 (1.2)
Female sex	257 (44.5)	261 (45.9)	.64	273 (45.3)	273 (45.6)
Birth weight <10th percentile for gestational age[d]	54 (9.3)	49 (8.6)	.68	54 (9.0)	51 (8.5)
Born at study hospital	538 (93.1)	516 (90.7)	.16	562 (93.4)	543 (90.7)
Singleton birth	383 (66.3)	392 (68.9)	.34	396 (65.8)	417 (69.6)
Apgar score at 5 min, median (IQR)	7 (6-8)	7 (6-8)	.52	7 (6-8)	7 (6-8)
Chest compressions in the delivery room	37 (6.4)	47 (8.3)	.26	38 (6.3)	49 (8.2)
First temperature after admission, mean (SD), °C	36.5 (0.9)	36.4 (0.8)	.21	36.4 (0.9)	36.4 (0.8)
Infants at randomization					
Age at randomization, median (IQR), h	17.5 (11.5-21.7)	18.4 (12.2-22.5)	.08	17.3 (11.4-21.7)	18.6 (12.2-22.5)
Supplemental oxygen	215 (37.2)	245 (43.1)	.05	223 (37.0)	256 (42.7)
Any use of positive airway pressure	566 (97.9)	548 (96.3)	.11	590 (98.0)	577 (96.3)
Endotracheal tube in situ	458 (79.2)	428 (75.2)	.11	477 (79.2)	448 (74.8)
Received surfactant	517 (89.4)	482 (84.7)	.02	539 (89.5)	508 (84.8)
Status at follow-up[e]					
Corrected age of surviving children at follow-up, median (IQR), mo	18.6 (18.2-19.5)	18.6 (18.2-19.6)	.79		
Primary caregiver[e,f]					
Level of education					
Did not finish high school	54 (11.2)	54 (11.2)	.72		
Completed high school or equivalent	88 (18.3)	104 (21.6)			
Some college or university	75 (15.6)	78 (16.2)			
University graduate	260 (54.1)	241 (50.1)			
Unknown	4 (0.8)	4 (0.8)			
Employment status					
Employed or self-employed	262 (54.5)	276 (57.4)	.56		
Full-time homemaker	155 (32.2)	150 (31.2)			
Student	20 (4.2)	15 (3.1)			
Unemployed	31 (6.4)	32 (6.7)			
Other	10 (2.1)	4 (0.8)			
Unknown	3 (0.6)	4 (0.8)			

Abbreviation: IQR, interquartile range.
[a] These data are for the 1147 children who had adequate data for the primary composite outcome of death or disability at a corrected age of 18 to 21 mo. Percentages may not sum to 100 because of rounding.
[b] Race or ethnic group was self-reported.
[c] Exposure to antenatal corticosteroids was unknown for 1 child in each of the 2 groups.
[d] The 10th percentile for gestational age in a normal population was as reported by Kramer et al.[25]
[e] Available only at follow-up.
[f] These data exclude the caregivers of 97 children in the lower saturation target group and 88 children in the higher saturation target group who died before a corrected age of 18 mo.

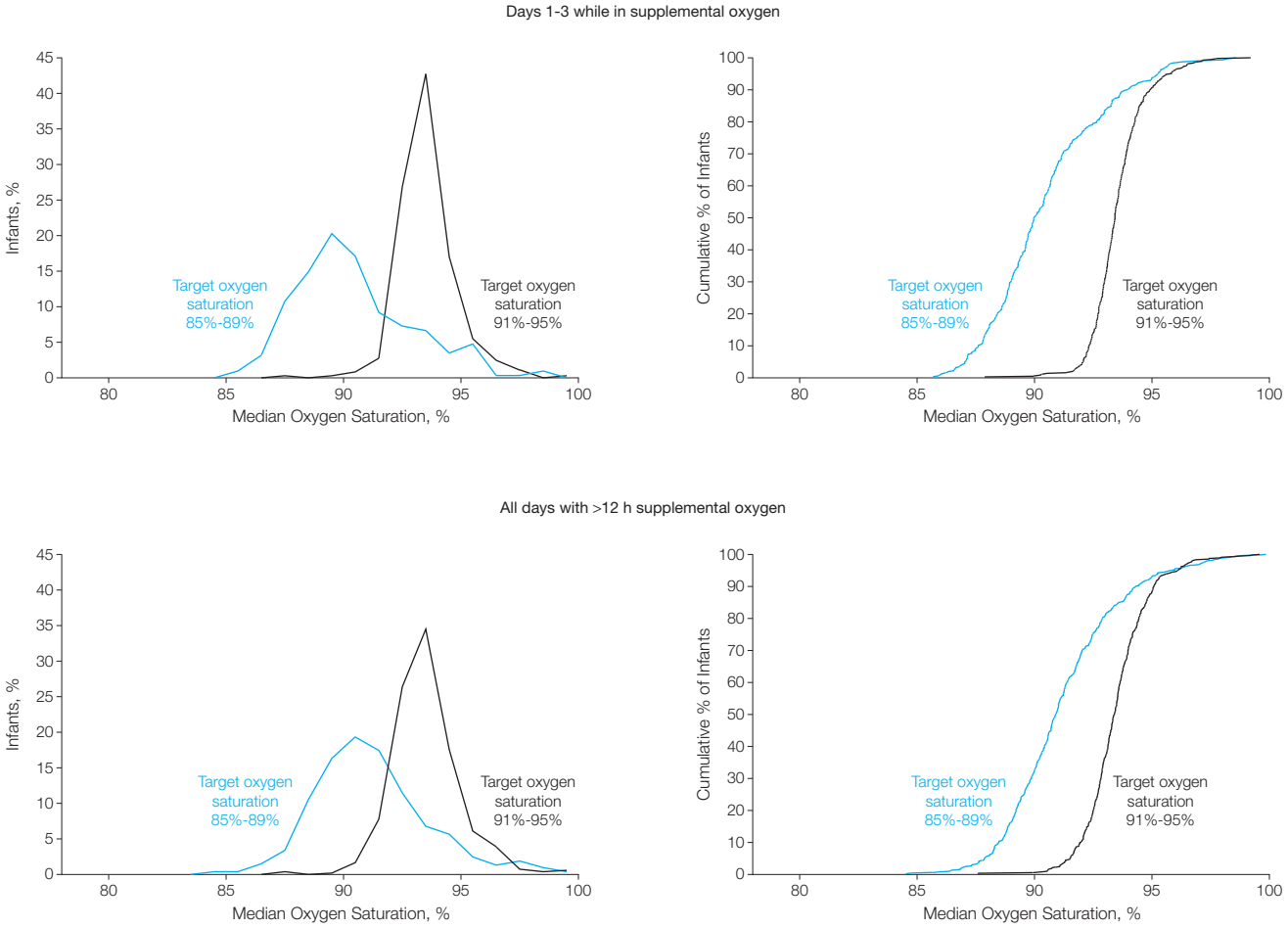
P=.52). A supportive analysis using a generalized estimating equation approach that allowed for sibling cluster intracorrelation yielded similar estimates (OR, 1.02; 95% CI, 0.82 to 1.28; P=.85). Variation in treatment effect over study centers was consistent with the play of chance (test of homogeneity P=.24). The rates of all components of the composite outcome were also similar in the 2 groups (Table 2 and eFigure 1). Of the 585 infants with known vital status at 18 months in the lower saturation target group, 97 (16.6%) had died compared with 88 of 577 (15.3%) in the higher saturation target group (adjusted OR, 1.11; 95% CI, 0.80 to 1.54; P=.54) (Table 2).

The subgroup analysis by oximeter software version showed no significant statistical interactions for either the primary composite outcome or mortality at 18 months (Table 2).

Secondary Outcomes

Targeting lower compared with higher saturations reduced the mean postmenstrual age at last use of oxygen therapy from 36.2 to 35.4 weeks (mean difference adjusted for center, −0.8; 95% CI, −1.5 to −0.1; P=.03) but had no significant effect on any other outcomes, including the rate of severe retinopathy of prematurity (TABLE 3). Respiratory management appears to have been comparable between groups because the postmenstrual age at last use of endotracheal intubation and last use of nasal positive airway pressure were similar in both groups.

Figure 2. Study Participants' True Median Arterial Oxygen Saturations in the Treatment Groups



The distribution of the individual study participants' true median arterial oxygen saturation is plotted for each treatment group according to the exact times spent receiving supplemental oxygen on days 1 through 3 (top left) and based on all study days with more than 12 hours of supplemental oxygen per day (bottom left). The cumulative percentages of infants with true median arterial oxygen saturations less than or equal to a specified value are plotted for each treatment group in the 2 right panels. The individual participants' median saturations in the left panels are grouped in 1% intervals and the respective percentages are plotted at the midpoint of the 1% interval (eg, the interval 90.00%-90.99% is plotted at 90.50%). In the right panels, cumulative percentages of infants are plotted at their exact individual median saturation values. A total of 316 infants in the 85%-89% target group and 365 infants in the 91%-95% target group contributed adequate saturation data to the analysis of median saturations on days 1 through 3, whereas 533 and 542 infants, respectively, contributed adequate saturation data on all days with more than 12 hours of supplemental oxygen.

DISCUSSION

We performed this randomized trial to help resolve the uncertainty of how to titrate oxygen therapy in preterm infants. Targeting saturations of 85% to 89% compared with 91% to 95% had no significant effect on the rate of death or disability at 18 months in this international cohort of extremely preterm infants. A post hoc calculation suggests that our study had 80% statistical power to detect absolute differences of 8.0% and 6.5% in the risks of death or disability and mortality, respectively, at 18 months. Our findings should apply to similar extremely preterm infants who are cared for with strict adherence to alarm limits for pulse oximetry of 85% at all times, and of 95% during oxygen therapy.

Our results do not completely agree with those of other investigators who studied the same saturation targets in extremely preterm infants. Consistent with our results, and although they defined neurodevelopmental impairments differently, the SUPPORT investigators found no significant difference between the treatment groups in the combined outcome of death or disability at 18 months.[14] However, in contrast to our results, these investigators observed that mortality was modestly increased in the lower saturation target group, whereas severe retinopathy was greatly reduced.[13,14] Recruitment in the Australian and UK trial was terminated early after an interim subgroup analysis showed that infants who were monitored with oximeters containing revised software had a higher rate of death at 36 weeks of postmenstrual age in the lower saturation target group. The total number of deaths among infants in the UK and Australia trial who were monitored with the revised software was 185.[15] Randomized trials that are stopped early after fewer than 500 events may result in large overestimations of the treatment effect.[26]

The differences between the results of these trials may be partly due to important differences in their design and implementation.[12] The trials have different primary outcomes and enrolled infants with different baseline characteristics.[27] The overall mortality rate at 18 months was 15.9% in COT compared with 20.1% in SUPPORT.[14]

Study oximetry also differed. Lower saturation thresholds that would trigger an alarm were not prescribed in the UK protocol.[28] However, alarm settings greatly influence how caregivers adjust the concentration of oxygen.[29] We standardized upper and lower alarm settings and performed monthly audits of the downloaded saturation data to provide feedback to the clinical centers on their compliance with those alarm settings. Some trials discontinued study oximetry when infants were breathing ambient air for more than 72 hours,[13,15] whereas we continued study oximetry until a postmenstrual age of at least 36 weeks, irrespective of the concentration of inspired oxygen. Decisions to resume oxygen therapy after its cessation were prescribed by the COT study protocol and not by local clinicians.

Finally, it will be important to compare how successful the study teams were in "hitting the target"[30] saturations. Targeting a narrow range of oxy-

Table 2. Primary Outcome of Death or Disability

Outcome	No./Total (%)		Unadjusted OR	Adjusted for Center		OR Adjusted for Center and Patient Characteristics (95% CI)[a]
	Target Saturation 85%-89%	Target Saturation 91%-95%		OR (95% CI)	*P* Value	
Composite						
Death or disability	298/578 (51.6)	283/569 (49.7)	1.08	1.08 (0.85-1.37)	.52	1.06 (0.83-1.37)
Components						
Death before 18 mo[b]	97/585 (16.6)	88/577 (15.3)	1.10	1.11 (0.80-1.54)	.54	1.12 (0.78-1.61)
GMFCS level of 2 to 5[c]	30/488 (6.1)	31/488 (6.4)	0.97	0.98 (0.57-1.67)	.94	0.88 (0.50-1.56)
Cognitive or language delay[c]	190/475 (40.0)	191/479 (39.9)	1.01	1.02 (0.78-1.34)	.86	0.99 (0.75-1.31)
Severe hearing loss[c]	18/487 (3.7)	12/489 (2.5)	1.53	1.53 (0.73-3.20)[d]	.26	1.42 (0.67-3.03)[d]
Bilateral blindness[c]	5/487 (1.0)	3/488 (0.6)	1.68	1.68 (0.40-7.06)[d]	.48	1.53 (0.36-6.51)[d]
Subgroup analysis by oximeter software[e]						
Death or disability						
Original software	140/275 (50.9)	138/264 (52.3)	0.95	0.97 (0.68-1.39)	.88	0.90 (0.62-1.31)
Revised software	143/272 (52.6)	124/266 (46.6)	1.27	1.31 (0.91-1.88)	.14	1.30 (0.89-1.90)
Test of interaction					.26[f]	
Death before 18 mo						
Original software	49/281 (17.4)	48/268 (17.9)	0.97	1.00 (0.63-1.59)	.99	0.97 (0.58-1.63)
Revised software	46/273 (16.8)	38/270 (14.1)	1.24	1.23 (0.75-2.01)	.41	1.18 (0.67-2.09)
Test of interaction					.55[f]	

Abbreviations: GMFCS, Gross Motor Function Classification System; OR, odds ratio.
[a] The OR has been adjusted for the gestational age and sex of the infant, the primary caregiver's education at the assessment, antenatal administration of corticosteroids, and multiple birth.
[b] This outcome is for children whose vital status was known at a corrected age of 18 mo.
[c] Data for this outcome exclude children who died before the scheduled tests and those who were alive but were not tested.
[d] The odds ratio for this outcome has not been adjusted for center because there were too few events.
[e] Data for this subgroup analysis exclude 70 infants who were exposed to both the original and revised software.
[f] Test of interaction between treatment and software.

gen saturations in unstable infants is difficult[31] and must be consistent with current best practice.[32] Extreme saturation data in the tails of the distributions will likely increase any differences in the outcomes between the 2 groups. However, results obtained in infants who spend potentially preventable amounts of time with very high or low saturations may not usefully contribute to clinical practice guidelines because a consensus already exists that extreme saturation values should be avoided whenever possible.[30] Smaller proportions of infants had median saturations below 85% or above 95% in COT than in SUPPORT, whereas between 85% and 95% our distributions of oxygen saturations in the 2 treatment groups overlapped less than the distributions of saturations in SUPPORT (eFigure 2). These important differences between the observed saturation profiles in the 2 trials may explain why we did not find excess mortality in the low target group and excess retinopathy in the high target group.

It has been reported that the change in oximeter software was associated with improved oxygen saturation targeting.[15] However, the reported comparisons between the original and revised software were not randomized. The apparent effect of the change in oximeter software on the accuracy of the saturation targeting may have been caused by unknown confounding variables. We changed the oximeter software midway through our enrollment and found little evidence that the revised software was associated with

Table 3. Secondary Outcomes

Outcome	No./Total (%)		Unadjusted, OR	OR (95% CI), Adjusted for Center	*P* Value
	Target Saturation 85%-89%	Target Saturation 91%-95%			
Retinopathy of prematurity					
Any retinopathy[a]	325/502 (64.7)	317/506 (62.6)	1.09	1.09 (0.84 to 1.41)	.53
Severe retinopathy[b]	64/500 (12.8)	66/503 (13.1)	0.97	0.95 (0.65 to 1.39)	.80
Brain injury[c]	123/598 (20.6)	136/589 (23.1)	0.86	0.85 (0.64 to 1.13)	.27
Patent ductus arteriosus					
Any therapy	324/602 (53.8)	332/599 (55.4)	0.94	0.93 (0.73 to 1.19)	.57
Surgical closure	97/602 (16.1)	93/599 (15.5)	1.05	1.05 (0.76 to 1.44)	.78
Necrotizing enterocolitis	74/602 (12.3)	56/599 (9.3)	1.36	1.38 (0.94 to 2.02)	.10
Severe BPD[d]	164/515 (31.8)	171/517 (33.1)	0.95	0.94 (0.71 to 1.23)	.64
Hospital readmissions for respiratory disease[e]	132/486 (27.2)	122/487 (25.1)	1.12	1.11 (0.83 to 1.49)	.48
Chronic use of respiratory medications[e]	139/486 (28.6)	153/487 (31.4)	0.87	0.87 (0.66 to 1.16)	.34

	Target Saturation 85%-89%		Target Saturation 91%-95%		Unadjusted Mean Difference	Mean Difference (95% CI), Adjusted for Center	*P* Value
	No.	Mean (95% CI)	No.	Mean (95% CI)			
Postmenstrual age at last use of respiratory support, wk[f]							
Endotracheal positive airway pressure	505	31.2 (30.8 to 31.7)	509	31.4 (31.0 to 31.9)	−0.2	−0.2 (−0.8 to 0.3)	.43
Nasal positive airway pressure	505	35.1 (34.7 to 35.4)	509	35.0 (34.6 to 35.3)	0.1	0.1 (−0.4 to 0.5)	.65
Supplemental oxygen	505	35.4 (34.9 to 35.9)	509	36.2 (35.7 to 36.7)	−0.8	−0.8 (−1.5 to −0.1)	.03
Growth at follow-up							
Height percentile	481	37.7 (35.0 to 40.4)	478	38.7 (36.0 to 41.4)	−1.0	−1.3 (−5.1 to 2.4)	.49
Weight percentile	486	29.2 (26.5 to 31.8)	487	30.9 (28.2 to 33.7)	−1.8	−1.6 (−5.3 to 2.2)	.41
Head circumference percentile	482	45.1 (42.2 to 48.0)	481	45.6 (42.8 to 48.5)	−0.6	−0.7 (−4.7 to 3.4)	.74
Bayley III composite scores corrected for prematurity							
Cognition	457	94.6 (93.2 to 96.0)	461	94.2 (92.8 to 95.7)	0.4	−0.2 (−1.7 to 2.2)	.83
Language	449	88.6 (87.0 to 90.2)	454	88.4 (86.8 to 89.9)	0.2	0 (−2.2 to 2.2)	.98
Motor	447	92.3 (90.9 to 93.7)	454	92.3 (90.8 to 93.7)	0.0	−0.1 (−2.0 to 1.8)	.93

Abbreviations: BPD, bronchopulmonary dysplasia; OR, odds ratio.
[a] This outcome is for infants who had at least 1 retinal examination.
[b] This outcome is for infants who survived to a postmenstrual age of 36 weeks with at least 1 retinal examination. Severe retinopathy was defined as unilateral or bilateral disease of stages 4 or 5 or receipt of retinal therapy in at least 1 eye.
[c] This outcome is for infants who underwent cranial ultrasonography at least once after randomization. The following lesions were analyzed as a group as evidence of brain injury: intraparenchymal echodense lesions (grade 4 hemorrhage), cystic periventricular leukomalacia, porencephalic cysts, and ventriculomegaly with or without intraventricular hemorrhage.
[d] This outcome is for infants who survived to a postmenstrual age of 36 weeks. Severe BPD was defined as receiving supplemental oxygen for more than 12 h on at least 28 d plus need for ≥30% oxygen or positive airway pressure at a postmenstrual age of 36 weeks.[19]
[e] This outcome is for children whose family provided a standardized medical history at 18 mo. Chronic use of respiratory medications was defined as prescription of inhaled or systemic corticosteroids or bronchodilators for at least 2 mo since the first discharge home.
[f] This outcome is for infants who survived to their first discharge home.

either improved targeting of oxygen saturations or a larger treatment effect on the primary outcome or mortality.

Our trial has several limitations. Perfect adherence to the narrow target range of 88% to 92%, as displayed on the offset study oximeters, would have resulted in a difference of 6% between the true arterial saturations in the 2 groups. We observed barely half of this difference on days with at least 12 hours of supplemental oxygen. Caregivers may have tolerated saturations approaching the upper alarm limit more often than saturations approaching the lower alarm limit. Furthermore, we did not record exact times spent receiving supplemental oxygen for all study participants beyond the first 3 days. The distributions of saturations we report are therefore confounded by time spent breathing 21% oxygen when caregivers were unable to modify arterial saturations. Last, we did not ascertain the primary outcome at 18 months for all study participants. However, at less than 5%, our attrition was low. Variation in the timing of assessment is unlikely to have affected the cumulative risk of the primary outcome because most component impairments manifest early in life and the Bayley Scale is age-standardized.

Clinicians who try to translate the disparate results of the recent oxygen saturation targeting trials into their practice may find it prudent to target saturations between 85% and 95% while strictly enforcing alarm limits of 85% at all times and of 95% during times of oxygen therapy. Our findings do not support recommendations that targeting saturations in the upper 80% range should be avoided.[13-15] Because it is very difficult to maintain infants in a tight saturation target range, such recommendations may lead to increased tolerance of saturations above 95% and an increased risk of severe retinopathy. Although no longer a major cause of bilateral blindness, severe retinopathy remains a marker of serious childhood disabilities.[33]

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