Randomized Controlled Trial of Oxygen Saturation Targets in Very Preterm Infants: Two Year Outcomes

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Objective To assess whether an oxygen saturation (Spo_2) target of 85%-89% compared with 91%-95% reduced the incidence of the composite outcome of death or major disability at 2 years of age in infants born at <28 weeks' gestation.

Study design A total 340 infants were randomized to a lower or higher target from <24 hours of age until 36 weeks' gestational age. Blinding was achieved by targeting a displayed Spo_2 of 88%-92% using a saturation monitor offset by ±3% within the range 85%-95%. True saturations were displayed outside this range. Follow-up at 2 years' corrected age was by pediatric examination and formal neurodevelopmental assessment. Major disability was gross motor disability, cognitive or language delay, severe hearing loss, or blindness.

Results The primary outcome was known for 335 infants with 33 using surrogate language information. Targeting a lower compared with a higher Spo_2 target range had no significant effect on the rate of death or major disability at 2 years' corrected age (65/167 [38.9%] vs 76/168 [45.2%]; relative risk 1.15, 95% CI 0.90-1.47) or any secondary outcomes. Death occurred in 25 (14.7%) and 27 (15.9%) of those randomized to the lower and higher target, respectively, and blindness in 0% and 0.7%.

Conclusions Although there was no benefit or harm from targeting a lower compared with a higher saturation in this trial, further information will become available from the prospectively planned meta-analysis of this and 4 other trials comprising a total of nearly 5000 infants. *(J Pediatr 2014;165:30-5)*.

See editorial, p 6

Oxygen is the most common treatment given to very preterm (<28 weeks' gestation [VP]) infants. Like any drug, too much and too little can cause harm, but it remains unclear where the balance should lie to minimize the competing adverse outcomes of retinal damage, chronic lung disease (CLD), neurodevelopmental impairment, and death.[1]

Prior to the 1990s, oxygen therapy in VP infants was usually monitored by either continuous or intermittent arterial oxygen tension, and a target range of 50-80 mm Hg was widely accepted, although this was based on professional opinion.[2] Through the 1990s, most neonatal intensive care units (NICUs) adopted pulse oximeter oxygen saturation (Spo_2) monitoring because it was simple and noninvasive and reduced complications, including the need for blood transfusions. With few data to guide Spo_2 targets many clinicians chose a range of 90%-95%, although surveys showed high and low limits varied from 100% to 80%.[3]

Several studies, including 2 randomized controlled trials in convalescing infants,[4,5] suggested lower targets might be beneficial. An observational study from England reported that units targeting a Spo_2 range of 80%-90% from

BII	Bayley Scales of Infant Development, Second Edition	IPD	Individual patient data
BIII	Bayley Scales of Infant Development, Third Edition	NICU	Neonatal intensive care unit
BOOST	Benefits Of Oxygen Saturation Targeting	ROP	Retinopathy of prematurity
CLD	Chronic lung disease	RR	Relative risk
COT	Canadian Oxygen Trial	Spo_2	Oxygen saturation
CP	Cerebral palsy	SUPPORT	Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial
CTC	Clinical Trials Centre	VP	Very preterm

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shortly after birth in VP infants had lower rates of severe retinopathy of prematurity (ROP) and CLD than did units adopting a range of 94%-98% but with no differences in mortality or cerebral palsy (CP) at 1 year.[6] A single-unit study from California reported that lowering the Spo_2 target to 85%-93% for infants of <32 weeks' gestation and to 83%-93% for the smallest and sickest infants was associated with a decrease in severe ROP and trends to increased survival in infants with birth weights <1250 g.[7] But while many NICUs adopted lower Spo_2 targets in these VP infants, there remained concerns that the risks and benefits of this therapeutic drift were unknown and particularly whether short-term benefits such as less ROP might be achieved at the expense of worse long-term neurodevelopmental outcomes.[8,9]

Because obtaining funding for a single large trial seemed unlikely, separate trials were planned and ultimately 5 were funded. There was agreement from the outset to adopt similar protocols and to plan for a prospective individual patient data (IPD) meta-analysis following publication of the individual trials.[10] The hypothesis for the Benefits Of Oxygen Saturation Targeting (BOOST)-New Zealand trial was that a lower Spo_2 target range (85%-89%), compared with a higher target range (91%-95%), would reduce the incidence of a composite outcome of death or major disability at 2 years of age corrected for prematurity in infants of <28 weeks' gestation.

Methods

This was a double-blind randomized controlled trial in 5 of the 6 regional NICUs in New Zealand. The BOOST-New Zealand coordinators in Christchurch managed the trial in collaboration with the National Health and Medical Research Council Clinical Trials Centre (CTC), Sydney, Australia, which was responsible for randomization and data analysis. The BOOST-New Zealand study was monitored by the independent data and safety monitoring committee appointed for the Australian BOOST II study. The study was approved by the Multi-region Ethics Committee of the Ministry of Health.

Eligible infants were <28 weeks' gestation, <24 hours of age, and either born in or transferred into a trial NICU. Exclusion criteria were a congenital anomaly affecting oxygenation or long-term development, imminent death, or the inability to follow up at 2 years (principally non–English-speaking parents or known to be moving overseas). Written informed parental consent was obtained.

Randomization occurred before 24 hours of age via telephone call to the CTC. Computer-generated randomization lists were prepared by an independent CTC statistician. Randomization was stratified by NICU, sex, gestation <26 or ≥26 weeks, and inborn or outborn. Multiple births were randomized separately. Each center had a pool of oximeters, identified by a unique number and maintained by the study coordinator in conjunction with the independent oximeter control center at Technical Services, Canterbury District Health Board, who alone were aware of the offset. Fifty study oximeters, 25 with a +3% and 25 with a −3% masked offset within the range of 85%-95%, were leased from Masimo Corporation (Irvine, California).

The Spo_2 target for all infants was 88%-92% when the infant was receiving supplemental oxygen. Nursing staff recorded the inspired oxygen concentration and Spo_2 hourly, and the stored histogram of the percentage of time the infant spent in different saturation bands over the past 24 hours was displayed and recorded at midnight each day. The infant remained on the assigned study oximeter for at least the first 2 weeks of life and until 36 weeks' gestational age unless not requiring supplemental oxygen or respiratory support and with a Spo_2 >96% for >95% of the time for 3 days. Study oximeters were prominently labeled and only used in the study. When first attached to the infant, this was after a gap of at least 5 minutes without saturation monitoring. When the study ended and the study oximeter was removed, there was a gap of at least 30 minutes before a standard nonstudy oximeter was attached. If deemed clinically necessary to monitor the infant with a nonstudy monitor without the offset, such as during surgery, the protocol required at least a 5-minute gap between discontinuing the study monitor and attaching a standard monitor.

The monitor alarm settings were recommended (but not mandated) to be at 87% and 93% when in supplemental oxygen. The Spo_2 levels were stored every 10 seconds. The stored data were downloaded every 14 days by the research nurse in each collaborating NICU. If an infant was transferred to a lower level (level II) NICU before 36 weeks' gestational age, the same study monitor and protocol were used.

Before the study, the collaborating centers, including level II centers, were visited by a study coordinator, who undertook education sessions on all aspects of the trial, optimizing compliance with saturation targets, viewing the oximeter histogram, and downloading stored data. A research nurse in each center facilitated ongoing education and surveillance and coordinated data collection and oximeter downloads and sent via courier oximeters to Christchurch, via courier, when an infant completed the study. Unlike similar studies in Australia and the United Kingdom[11] and in Canada,[12] the New Zealand trial did not change the oximeter software during the conduct of the trial.

Research nurses recorded all data using standardized definitions. Data were entered into the CTC web-based data collection (Inform) system. The BOOST-New Zealand coordinators audited data from each site at least annually. All infants were assessed as close to 2 years' corrected age as possible based on pediatric examination and a neurodevelopmental assessment by a registered psychologist. All caregivers and assessors remained blinded as to the treatment group of the infant.

The prespecified primary outcome for the study was a composite of death or major disability at 24 months' corrected age. Major disability was originally defined as any of a Mental Developmental Index on the Bayley Scales of Infant Development, Second Edition[13] (BII) <70, CP with Gross Motor Function Classification System level ≥2, severe visual loss (legally blind, <6/60 vision), or deafness requiring