

# Pulse Oximetry Targets in Extremely Premature Infants and Associated Mortality: One-Size May Not Fit All

Thomas M. Raffay and Michele C. Walsh\*

Department of Pediatrics, University Hospitals Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, Ohio, USA

**Oxygen saturation targets in premature infants have been investigated in multiple international randomized controlled trials. Some trials have shown increased mortality with targeting lower (85% to 89%) compared to higher (91% to 95%) oxygen saturation ranges, while others have not. We will review the mortality outcomes of the largest multi-centered trials and a post hoc study that observed increased mortality at lower target ranges among small for gestational age infants. The planned Neonatal Oxygen Prospective Meta-analysis (NeOProM) collaborative will hopefully provide further insight into patient-specific risks, which include growth status.**

Prematurity | Oxygen saturation | Mortality | Neonatal | Growth

The premature infant often needs life-saving respiratory support due to their immature lung development and control of breathing. Supplemental oxygen, among other therapies, is frequently required to sustain these infants in the *ex utero* world. Oxygen is a medication, and is not without its own potentially harmful side effects - including eye, lung, and brain injury. In the 1970's, transcutaneous pulse oximetry provided a means to monitor the effectiveness of supplemental oxygen in hopes of achieving a balance of oxygen delivery to support aerobic energy demands while attempting to avoid potential toxicity from oxidative stress.

International multi-centered trials have sought to investigate the association of pre-defined oxygen saturation targets on neonatal outcomes including retinopathy of prematurity, bronchopulmonary dysplasia, brain injury, neurodevelopmental impairments, necrotizing enterocolitis, and death (1-3). These studies were prospectively designed to use similar oxygen targets, to facilitate an individual patient prospective meta-analysis entitled the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) (4). The meta-analysis will examine differences between over 4900 infants randomized to either saturation targets of 85-89% or 91-95%. The Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) (2), performed in the United States, aimed to examine if higher or lower saturation targets were associated with differences in the combined outcome of retinopathy of prematurity or death. While rates of the combined outcome did not differ between low vs high targets (28.3% compared to 32.1%, respectively;  $p=0.21$ ), SUPPORT identified an unanticipated increase in mortality before discharge in the lower saturation target group (19.9% compared to 16.2%;  $p=0.04$ ). The Benefits of Oxygen Saturation Targeting (BOOST II) (1) trials in the United Kingdom, Australia, and New Zealand also reported increased mortality prior to discharge among their combined lower saturation target groups (23.1% compared to 15.9%;  $p=0.002$ ). While, the Canadian Oxygenation Trial (COT) (3) conducted in 25 hospitals across Canada, the United States, Argentina, Finland, Germany, and Israel did not show significant differences in 18 month mortality between the low and high saturation target groups (16.6% compared to 15.3%;  $p=0.54$ ).

While awaiting the individual patient data NeOProM conclusions, several interim systemic reviews and meta-analyses

have been performed on the published results of these trials (5-8). The 2017 Cochrane review by Askie *et al.* included the published and unpublished major outcomes of the NeOProM trials and did not show a relative effect of high vs low saturation target on the composite outcome of death or major disability at 18 to 24 months corrected age (5). However, the outcomes of death (both at discharge and at 18 to 24 months corrected age) and necrotizing enterocolitis were increased among infants randomized to the low saturation targets. Whereas, the risk for developing retinopathy of prematurity requiring treatment was decreased in the low saturation target group.

The SUPPORT cohort investigators noted that small for gestational age (SGA, birthweight <10%) (9) infants were missing childhood follow-up compared to appropriately grown infants (AGA). This observation led the investigators to perform a *post hoc* analysis (10) which found an interaction between SGA status and lower saturation targets with an unanticipated increase in mortality (56.1% compared to 25.5%;  $p<0.01$ ). In contrast, in AGA infants mortality did not differ significantly between saturation targets (17.6% compared to 15.2%;  $p=0.17$ ). Further, in the AGA survivors severe retinopathy of prematurity was decreased in the lower saturation target group (8.5% compared to 16.5%;  $p<0.001$ ). The primary causes of death among these SGA infants were respiratory distress syndrome and bronchopulmonary dysplasia, whereas the leading causes of death among AGA infants were respiratory distress syndrome and infection. SGA infant survival plots diverged based upon low vs high saturation targets beyond the first weeks of life, as such, it was unlikely an effect of early death among the lower saturation target group. Thus, it was speculated that SGA infants are particularly vulnerable to lower saturation targets given their propensity to develop pulmonary hypertension with bronchopulmonary dysplasia (11) in addition to other co-morbidities associated with their growth restriction.

It has been well described that as a group premature SGA infants are at increased risk for neonatal morbidity and mortality when compared to AGA infants of a similar gestation (12, 13). The causes of intrauterine growth restriction, as well as, the pathophysiology underlying an SGA infant's elevated risks for morbidity and mortality are complex. The hypothesis-generating work of the SUPPORT investigators in the vulnerable SGA population suggests an association with lower saturation exposure as a potential contributor to mortality. This novel finding may inform the NeOProM collaborative, as well as, guide future trial designs.

A consensus regarding saturation targets is unlikely. The recent Cochrane review (5) and American Academy of Pediatrics clinical report (14) acknowledge the controversy of saturation

Conflict of Interest: No conflicts declared.

\* Corresponding Author. Email: michele.walsh@uhhospitals.org  
© 2018 by the Authors | Journal of Nature and Science (JNSCI).

target ranges and a potential need for a patient-specific approach. Despite the controversy, individual neonatal intensive care units are examining their own saturation policies much more closely with a propensity towards adjustments to higher targets while awaiting the findings of NeOProM (15, 16). Such decisions should take into account both characteristics of individual units (staffing ratios, availability to tightly regulate saturation goals, unit outcomes) and individual patients, including growth status.

### Abbreviations

small for gestational age (SGA), appropriate for gestational age (AGA)

### Acknowledgments

TMR is supported by the NHLBI (K08HL133459) and MCW is supported by the NICHD (UG1HD021364). Authors report no conflicts of interest.

1. Group, B.I.U.K.C., Group, B.I.A.C., Group, B.I.N.Z.C., Stenson, B.J., Tarnow-Mordi, W.O., Darlow, B.A., Simes, J., Juszczak, E., Askie, L., Battin, M., et al. 2013. Oxygen saturation and outcomes in preterm infants. *N Engl J Med* 368:2094-2104.
2. Network, S.S.G.o.t.E.K.S.N.N.R., Carlo, W.A., Finer, N.N., Walsh, M.C., Rich, W., Gantz, M.G., Laptook, A.R., Yoder, B.A., Faix, R.G., Das, A., et al. 2010. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 362:1959-1969.
3. Schmidt, B., Whyte, R.K., Asztalos, E.V., Moddemann, D., Poets, C., Rabi, Y., Solimano, A., Roberts, R.S., and Canadian Oxygen Trial, G. 2013. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. *JAMA* 309:2111-2120.
4. Askie, L.M., Brocklehurst, P., Darlow, B.A., Finer, N., Schmidt, B., Tarnow-Mordi, W., and Ne, O.C.G. 2011. NeOProM: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol. *BMC Pediatr* 11:6.
5. Askie, L.M., Darlow, B.A., Davis, P.G., Finer, N., Stenson, B., Vento, M., and Whyte, R. 2017. Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. *Cochrane Database Syst Rev* 4:CD011190.
6. Saugstad, O.D., and Aune, D. 2014. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. *Neonatology* 105:55-63.
7. Manja, V., Lakshminrusimha, S., and Cook, D.J. 2015. Oxygen saturation target range for extremely preterm infants: a systematic review and meta-analysis. *JAMA Pediatr* 169:332-340.
8. Manja, V., Saugstad, O.D., and Lakshminrusimha, S. 2017. Oxygen Saturation Targets in Preterm Infants and Outcomes at 18-24 Months: A Systematic Review. *Pediatrics* 139.
9. Olsen, I.E., Groveman, S.A., Lawson, M.L., Clark, R.H., and Zemel, B.S. 2010. New intrauterine growth curves based on United States data. *Pediatrics* 125:e214-224.
10. Walsh, M.C., Di Fiore, J.M., Martin, R.J., Gantz, M., Carlo, W.A., and Finer, N. 2016. Association of Oxygen Target and Growth Status With Increased Mortality in Small for Gestational Age Infants: Further Analysis of the Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial. *JAMA Pediatr* 170:292-294.
11. Check, J., Gotteiner, N., Liu, X., Su, E., Porta, N., Steinhorn, R., and Mestan, K.K. 2013. Fetal growth restriction and pulmonary hypertension in premature infants with bronchopulmonary dysplasia. *J Perinatol* 33:553-557.
12. Baer, R.J., Rogers, E.E., Partridge, J.C., Anderson, J.G., Morris, M., Kuppermann, M., Franck, L.S., Rand, L., and Jelliffe-Pawlowski, L.L. 2016. Population-based risks of mortality and preterm morbidity by gestational age and birth weight. *J Perinatol* 36:1008-1013.
13. Mendez-Figueroa, H., Truong, V.T., Pedroza, C., and Chauhan, S.P. 2017. Morbidity and Mortality in Small-for-Gestational-Age Infants: A Secondary Analysis of Nine MFMU Network Studies. *Am J Perinatol* 34:323-332.
14. Cummings, J.J., Polin, R.A., Committee On, F., and Newborn. 2016. Oxygen Targeting in Extremely Low Birth Weight Infants. *Pediatrics* 138.
15. Hagadorn, J.I., Sink, D.W., Buus-Frank, M.E., Edwards, E.M., Morrow, K.A., Horbar, J.D., Ferrelli, K., and Soll, R.F. 2017. Alarm safety and oxygen saturation targets in the Vermont Oxford Network iNICQ 2015 collaborative. *J Perinatol* 37:270-276.
16. Huizing, M.J., Villamor-Martinez, E., Vento, M., and Villamor, E. 2017. Pulse oximeter saturation target limits for preterm infants: a survey among European neonatal intensive care units. *Eur J Pediatr* 176:51-56.