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Oxygen saturation targets in extremely premature neonates

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SUMMARY

Several observational studies have shown a decrease in the incidence of retinopathy of prematurity (ROP) among preterm neonates when lower oxygen saturation is targeted.[1,2] In these studies, lower oxygen saturation targets have also been shown to be associated with shorter duration of respiratory support and decreased incidence of bronchopulmonary dysplasia. However, the effects of maintaining lower oxygen saturation values during acute illness and recovery on survival and neurodevelop-mental outcome had not been reported. A number of international studies were planned with identical research hypothesis, eligibility criteria, intervention targets and outcomes. A meta-analysis of the results of these studies has also been planned (Neonatal Oxygenation Prospective Meta-analysis [NeOProM] Collaboration).[3] These studies include the SUrfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), Benefits Of Oxygen Saturation Targeting (BOOST) II trials in the UK, Australia and New Zealand[4] and the Canadian Oxygen Trial (COT). These studies enrolled neonates born at <28 weeks of gestation receiving supplemental oxygen after birth. Neonates were randomized to target oxygen saturations of 85%–89% (lower-target group) versus 91%–95% (higher-target group). Blinding of the caregivers to intervention was ensured by modifying the pulse oximeters in such a manner that the displayed saturations were either 3% above or below the true values. Therefore, in both groups the displayed and targeted values were 88%–92%. The main outcome measures for these trials were death or severe ROP at discharge from hospital and death or disability at 18 months of corrected age.

Results

The first study to report results among these multisite studies was SUPPORT. It enrolled 1316 neonates randomized to lower (*n*=654) or higher (*n*=662) oxygen saturation groups. Although, there was no difference in the composite outcome of severe ROP and/or death before discharge (relative risk [RR] with lower oxygen saturation, 0.90, 95% CI 0.76–1.06), neonates in the lower oxygen saturation group had a lower risk of severe ROP (RR 0.52, 95% CI 0.37–0.73) but higher risk of death before discharge from hospital (RR 1.27, 95% CI 1.01–1.60). The rates of bronchopulmonary dysplasia among survivors, as determined by the physiological test of oxygen saturation at 36 weeks did not differ significantly between the treatment groups. The risk of death or neurodevelopment impairment at 18–22 months of corrected age was similar in the lower or higher oxygen saturation groups (RR 1.12, 95% CI 0.94–1.32). However, the risk of death remained higher in the lower oxygen saturation group (RR 1.25, 95% CI 1.00–1.55).

While the results of SUPPORT were published, COT had already completed recruitment and was following up the neonates for outcomes at 18 months of corrected age. The BOOST II trial in New Zealand had also completed enrolment while the UK and Australian BOOST II trial arms were still recruiting. A joint safety analysis of survival at 36 weeks was conducted and in view of increased risk of death in the lower oxygen saturation group, the UK and Australian BOOST II trials stopped further enrolment.

The BOOST II trials recruited 2448 neonates. However, it was observed midway during the study that the study pulse oxymeters displayed fewer than expected oxygen saturation values in the range of 87%–90%. This resulted in a significant overlap of actual oxygen saturation values in both groups. This was corrected by a modification of the software algorithm and among a total of 2448 neonates enrolled in the BOOST II trials, 1187 neonates were monitored by pulse oximeters with the revised algorithm. In these neonates, the rate of death at 36 weeks post-menstrual age was significantly higher in the lower-target group than in the higher-target group (RR 1.59, 95% CI 1.24–2.04). The relative increase in risk of death, though low, remained significant when all 2448 neonates were included in the analysis. Similar to results of the SUPPORT study, the risk of ROP was reduced among neonates in the lower oxygen saturation groups (RR 0.79, 95% CI 0.63–1.00). The results of outcome at 18 months are awaited.

Recently, the COT trial has also reported the long-term outcome of neonates enrolled in the Canadian study. This study enrolled a total of 1201 neonates. Contrary to the SUPPORT and BOOST II trials, no increase in risk of death was observed among neonates enrolled in the low oxygen saturation group. The rate of primary outcome (composite of death, gross motor disability, cognitive or language delay, severe hearing loss or bilateral blindness at a corrected age of 18 months) was similar in the two groups (RR 1.08, 95% CI 0.85–1.37). Interestingly, the incidence of severe ROP was also comparable in the two groups (RR 0.95, 95% CI 0.65–1.39).

COMMENT

Administration of oxygen in preterm neonates is like administering a drug with long-term consequences and with a possible role in many multifactorial neonatal conditions such as ROP, broncho-pulmonary dysplasia, cerebral palsy, cognitive impairment and poor physical growth. Immature organs in preterm neonates have limited antioxidative defence mechanisms and are prone to cellular damage by hyperoxia-induced free radicals.[5] On the other hand, repeated or prolonged hypoxia may result in suboptimal cellular organ growth and impaired cognition. Therefore, finding the right balance in the tissue oxygenation status of a preterm neonate is vital to optimize the neonate's disability-free survival.

The conduct and reporting of these trials underlines the important role of randomized controlled trials in the advancement of clinical practice. When these trials were planned, recommendations for oxygen therapy monitoring were to target 50–80 mmHg partial pressure of arterial oxygen (PaO_2). The corresponding oxygen saturation values for this PaO_2 range are 85%–95%. Many clinical practice guidelines and textbooks recommended lower values within this range based on findings of observational studies which indicated decreased risk of ROP without an observed increase in mortality. Based on the results of these randomized controlled trials, it appears that oxygen saturations between 90% and 95% are to be recommended for extremely premature neonates. This may translate into a higher risk of severe ROP. This has huge implications for India where there is a remarkable increase in the number of

health facilities offering neonatal intensive care thereby resulting in improved survival of very low birth-weight neonates. Obviously, this highlights the need to establish effective ROP screening programmes and reporting outcomes in all health facilities across India caring for such preterm infants. In the long run, more basic research is needed to find interventions that can reduce the risk of severe ROP and treat it non-invasively. Collaborative neonatal networking, standardized data collection and quality improvement initiatives can be instrumental in the uptake of evidence-based practices.[6]

The SUPPORT, BOOST II and COT studies have enrolled neonates born at <28 weeks of gestation. However, in India and other developing countries neonates born at 28–32 weeks of gestation account for most of the neonatal intensive care unit (NICU) graduates and remain at high risk of death, ROP and bronchopulmonary dysplasia. Research is needed to evaluate how oxygen saturation targeting influences the outcome of these neonates. Clinical research is also needed to evaluate the role of targeting PaO_2 instead of oxygen saturation for improving outcomes among extremely preterm neonates needing respiratory support. Transcutaneous PO_2 has been observed to agree closely with PaO_2 and may have an increasing role in the clinical care of preterm neonates.

For a country such as India with an evolving clinical research scenario, these studies highlight important lessons for researchers, funding agencies and policy-makers. First, it strengthens the importance of large, collaborative, randomized controlled trials in identifying interventions which improve clinical outcomes. The research output of India cannot rise to practice-changing levels unless the neonatal care-provider community and funding agencies wake up to this challenge of planning, conducting and facilitating networked clinical research of high quality. Second, the role of steering groups and data safety monitoring boards in ensuring proper conduct of clinical trials and safety of study subjects is essential. Centre-to-centre variation in how clinical trial protocols are implemented and protocol deviations are inherent part of the multisite collaborative research and should be reported with truth and handled appropriately. Third, an unexpected increase in the risk of an adverse outcome (as observed in SUPPORT and BOOST II studies) in a clinical trial does not mean that the study protocol is flawed or that the investigators unethically exposed participants to undue risk. Observational studies can produce biased estimates of treatment effect. When conducted in a state of equipoise, randomized clinical trials are the only way to identify beneficial or harmful interventions.

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