Study Looks at Oxygen Saturation in Preemies

BY DIANA MAHONEY

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Using lower target ranges of oxygen saturation in extremely preterm infants reduces the risk of severe retinopathy from oxygen toxicity, but increases the risk of death before discharge, according to one of two trials within the same neonatal study.

In the second trial, continuous positive airway pressure (CPAP) was determined to be an effective alternative to early surfactant administration followed by conventional intubation, with fewer complications.

Researchers in the multicenter Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) used a 2x2 factorial design to compare two target ranges of oxygen saturation in 1,316 infants who were born between 24 weeks and 27 weeks 6 days of gestation. In addition, they compared intubation and surfactant treatment initiated within 1 hour after birth and CPAP treatment initiated in the delivery room with subsequent use of a limited ventilation strategy.

For the oxygen range arm of the study, the infants were randomly assigned to the lower oxygen saturation target range of 85%-89% or the higher target range of 91%-95%. At the same time, they were randomly assigned to receive the oxygen through a ventilator or through a CPAP machine.

The primary outcome of the oxygen saturation investigation was a composite of severe retinopathy of prematurity (defined as the presence of threshold retinopathy, the need for surgical ophthalmologic intervention, or the use of bevacizumab), death before hospital discharge, or both, wrote Dr. Waldemar A. Carlo of the University of Alabama at Birmingham, and colleagues.

Although there was no overall difference between the two oxygen saturation groups using the composite outcome measure, marked differences were observed when the two components of the measure were considered independently, the authors wrote. Specifically, death before discharge occurred in 20% of the infants in the lower target group compared with 16% of those in the higher group. In contrast, severe retinopathy among the surviving infants occurred significantly less often in the lower group, at 9%, compared with the higher group, at 18%. These findings, the authors note, "add to the concern that oxygen restriction may increase the rate of death among preterm infants." As such, they advise exercising caution when considering a strategy that targets oxygen levels in the low range (N. Engl. J. Med. 2010;362:1959-69).

For the CPAP vs. early intubation/surfactant study arm, the primary outcome was death or bronchopulmonary dysplasia, defined by the need for supplemental oxygen at 36 weeks, wrote Dr. Neil N. Finer of the University of California at San Diego, and colleagues. After adjusting for gestational age, medical center, and family clustering, the need for supplemental oxygen was similar in both groups, although the CPAP infants less frequently required intubation or postnatal corticosteroids for bronchopulmonary dysplasia than the surfactant group, and they also required fewer days of mechanical ventilation and were more likely to be alive by day 7, the authors wrote.

Considering the lower complication rate, the findings "support consideration of CPAP as an alternative to routine intubation and surfactant administration in preterm infants," the authors wrote (N. Engl. J. Med. 2010;362:1970-9).

In an accompanying editorial, Dr. Colin J. Morley of the University of Melbourne stressed that caution is warranted in interpreting the "most important outcome" linking the lower target oxygen saturation range and death before discharge. "Additional research is needed to clarify this finding," he said. "There were no significant differences between the groups in short-term outcomes that have been associated with relative ischemia." ■

VITALS

Major Findings: Death before discharge occurred in 20% of the infants in the lower oxygen saturation, compared with 16% of those in the higher group. In contrast, severe retinopathy among the surviving infants occurred significantly less often in the lower group at 9%, compared with the higher group at 18%.

Data Source: The multicenter Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) comprising 1,316 preterm infants from 24 weeks to 27 weeks and 6 days gestation.

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DRUGS, PREGNANCY, AND LACTATION

Hypertensive Disorders of Pregnancy

BY CHRISTINA CHAMBERS, PH.D., M.P.H.

Hypertensive disorders of pregnancy complicate 5%-10% of pregnancies and are a leading cause of maternal and perinatal mortality and morbidity. Treatment with antihypertensive medications is intended to prevent adverse maternal and infant outcomes. However, there is no clear consensus regarding the benefit of treatment for mild to moderate gestational hypertension. The maternal/fetal risks of no treatment, such as possible progression to severe hypertension and its associated consequences, have not been shown to clearly outweigh the fetal risks of treatment with antihypertensive medications, which may include intrauterine growth restriction and other neonatal complications.

A recent study published on-line in May in the BJOG: An International Journal of Obstetrics & Gynaecology suggests that the decision to treat mild to moderate hypertension should include consideration of possible long-term neurobehavioral consequences for the child (BJOG 2010 [doi: 10.1111/j.1471-0528.2010.02568.x]). In an hypothesis-generating historical cohort study conducted in the Netherlands, the authors identified 202 singleton children born in 1 of 12 hospitals between 1983 and 1987, whose mothers had developed pregnancy-induced or pregnancy-aggravated hypertension and were treated with either methyldopa (61), labetalol (58), or bed rest (83). The children underwent a battery of tests to measure IQ, gross motor development, fine motor development, and memory between approximately ages 4 and 9 years. In addition, parents and teachers were asked to evaluate the child's behavior.

Overall, mean scores on most areas of functional development did not differ significantly between the groups. However, children prenatally exposed to labetalol were about four times more likely to exhibit characteristics of ADHD than were children in the bed rest group based on a standardized Dutch version of the Teacher Report Form (OR 4.1). Children in the labetalol group were also more likely to exhibit these behaviors than were children in the methyldopa group but not significantly so (OR 2.3). Odds ratios were not adjusted for other factors because of the small number of children in each group who were classified as ADHD. The authors suggest that there is biological plausibility for the effect of prenatal exposure to labetalol on subsequent attention and hyperactivity in primary school children, and that this effect could be mediated by drug-induced fetal growth restriction and neonatal beta blockade.

This interesting study illustrates two critically important points: The first is the difficulty in conducting observational studies of prenatal medication exposure and long-term neurobehavioral outcomes, and the second is the importance of doing these studies in the first place. With respect to the former, even under the best of circumstances, without a randomized controlled trial it is very difficult to account for differences inherent in the three groups in the Dutch study. These include differences between groups in maternal overweight or obesity, tobacco use, preterm or very preterm delivery, infants born small for gestational age, maternal stress, other drug use, etc., all of which may contribute to risk for ADHD. Severity of the underlying maternal condition as measured by highest diastolic blood pressure, as well as gestational age at which treatment was initiated, varied by group.

Furthermore, differences in age at which the child was tested could have influenced the prevalence of ADHD-like symptoms that were likely to be identified by teacher report. And finally, the study was conducted during a period in time when standards of clinical practice were in transition in terms of which medication the obstetrician chose to use for treatment, if any. This common occurrence can lead to "channeling" of patients with certain characteristics to treatment with one or the other drug, which can carry with it inherent underlying differences in patients that are potentially confounding with respect to the outcome.

Nevertheless, these kinds of studies need to be done. Just as there is a need for systematic postmarketing studies for drug safety with respect to risk for birth defects, there is an equally important need for systematic surveillance for neurobehavioral outcomes. Improved efforts are needed to carefully match comparison groups on key maternal and child characteristics and to address the growing number of potential environmental factors that accumulate the longer the period of time to follow-up developmental assessment. Study designs that involve sufficient sample size to generate enough power to evaluate the outcomes of interest, although difficult to come by, are needed.

All of these issues call for a systematic coordinated approach to evaluating long-term functional outcomes following prenatal exposures, which in the end may have the most potential public health importance.

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