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Post-Test

In this issue... Volume 1, Number 8

While supplemental oxygen is probably the most common therapy given to neonates, the optimal dosage for its use in the newborn period remains controversial. As the eminent neonatologist, Professor William Silverman, described in a 2004 Pediatrics editorial:

> ***"...there has never been a shred of convincing evidence to guide limits for the rational use of supplemental oxygen in the care of extremely premature infants. For decades, the optimum range of oxygenation (to balance four competing risks: mortality, ROP-blindness, chronic lung disease and brain damage) was, and remains to this day, unknown.[1]"***

The dilemma is that while oxygen is essential for normal metabolism, newborns, particularly those born extremely preterm, are particularly sensitive to its toxic effects. The papers reviewed in this month's issue highlight the potentially conflicting consequences of oxygen therapy for these patients.

References

1.Silverman WA. A cautionary tale about supplemental oxygen: The albatross of neonatal medicine. Pediatrics 2004;113:394-396.

Reviews:
Pamela Donohue, ScD

Commentary:
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→ **Commentary**
Our guest editor opinion

Guest Editors of the Month

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COMMENTARY

The papers reviewed herein clearly highlight the dilemmas inherent in oxygenating neonates. Firstly, oxygen is a ***therapy*** - i.e. an ***intervention*** - commonly administered to newborns. Surprisingly there have been only two studies in the modern era that have used the randomized controlled trial[2], the methodology that is known to best assess the effects of an intervention while minimizing bias, to assess the effects of oxygen therapy. Both these trials[3-4] found conflicting results regarding the possible benefits of higher oxygen levels for ***treating*** established retinopathy of prematurity (ROP) with the potential adverse effects of chronic lung disease (CLD) exacerbation and the lack of improvement in long term growth and development. Unfortunately, ***no*** randomized trials have been conducted to address the question of the best range to target oxygenation ***from birth*** in order to maximize benefits while minimizing harms, including the assessment of important outcomes such as ***preventing*** ROP, CLD, death and long term major disability.

Nevertheless, evidence has been mounting from many non-randomized study designs and from animal work - including results from the Tin[6], Chow[7] and McColm[8] papers summarized herein - that targeting lower oxygen levels from birth ***may*** reduce some of the common morbidities seen in preterm infants without adversely affecting death and disability. However, the disastrous lessons of the 1950s[1] should indeed be a cautionary tale that practices must not be universally adopted without first carefully assessing both the benefits and harms in the least biased way. After the discovery in the early 1950s that high, unrestricted levels of ambient oxygen "caused" severe ROP[5], the virtually universal practice of restricting inspired oxygen for newborns to less than 40% is estimated to have resulted in approximately 16 additional neonatal deaths for every baby whose sight was saved[9], and many more who developed spastic diplegia.

Observational studies, even good quality ones like those included in this review, can never fully demonstrate "cause and effect" regarding lower oxygen levels and improved neonatal outcomes. A causal association between an intervention and an outcome can only be established through a rigorously designed randomized trial, with sufficient numbers of enrolled infants; only such a trial (or trials) can establish with confidence that the implementation of the intervention "caused" the outcomes seen.

History has shown that neonatal medicine is all too keen to adopt practices that appear to be beneficial without first confidently ruling out potentially significant harms. It is imperative, therefore, that before the "window of opportunity" is shut — i.e. before these generally accepted but clinically unproven practices become codified into "laws" for neonatal treatment — such trials be

undertaken so that the uncertainty of the past 50 years regarding oxygenation and outcomes in neonates may be finally and conclusively resolved[10].

References

2.Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-412.

3.The STOP-ROP Multicenter Study Group. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics 2000;105:295-310.

4.Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003;349: 959-967.

5.Askie LM, Henderson-Smart DJ. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

6.Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106-F110.

7.Chow L, Wright KW, Sola A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics 2003;111:339-345.

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9.Cross KW. Cost of preventing retrolental fibroplasia? Lancet 1973;2:954-956.

10.Cole CH, Wright KW, Tarnow-Mordi W, Phelps DL. Resolving our uncertainty about oxygen therapy. Pediatrics 2003;112:1415-1419

CURTAILING ROP WITH SUPPLEMENTAL OXYGEN

The STOP-ROP Multicenter Study Group. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics 2000; 105(2): 295-310.

Testing the hypothesis that the liberal use of supplemental oxygen may curtail the progression of retinal neovascularization without adverse side effects.

In this multicenter study, 649 infants with prethreshold ROP were randomized to receive supplemental oxygen to maintain oxygen saturation in the range of 89-94% (conventional group) or 96-99% (treatment group). Infants with saturations above 94% in room air were excluded from the trial). Prethreshold disease was defined as any ROP less than threshold, with threshold defined as:

- Zone I: any Stage of ROP with at least two quadrants of plus disease (dilated/tortuous vessels in the posterior pole) or any Stage III disease;
- Zone II: Stage III disease in 5 contiguous or 8 total clock hours, and at least 2 quadrants of plus disease.

The intervention continued for a minimum of two weeks or until at least one eye reached threshold. The primary outcome was considered unfavorable if ROP progressed to threshold disease in at least one eye or favorable if ROP regressed into Zone III on serial examinations, or full retinal vascularization was achieved. Secondary outcomes included pulmonary status, and growth at three months, corrected age.

The conventional saturation group (n=325) and treatment saturation group (n=324) had similar

baseline characteristics, including birthweight (721±160 vs. 731±161), gestational age (25.4±1.5 vs. 25.4±1.5) and PMA at the time of randomization (35.3±2.6 vs. 35.4±2.5). There was no difference between the groups on the primary ophthalmic outcome: 48.5% of the conventional saturation group and 40.9% of the treatment saturation group developed threshold ROP (p=0.032, significance level set at 0.025 for repeat measures). On subgroup analysis of infants without plus disease at the time of randomization, significantly more infants in the conventional arm progressed to threshold disease than infants in the treatment arm, 46% vs. 32%, respectively (p< 0.004). Progression of ROP among infants with plus disease at the time of randomization was not different between the two groups (52% conventional group vs.57% treatment group).

At three months corrected age, a greater proportion of infants in the treatment group had a poorer pulmonary outcome than did infants in the conventional saturation group, 12.7% vs. 6.8% remained hospitalized (p=0.012), 46.8% vs. 37% remained on oxygen (p=0.02), and 35.8% vs.24.4% remained on diuretics (p=0.002). Growth was similar in the two groups.

In this study, providing supplemental oxygen to keep saturations in the 96-99% range did not reduce the incidence of threshold ROP. The authors point out however, that the progression of ROP, expected to be approximately 33% based on the CRYO-ROP study, occurred at a much higher rate in the conventional saturation range (48%). This resulted in a less than expected ability to detect a significant difference between the groups with the number of infants enrolled. The authors also suggest that the subgroup of infants without plus disease may benefit from the higher saturation range. The poorer pulmonary outcome of the treatment arm serves to remind us of the toxic effect of oxygen to developing lung tissue, as well as the need to balance risks and benefits across a number of outcomes when looking for therapeutic strategies for extremely premature infants.

The STOP-ROP Multicenter Study Group. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics 2000; 105(2): 295-310.

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DEVELOPMENTAL OUTCOME AND OXYGEN SATURATION

Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003; 349(10):959-67.

A second multicenter study evaluating the effect of maintaining oxygen saturation in preterm infants.

The Benefits of Oxygen Saturation Targeting (BOOST) trial was the second multicenter study to evaluate the effect of maintaining oxygen saturation in the upper 90s in preterm infants. The primary endpoints for this study were growth and developmental outcome at 12 months corrected age. Secondary endpoints included ROP, duration of respiratory support, health care utilization after hospital discharge, and parental stress. The study sample consisted of 358 infants born at less than 30 weeks gestation who remained oxygen dependent at 32 weeks PMA. Infants were randomized to a target saturation range of either 91-94% (standard group) or 95-98% (high group). Masking of the study group assignment was accomplished by equipping each enrolled child a pulse oximeter that displayed values either 2% higher (standard group) or lower (high group) than the actual oxygen saturation. Caregivers were instructed to maintain oxygen saturation in the masked range of 93-96%.

The standard (n=178) and high (n=180) saturation groups had similar baseline characteristics including birthweight (918±229 vs. 916±231), gestational age (26.6±1.7 vs. 26.5±1.6), and gender (52% male vs. 54%). Primary endpoints were assessed for 93% of infants in both groups. There was no difference between the groups for weight, length, or head circumference at 12 months corrected age. A similar proportion of children in each group (24% standard and 23% high) had poor developmental outcome, defined as cerebral palsy, a score more than 2 SD below the mean on the Revised Griffiths Mental Development Scales, or blindness.

The risk of developing severe ROP (Stage III or IV) was similar between the groups (16% standard and 12% high), as was the need for retinal surgery (11% standard and 6% high, p= 0.09). The need for surgery for severe ROP approached significance in the subgroup of children born before 28 weeks gestation (16% standard and 8% high, p=0.06). A greater proportion of children in the high saturation group remained oxygen dependent at 36 weeks PMA (64% high vs. 46% standard, p<0.001) and at the time of hospital discharge (30% high vs.17% standard, p< 0.001) than did the standard saturation group. There was no difference between the groups on the proportion of children rehospitalized, the amount of healthcare resources utilized (as measured by number of health services visits), or parental stress (as measured by the Parenting Stress Index).

Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003; 349(10):959-67.

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OXYGEN SATURATION LIMITS AND DEVELOPMENTAL OUTCOMES

Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001; 84(2):F106-10.

A retrospective study examining the relationship between hospital policies concerning oxygen saturation limits and developmental outcomes.

In this population based, retrospective study, Tin et.al examined the relationship between hospital policies concerning oxygen saturation limits, and the survival, ophthalmic and developmental outcomes of children born at less than 28 weeks gestation. Hospital policies during the study period (1990-1994) were consistent with four different - but overlapping - targeted oxygen saturation ranges: 88-98%, 85-95%, 84-94%, and 70-90%. All 295 surviving children were assessed by both a pediatrician for cerebral palsy at 18 months of age or older as well as by an ophthalmologist, until retinal vascularization was complete or Retinopathy of Prematurity (ROP) regressed.

No difference was found in the survival rates between the children nursed under the different oxygen saturation policies. The lowest incidence of threshold ROP, 6.2% (95% confidence interval, 1.7%, 15%) was found among the children cared for in nurseries accepting the lowest oxygen saturations, 70-90%. The highest incidence of threshold disease, 27.7% (17.3%, 40.2%), occurred among those nursed in the highest saturation range, 88-98%. Threshold retinopathy was diagnosed in a similar proportion of children cared for in the two mid-saturation ranges (15.6% and 13.2%, for 85-95% and 84-94% respectively). Approximately fifteen percent of children in each group had cerebral palsy.Children with saturations in the 70-90% range were also ventilated for a shorter period of time and received oxygen for fewer days than the children in the 88-98% range (on average, 14 and 40 days, respectively vs. 31 and 96 days).

Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001; 84(2):F106-10.

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ROP AND OXYGEN THERAPY MANAGEMENT

Chow LC, Wright KW, Sola A, Group COAS. Can changes in clinical practice decrease the

incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics 2003; 111(2): 339-45.

Charting the effect of oxygen therapy management and the incidence of ROP.

In this observational study, the incidence of severe ROP was compared before and after a NICU adopted strict new guidelines for managing oxygen therapy. The goal of the change in practice was to avoid hyperoxia and fluctuating episodes of hypoxia/hyperoxia in very low birthweight infants (VLBW = birthweight less than 1500 grams). Infants were monitored with pulse oximetry from the time of delivery throughout the hospitalization. The targeted saturation range was 85-93% for infants less than 32 weeks gestation, and 85-95% and for infants greater than 32 weeks gestation. Under the new guidelines the percent of inspired oxygen could be changed by no more than 5% in response to desaturations or episodes of hyperoxia. Once the oxygen was changed, nurses were required to stay at the bedside until the infant was stable. If further manipulation in oxygen management was necessary to obtain the desired saturation range, a physician was called to the bedside. All members of the clinical team received extensive education about the new guidelines.

Over a five-year period, from 1997, the year before the guidelines went into effect, through 2001, the incidence of Stage III or IV ROP fell from 12.5% to 2.5%. The greatest change was seen in the infants with birthweight less than 750 grams with the incidence falling from 38% to 12%. The need for laser surgery fell from 4.4% in 1997 to zero by the year 2000 and remained at that level for the duration of the study period.

The authors concluded that vigilance concerning oxygen management was at least partially responsible for the decline in severe ROP.

Chow LC, Wright KW, Sola A, Group COAS. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics 2003; 111(2): 339-45.

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HYPEROXIC VS HYPOXIC FLUCTUATIONS AND ROP

McColm JR, Cunningham, S., Wade, J., Sedowofia, K., Gellen, B., Sharma, T., McIntosh, N., Fleck, B. W. Hypoxic oxygen fluctuations produce less severe retinopathy than hyperoxic fluctuations in a rat model of retinopathy of prematurity. Pediatr Res 2004; 55(1): 107-13.

An animal study assessing the effects of oxygen fluctuation.

The purpose of this animal study was to see if small fluctuations of oxygen around a hyperoxic or hypoxic mean influenced the development of retinal vessels. Rat pups were exposed to one of three fluctuating oxygen environments from four hours after delivery to 14 days of age. The hyperoxic group was reared in oxygen that varied around a mean of 24.7%. These pups spent 91.8% of the study period in greater than 21% oxygen. The hypoxic group was exposed to a mean of 17.9% oxygen, and spent 88.7% of the time in less than 21% oxygen. A normoxic group's environment varied around a mean of 21.3%, spending approximately half of the time above room air and half below. A fourth group (controls) was reared in room air with no manipulation of the environmental oxygen.

At the end of the study period, a larger area of the retina in the hyperoxic group was avascular (2.7%), suggesting retarded vessel growth compared to the other three groups (normoxic group 1.7% avascular, and retinas fully vascularized in both the hypoxic and control group, $p<0.001$, χ^2 likelihood ratio for multiple group comparison). A greater proportion of the terminal vessels between the avascular and vascularized retina were also abnormal in the hyperoxic group, compared with the other groups (42.5% vs. 21% normoxic group, and 0% in the hypoxic and control groups).

The control group weighed significantly more than any of the three oxygen fluctuation treatment groups (29.2 g compared to 25.2 g in the hyperoxic group ($p<0.05$), 23 g in the hypoxic group ($p< 0.001$), and 23.7 g in the normoxic group ($p<0.001$).

The experimental environments to which the rat pups were exposed were designed to more closely approximate the environmental conditions experienced by infants born at less than 28 weeks gestation than in previous studies. The immaturity of the retinal vasculature in the hyperoxic group increased the risk of the development of severe retinopathy of prematurity. A mildly hypoxic environment seems to be protective for retinal vessel growth but restricts body weight and may have adverse effects on other organ systems including the brain.

The authors suggest that early exposure to small fluctuations in oxygen in a mildly hyperoxic range "sets the stage" for the development of ROP.

McColm JR, Cunningham, S., Wade, J., Sedowofia, K., Gellen, B., Sharma, T., McIntosh, N., Fleck, B. W. Hypoxic oxygen fluctuations produce less severe retinopathy than hyperoxic fluctuations in a rat model of retinopathy of prematurity. Pediatr Res 2004; 55(1): 107-13.

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- Evaluate the research presented to develop a more complete understanding of the relationships between oxygen levels and morbidity.
- Demonstrate a more complete understanding of the advantages/disadvantages of supplemental oxygenation therapy as regards potential ophthalmic, pulmonary, and long term growth outcomes.
- Use the information presented herein as a basis for decision making in determining proper supplemental oxygen levels for appropriate patients in your clinical practice.

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- Dr. Nogee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/ material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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