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RESEARCH NEWS

Oxygen Toxicity at Birth: The Pieces Are Put Together

A review of: Naumburg E, Bellocco R, Cnattingius S, *et al.* 2002 Supplementary oxygen and risk of childhood lymphatic leukaemia. Acta Paediatr 91:1328–1333; and Vento M, Asensi M, Sastre J, *et al.* 2003 Oxidative stress in asphyxiated term infants resuscitated with 100% oxygen. J Pediatr 142:240–246

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Recently Naumburg et al. (1) presented data indicating there is an association between a brief exposure of pure oxygen at birth and childhood lymphatic leukemia. In a population based case-control study, the authors searched for predisposing factors exerting their influence early in life. Five hundred seventy-eight children with lymphatic leukemia were identified through the Swedish Cancer Register and each matched with one control randomly selected from the Swedish Birth Register.

Fortunately, no association was found between childhood lymphatic leukemia and birth related factors such as mode of delivery, birth weight, gestational age, small or large for gestational age, pulmonary disorders, or congenital malformations. Low Apgar scores (1 min $<$ 4, or 5 min $<$ 6) did not give significant increased risk for developing leukemia. By contrast, oxygen given by mask resulted in an odds ratio (OR) of 2.87 (95% CI = 1.21–6.82). When these data were split up into 0–2 min and 3–10 min oxygen exposure an OR for the latter group of 3.54 (95% CI = 1.16–10.80) was found. Oxygen exposure later in the neonatal period did not reveal an increased risk for childhood lymphatic leukemia.

Although these findings must be controlled preferably by larger, prospective studies, they still are alarming. Especially on the basis that it now becomes more and more clear that oxygen administration is not needed routinely for newborn resuscitation and might even increase neonatal mortality (2).

How can such a brief exposure to oxygen be toxic? Previous review articles in Pediatric Research have described the critical aspects of oxidative stress and important clues might be found in perinatal/neonatal research (3–5). Toxicity may be the end result because our patients are so often exposed to augmented oxidative stress either caused by oxygen, inflammation/infections, or low oxidative defense.

In this context, another study is of particular interest. Vento et al previously have demonstrated that resuscitation at birth with 100% oxygen by contrast to resuscitation with room air, triggers an increased oxidative stress at least four weeks postnatally (6). In a recent study, this same group of investigators analyzed these aspects in more detail, from birth until 10 min after clinical stabilization in 51 asphyxiated newborn infants resuscitated with room air and 55 with 100% oxygen (7). Pure oxygen delays the first cry and breath, this was once more confirmed and should by now be considered an established fact. Hence, duration of supportive efforts such as oxygen supplementation is prolonged in infants given pure oxygen. Needless to say, the babies resuscitated with pure oxygen were hyperoxemic with a paO_2 of 126 ± 22 mm Hg versus the normal level of 72 ± 7 mm Hg in the room air group at 5-6 min of age and still 10 min after stabilization a higher paO_2 was detected in the former group. On this basis, the authors calculated that on average infants resuscitated with 100% oxygen received 350 mL more oxygen than those given room air. Oxidized glutathione was higher and reduced glutathione lower in the oxygen than in the room air group demonstrating higher oxidative stress in the former group.

Elevated oxidative stress can alter signal transduction, DNA and RNA synthesis, protein synthesis, enzyme activation, and directly influence the cell cycle. Oxidative stress might influence both cell growth and development, as well as cell death, both apoptosis and necrosis. Since a brief oxygen exposure at birth seems to induce relatively long lasting oxidative stress, the results from Vento *et al.* therefore might give us a key to understand the results of the Swedish study. Although the toxic nature of high oxygen concentrations has been known for more than two centuries, only recently an understanding is emerging that oxygen might be more toxic than believed up to now (8). Therefore any possible mutagenic, carcinogenic or other long-term detrimental effects of oxygen exposure immediately after birth urgently need to be investigated.

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