

Steroids and other adverse influences on the neonatal brain

Eric S. Shinwell, MD

Department of Neonatology, Kaplan Medical Center, Rehovot and Hebrew University, Jerusalem, Israel

Tel: (972) 89441218

Fax: (972) 89441768

E-mail: eric_s@clalit.org.il / www.kenes.com

Introduction

In the last decade, the field of neonatology has witnessed continuing improvement in the survival and outcome of extremely preterm infants. However, this progress has been accompanied by increased understanding of the extreme vulnerability of the preterm human brain. Accordingly, a number of risk factors and therapeutic interventions that are now recognized as potentially harmful will be reviewed in this article.

Disturbance of normal brain development

The developing human brain undergoes a highly complex process of growth and differentiation that includes continued cortical development through the first year of life.(1) The representative cranial MRI scans in the figure demonstrate the process that the brain needs to undergo between 24 and 40 weeks of gestation and emphasizes how preterm birth disturbs this delicate process. Three-dimensional magnetic resonance imaging studies have shown that even in the absence of structural injury such as intraventricular hemorrhage (IVH) or periventricular leucomalacia (PVL), the brain at term of infants born extremely preterm has markedly reduced volume and convolution when compared with infants born at term.(2) This may partly explain the increased risk for neurosensory sequelae in preterm infants with normal cranial ultrasound examinations.

Prenatal and postnatal steroids

Steroids, both endogenous and exogenous, are potent hormones that exert a wide spectrum of influences on developing fetal organs, including the brain. However, the short and long-term effects of pharmacological levels of single or repeated courses of exogenous steroids on the developing brain vary from neuro-protective to neurotoxic. This spectrum depends on the specific steroid, dose, potency, site of administration and the stage of fetal development at the time of administration.(3-5) Single courses of prenatal steroids are associated with significant reduction in risk for IVH (OR 0.48, 95% CI: 0.32-0.72).(6) The risk for PVL appears also to be reduced, although one study has suggested that this may be only with betamethasone and not after dexamethasone therapy.(7) However, evidence has accumulated from both animal and human studies to suggest that multiple courses of prenatal steroids are associated with reduced brain growth.(2,8,9) Despite, or perhaps in view of these conflicting influences, long-term neurodevelopmental outcome is unaltered by either single or multiple courses of prenatal steroids.

Postnatal steroids are widely used in the management of preterm infants with chronic lung disease. This therapy facilitates earlier extubation and may reduce long-term oxygen requirement, although

no clear reduction in mortality has been demonstrated.(10-12) However, recent studies have shown that postnatal steroid therapy, particularly in the first week of life and when administered in high dose, appears to be associated with increased risk for cerebral palsy and neurodevelopmental delay.(13) As a result of these findings, the American Academy of Pediatrics and the Canadian Pediatric Society have published evidence-based guidelines restricting the use of this therapy to either randomized controlled trials or to exceptional clinical circumstances.(14) As a result, there has been a marked reduction in the use of this therapy, although, to date, there is limited data on the effect of this change on the incidence or severity of chronic lung disease or its' associated mortality.(15)

Oxygen

Despite more than 50 years of oxygen therapy in neonatal medicine, neonatal care providers still do not know how best to use oxygen in the most vulnerable infants.(Tin) The history of oxygen use in modern neonatology has been marred by recurring disaster. Unrestricted use in the 1940's and 50's was associated with an epidemic of retrolental fibroplasia (retinopathy of prematurity). Subsequently, excessive restriction of oxygen resulted in less retinopathy, but more mortality and cerebral palsy. Although it is now standard practice to closely monitor oxygenation in order to guide inspired oxygen concentrations, the desired range of oxygenation is still unknown. This is of particular importance in two settings – the preterm infant at risk for retinopathy and any neonate requiring resuscitation.

Continuous monitoring of oxygenation in preterm infants is routinely performed with pulse oximetry. However, the ease of use of this technique stands in contrast with its lack of accurate correlation with pO₂, particularly at the high end of the range of values. Recent studies have compared the effects of different target ranges during routine care in small preterm infants. Both randomized trials and observational studies have compared target saturations in the low or high 90's and found little or no difference in the incidence or severity of retinopathy. However, a higher incidence of chronic lung disease was found in the higher saturation group. In addition, a recent, retrospective but provocative study compared 4 neonatal units with varying policies of oxygen targeting. The unit with the lowest target range (70-90%) had significantly less infants with retinopathy and no associated increase in either mortality or neurologic sequelae. These findings, while limited somewhat by the methodology employed, provide a strong justification for a large, international, multicenter randomized trial of variable target ranges for oxygenation that is sufficiently powered to detect differences in both short-term outcomes such as retinopathy, chronic lung disease and mortality and also long-term outcomes such as cerebral palsy or other neurosensory impairment.(Cole, Pediatrics)

The second area of major uncertainty regarding oxygen therapy is whether widely accepted practice of resuscitation with 100% oxygen is preferable to resuscitation with room air. In recent years, data has been accumulating from animal studies and randomized clinical trials that challenge the conventional wisdom on this issue. It is now clear that most infants requiring resuscitation at birth do not require 100% oxygen and may even be harmed by it. Exposure to pure oxygen may be associated with increased neonatal mortality, prolonged oxidative stress and adverse neurologic outcome. As with the above issue, there is currently a compelling need for a large well-designed randomized trial that may finally answer this question. In the meantime, it seems reasonable practice

to recommend that resuscitation at birth be initiated with room air, with pure oxygen available to be supplemented in the absence of a good rapid response.(Saugstad)

Mechanical ventilation and hypocapnia

Mechanical ventilation (MV) saves the lives of preterm infants. However, since the early days of its use, MV has been recognized as harmful to the preterm lung, particularly in combination with oxygen therapy. MV is a major risk factor for the development of Chronic Lung Disease (CLD) and accordingly, much effort has been focused on ways to minimize its excess use. In recent years, this has received support from observation of an association between iatrogenic hypocapnia and cerebral palsy (CP), possibly mediated via cerebral vasoconstriction and reduced cerebral blood flow in the neonatal period.(Collins) In one study, the risk for CP was three times higher for ventilated preterm infants who had hypocapnia when compared with infants without hypocapnia. There is also evidence from animal studies of a neuroprotective effect of mild hypercapnia when compared with normocapnia.(Vanucci)

Other known adverse influences

Together with the recognition of the vulnerability of the extremely preterm brain has come information regarding a number of additional potential risk factors for neurodevelopmental impairment. Prominent among these is chorioamnionitis, which raises the risk for cerebral palsy in preterm infants. The mechanism of this influence is unclear, as it has recently been shown that, whereas in term infants raised cytokine levels at birth correlate with CP, this is not so in preterm infants.(Nelson)

Another area of active research is the assessment of the effect of other medications on the developing central nervous system. Medications that have so far been implicated as possibly harmful include caffeine, indomethacin, pancuronium and midazolam.

Summary

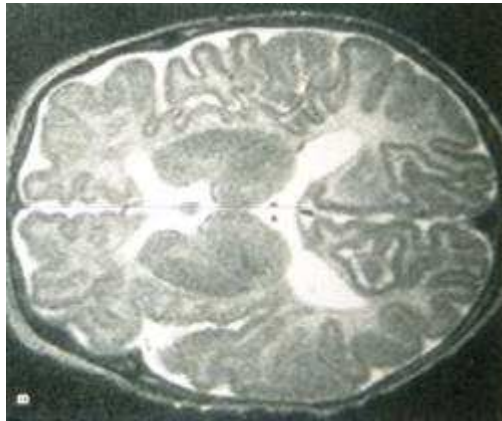
This review highlights the marked vulnerability of the extremely preterm brain and the urgent need for studies specifically designed to answer the questions raised herein.

References

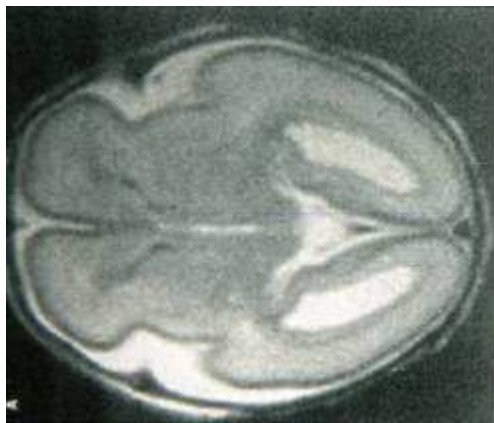
1. Matthews SG. Antenatal glucocorticoids and the developing brain: mechanisms of action. *Semin Neonatol* 2001;6:309-317
2. Murphy BP, Inder TE, Huppi PS, Warfield S, Zientara GP, Kikinis R, et al. Impaired cerebral cortical grey matter growth after treatment with dexamethasone for neonatal chronic lung disease. *Pediatrics* 2001;107:217-221
3. Bertram CE, Hanson MA. Prenatal programming of postnatal endocrine responses by glucocorticoids. *Reproduction* 2002;124:459-467.
4. Yeung MY, Smyth JP. Hormonal factors in the morbidities associated with extreme prematurity and the potential benefits of hormonal supplement. *Biol Neonate* 2002;81:1-15.
5. Jobe AH, Newnham J, Willet K, Sly p, Ikegami M. Fetal versus maternal and gestational age effects of repetitive antenatal glucocorticoids. *Pediatrics* 1998;102:1116-1125
6. Crowley P. Prophylactic corticosteroids for preterm birth (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd
7. Baud O, Foix-L'Helias L, Kaminski M, Audibert F, Jarreau PH, Papiernik E, et al. Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very premature infants. *N Eng J Med* 1999;341:1190-1196
8. Abbasi S, Hirsch D, Davis J, Tolosa J, Stouffer N, Debbs R, et al. Effect of single versus multiple courses of antenatal corticosteroids on maternal and neonatal outcome. *Am J Obstet Gynecol* 2000;182:1243-1249.
9. French NP, Hagan R, Evans SF, Godfrey M, Newnham JP. Repeated antenatal corticosteroids: Size at birth and subsequent development. *Am J Obstet Gynecol* 1999;180:114-12

10. Halliday HL, Ehrenkrantz RA, Doyle LW. Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants. The Cochrane Library, 2003, Update software
11. Halliday HL, Ehrenkrantz RA, Doyle LW. Moderately early postnatal (7-14 days) corticosteroids for preventing chronic lung disease in preterm infants. The Cochrane Library, 2003, Update software
12. Halliday HL, Ehrenkrantz RA, Doyle LW. Delayed (>3 weeks) corticosteroids for chronic lung disease in preterm infants. The Cochrane Library, 2003, Update software
13. Shinwell ES, Karplus M, Reich D, Weintraub Z, Blazer S, Bader D, et al. Early postnatal dexamethasone treatment and increased incidence of cerebral palsy. Arch Dis Child Fetal Neonatal Ed 2000;83:F177-F181
14. American Academy of Pediatrics Committee on Fetus and Newborn. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. Pediatrics 2002;109:330-338
15. Shinwell ES, Karplus M, Bader D, Dollberg S, Gur I, Weintraub Z, et al. Neonatologists are using much less dexamethasone. Arch Dis Child Fet Neo Ed 2003;88:F36-F40

Figure 1: Magnetic Resonance Imaging of human brain at 24 and 40 weeks of gestation



Term (40 weeks) brain



24 week brain