

Pilot Randomized Trial of Hydrocortisone in Ventilator-Dependent Extremely Preterm Infants: Effects on Regional Brain Volumes

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Objective To test the hypothesis that high-risk ventilator-dependent extremely low birth weight (birth weight ≤ 1000 g) infants treated with 7 days of hydrocortisone will have larger total brain tissue volumes than placebo treated infants.

Study design A predetermined sample size of 64 extremely low birth weight infants, between 10-21 days old and ventilator-dependent with a respiratory index score ≥ 2 , were randomized to systemic hydrocortisone (17 mg/kg cumulative dose) or saline placebo. Primary outcome was total brain tissue volume. Volumetric magnetic resonance imaging was performed at 38 weeks postmenstrual age; brain tissue regions were segmented and quantified automatically with a high degree of accuracy and 9 structures were segmented manually. All analyses of regional brain volumes were adjusted by postmenstrual age at magnetic resonance imaging scan.

Results The study groups were similar at baseline and 8 infants died in each arm. Unadjusted total brain tissue volume (mean $\pm$ SD) in the hydrocortisone (N = 23) and placebo treated infants (N = 21) was 272 ± 40.3 cm³ and 277.8 ± 59.1 cm³, respectively (adjusted mean difference: 6.35 cm³ (95% CI: (-20.8, 32.5); $P = .64$). Three of the 31 hydrocortisone treated infants and 5 of the 33 placebo treated infants survived without severe bronchopulmonary dysplasia (relative risk 0.62, 95% CI: 0.13, 2.66; $P = .49$). No significant differences were noted in pre-specified secondary outcomes of regional structural volumes or days on respiratory support. No adverse effects of hydrocortisone were observed.

Conclusions Low dose hydrocortisone in high-risk ventilator-dependent infants after a week of age had no discernible effect on regional brain volumes or pulmonary outcomes prior to neonatal intensive care unit discharge. (*J Pediatr* 2013;162:685-90).

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Bronchopulmonary dysplasia (BPD), an inflammatory disease of arrested lung development in extremely low birth weight (ELBW; birth weight [BW] ≤ 1000 g) infants, is strongly associated with neurodevelopmental impairments.^{1,2} Postnatal dexamethasone significantly reduces the risk of BPD, especially following early administration, but also increases risk of neurodevelopmental impairments,³ which appears to be dependent on dose and baseline BPD risk.^{4,5} A meta-regression of all corticosteroid trials assessing death or cerebral palsy, reported this outcome to be inversely related to BPD risk at trial entry.⁵ When baseline BPD risk was below 35%, corticosteroid treatment significantly increased the risk of death or cerebral palsy, whereas when BPD risk exceeded 65%, it reduced this risk. Use of even moderate doses of dexamethasone in high-risk infants was associated with regional brain volume deficits in observational studies.^{6,7} It is unclear if this reflects dexamethasone toxicity or risks of the underlying lung disease.

Hydrocortisone may have less glucocorticoid receptor mediated toxicity to the central nervous system by additionally binding mineralocorticoid receptors. Hydrocortisone has no sulfite preservatives and is identical to native cortisol.^{8,9} Low dose hydrocortisone (11.5-13.5 mg/kg cumulative), given soon after birth may increase risk of intestinal perforations when used concomitantly with indomethacin with limited pulmonary benefits.^{10,11} However, a new trial that restricts treatment to the highest risk ventilator-dependent infants after 1 week of age and uses a 25%-50% higher dose, deserves further investigation and may reduce both pulmonary and neurologic morbidities. We designed a pilot randomized placebo-controlled trial in high-risk ventilator-dependent infants after a week

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BPD	Bronchopulmonary dysplasia
BW	Birth weight
ELBW	Extremely low birth weight
IV	Intravenous
MRI	Magnetic resonance imaging

of age to test the hypothesis that treatment with hydrocortisone would result in larger total brain tissue volume at term-equivalent age.

Methods

Ventilator-dependent ELBW (BW ≤ 1000 g) infants in the neonatal intensive care unit at Children's Memorial Hermann Hospital between the ages of 10 and 21 days were eligible for inclusion in this parallel group trial if their respiratory index score (mean airway pressure $\times$ fraction of inspired oxygen) was ≥ 2.0 and stable or increasing or if the respiratory index score was ≥ 3.0 when improvement was noted in the previous 24-hour period. Such infants are at 75% or greater risk of BPD or death based on our local data and results from a multicenter study.¹² Infants were excluded if they were < 23 weeks gestation at birth, were previously treated with corticosteroids, were receiving indomethacin treatment or likely to receive it within 7 days, had presumed sepsis or necrotizing enterocolitis, or had a major congenital anomaly of the cardiopulmonary or central nervous system. The institutional review board approved the research protocol. Written informed consent was obtained from a parent or guardian of each infant. The trial was registered with [ClinicaTrials.gov](https://clinicaltrials.gov) (NCT00167544).

Randomization was stratified by BW (≤ 750 g or 751–1000 g) and respiratory index score (2.0–4.0 or > 4.0) using a blocked random allocation (1:1) with variable block sizes. An individual not involved with the study generated the random allocation sequence. Access to this sequence assignment was limited to 2 study pharmacists. An independent study monitor reviewed the study data after 50% enrollment. Only this study monitor and pharmacists were aware of the subjects' group assignment until analysis.

Intervention and Co-Interventions

All ELBW infants between 10 and 21 days of age were screened for eligibility and parents were approached for consent on the day their infant met eligibility criteria. Following consent, infants were randomly allocated and initiated on a 7-day course of intravenous (IV) hydrocortisone sodium succinate (Solu-Cortef; Pfizer, New York, New York) every 12 hours (3 mg/kg per day for first 4 days, 2 mg/kg per day for 2 days, and 1 mg/kg per day for 1 day; total of 17 mg/kg over 7 days) or an equivalent volume of identical appearing 0.9% sterile saline placebo. The IV route was preferred. Per protocol, after failed IV access attempts, 1 infant in each study group received identical appearing oral study drug. Concurrent use of indomethacin was prohibited.^{10,11} Doses of study drug were to be discontinued if intestinal perforation developed, indomethacin was started, or systemic hypertension (systolic blood pressure > 3 SD for postmenstrual age) persisted for ≥ 24 hours. Use of other steroid preparations was prohibited during the study drug intervention period. To minimize later indiscriminant use of postnatal corticosteroids, we defined a suitable high-risk subgroup (respiratory index score > 10 after 28 days old) and an accept-

able regimen of dexamethasone (0.89 mg/kg cumulative dose over 10 days) where benefits appear to outweigh harms.^{5,13} Clinical respiratory management was not dictated by the study protocol other than recommendations to restrict use of postnatal corticosteroids and to wean support following study initiation as clinically indicated.

Determination of Outcomes

The primary outcome was total brain tissue volume as measured by volumetric magnetic resonance imaging (MRI) at 38 weeks postmenstrual age. Secondary outcomes included survival without severe BPD, days on positive pressure support, and days on supplemental oxygen before 36 weeks postmenstrual age. The National Institutes of Health Consensus definition of BPD was used; severe BPD was defined as oxygen treatment for at least 28 days plus physiologic need for $\geq 30\%$ oxygen and/or positive pressure at 36 weeks postmenstrual age.¹ Positive pressure support was defined as respiratory support with mechanical ventilation or continuous positive airway pressure. Safety evaluations included baseline and daily assessments of blood pressure, serum glucose, intestinal perforation, sepsis, and gastrointestinal bleeding. Concurrent use of indomethacin or dexamethasone was monitored to evaluate compliance. Baseline and 36 weeks postmenstrual age weight, length, and head circumference measurements were also collected.

Additional secondary outcome measurements included individual tissue volumes of cortical gray matter, cerebral white matter, and cerebrospinal fluid (ventricular and subarachnoid space) and structural volumes of caudate, accumbens, lenticular nuclei, thalamus, subcortical gray matter (combination of these 4 nuclei), cerebellum, hippocampi, amygdalae, corpus callosum, and brain stem. We previously reported our detailed methods with high reliabilities observed for tissue and structural volume measurements in very preterm infants.¹⁴ Briefly, MRI of the brain was performed on a 1.5 Tesla GE-LX scanner (General Electric, Milwaukee, Wisconsin) after feeding, during natural sleep whenever possible (90% unседated). Axial proton density/T2-weighted scans were used for volumetry with echo time 15/175 ms; repetition time 10 000 ms; field of view 18×18 cm; matrix 512×512 ; voxel dimensions: 0.36 height $\times$ 0.36 width $\times$ 1.98 depth mm. Cerebral tissues were segmented automatically using in-house developed software specifically designed for preterm newborn brains. Tissue segmentation accuracy was high.¹⁴ Analyze 8.1 (Biomedical Imaging Resource, Mayo Clinic, Rochester, Minnesota) was used for manual segmentation of all structures by a single masked rater, using well-known defined landmarks distinguished by spatial location, shape, and image intensity. Intra- and inter-rater measurement reliability was also high (range: 0.942–0.998).¹⁴

Statistical Analyses

Assuming an alpha error of 0.05, a 25% mortality, and total brain tissue volume of 357 ± 50 cm³ for infants with BPD, 32 infants per group provided 80% power to detect a 43 cm³ absolute improvement in the primary outcome. This

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